ISSN 0029–540X
e-ISSN: 2300-2115

Volume 72 | Number 3 | Year 2022

Nowotwory

Journal of Oncology

90 years
since the opening of Radium Institute in Warsaw

Indexation in: Scopus, EMBASE, Google Scholar, CrossRef, MEiN: 100 points

VIA MEDICA

3/2022

Nowotwory

Journal of Oncology

established in 1923
as the *Bulletin of the Polish Committee Against Cancer*
renamed *NOWOTWORY* in 1928
renamed *NOWOTWORY Journal of Oncology* in 2001

bimonthly

official organ of the

POLISH ONCOLOGICAL SOCIETY

M. SKLODOWSKA-CURIE NATIONAL
RESEARCH INSTITUTE OF ONCOLOGY

journal of the

POLISH SOCIETY
OF SURGICAL ONCOLOGY

21-0530.003.001

Nowotwory

Journal of Oncology

Address of the Editor Office:
Narodowy Instytut Onkologii im. M. Skłodowskiej-Curie – Państwowy Instytut Badawczy
ul. Roentgena 5
02-781 Warszawa, Poland

Address for correspondence:
Krakowska Akademia im. Andrzeja Frycza-Modrzewskiego
ul. Gustawa Herlinga-Grudzińskiego 1
30-705 Kraków, Poland
room 309
phone: 512 177 774

Address of the Publisher:
VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73, 80-180 Gdańsk, Poland
e-mail: viamedica@viamedica.pl, www.viamedica.pl

Managing Editors: Agnieszka Wrzesień, Aleksandra Cielecka

NOWOTWORY Journal of Oncology
is indexed in: Biochemistry & Biophysics Citation Index, CAS, CrossRef, EMBASE, Free Medical Journals, Google Scholar, Index Copernicus (108.30), MEiN (100), Polska Bibliografia Lekarska, Scopus, SJR and Ulrich's Periodicals Directory

Editorial policies and author guidelines are published on journal website:
www.nowotwory.edu.pl

FUNDACJA im. Jakuba hr. Potockiego
ROK ZAŁOŻENIA 1934

NOWOTWORY Journal of Oncology is published with the generous support from the Count Jakub Potocki Foundation

ISSN 0029–540X
e-ISSN: 2300-2115

Contents

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 139–154
DOI: 10.5603/NJO.2022.0028

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

VIA MEDICA

An outline of the history of the Oncology Institute in Warsaw, on the 90th anniversary of its opening

Janusz Meder, Aleksandra Towpik, Jan Walewski

Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Ninety years ago, The Maria Sklodowska-Curie Radium Institute in Warsaw was officially opened. The ceremony was marked by Skłodowska's honourable presence as the author of the idea, the co-founder and patron of the Institute. The opening of the first modern institution which combined research and clinical activity was a breakthrough moment in the history of Polish oncology. This article presents an outline of the history of the Institute from the moment of the creation of the idea, through the hardships undertaken by the distinguished personalities involved in the organisational work during the first years of the existence of the centre, the busy period during its medical and academic heyday interrupted by the outbreak of the Second World War and then the period of restoration from the destruction that had previously ensued. The paper also presents the period when new oncological specialisations were created, which started at the Institute at Wawelska street and the invaluable role the Institute staff played in the creation of the structures of modern oncological care in Poland. The intellectual resources were created by a generation of the Institute staff on the foundation of the innovative concept laid down by Maria Skłodowska-Curie. She always emphasised the necessity of the continual connection between clinical work and research and the role of interdisciplinary work as the basis for progress in combating oncological diseases. These efforts consist of a unique and special value, which is also a commitment to and challenge for the future.

Key words: history of oncology, Radium Institute in Warsaw, the history of the Maria Sklodowska-Curie Institute of Oncology

Introduction

Ninety years ago, on Sunday, 29th May 1932 in Warsaw, at Wawelska 15, in the vicinity of the Lubecki Colony, the Maria Sklodowska-Curie Radium Institute was officially opened. The ceremony was marked by Skłodowska's honourable presence as the author of the idea, the co-founder and patron of the Institute. This event marks the beginning of modern institutionalised oncological care in Poland.

The creation of the Institute was by all means an exceptional effort – both on the part of the people directly involved in the creation of the Institute, among whom special attention should be paid to the sister of the great Polish researcher, doctor Bronisława Dłuska, and also the contributions of much of society which was involved in the creation of the Institute on an unprecedented scale, providing donations, buying shares ("bricks" to build the Institute) and taking part in numerous fundraising events.

How to cite:

Meder J, Towpik A, Walewski J. ***An outline of the history of the Oncology Institute in Warsaw, on the 90th anniversary of its opening.*** *NOWOTWORY J Oncol* 2022; 72: 139–154.

The building of the Institute was an unprecedented event, not only on the scale of an impoverished and devastated country, as Poland was, but it was also one of the most modern medical institutions in Europe, or perhaps even worldwide. This carefully planned and designed centre added new value, but failed to match the Polish reality with its potential initially unappreciated. Professor Franciszek Łukaszczyk, the first director of the institute, observed that this event was much ahead of the times, and the country was in fact not ready for such a modern institution [1]. Within a few years of the opening, however, great progress was being made. Its significance is seen even more clearly once we realise the hardship of the work and the contemporary challenges of the time that were being faced.

The beginnings of oncology in Poland

In 1921, Maria Skłodowska-Curie made her first journey to America. The main purpose of the trip was to accept, from the hand of President Warren Harding, one gram of radium for the Radium Institute in Paris. The purchase of this precious element was possible thanks to the fundraising action initiated by journalist and activist, William B. Meloney (proper name: Marie Mattingly Meloney) [1]. On 15th June, during a meeting with the representatives of the Polish diaspora, in Chicago, Skłodowska said:

Independent Poland, like any other country should have its own radium institute. The beginning of this Institute was in the radiological laboratory, started, on my initiative in Warsaw by the Warsaw Scientific Society. We need a large sum to transform this laboratory into an institute created not only for scientific research, but also for the treatment of patients, irrespective of their financial status. If the Polish Colony in America could set itself the goal of the creation of this Institute as fast as possible, this would be by all means an act of great merit… [2, 3].

With these words, Maria Skłodowska Curie, for the first time publicly, called for the support of the idea to create the institute in Warsaw [4]. Given, the time period, this was an extremely daring idea – as it was just a few months after the end of the Polish-Bolshevik war. The Polish Republic had been an independent country for only three years, whilst the restoration of the state after partition and after the destruction of the war was a tedious process, requiring a lot of time and effort. All state institutions had to be created from scratch and diverse administrative systems integrated. Divisions were also present and always increasing in society and the academic life; the currency was unstable, the quality of life much lower than in the West; whilst unemployment and inflation were on the continual rise. Not only was infrastructure lacking, there was also significant shortage of staff. People living in urban areas particularly had very poor access to healthcare, whilst the number of doctors insufficient. However, at the same time, civil attitudes and self-government were being coined, with intellectual elites playing a key role in their work towards a better society and the young developing state.

Maria Skłodowska-Curie, during her address in Chicago, mentioned the Mirosław Kernbaum Radiology Laboratory, created at the Warsaw Scientific Society on Kaliksta street (currently Śniadeckich) in Warsaw; it was the first scientific institution on the Polish territories which was actively co-created by Maria Skłodowska-Curie. She agreed to manage the institution from Paris, sending to Warsaw two of her most talented assistants: Jan Danysz and Ludwik Wertenstein. In November 1913, she took part in the opening ceremony in person. Maria Skłodowska-Curie planned to pay regular visits to the laboratory, planning organisational and research undertakings [5–8] and in 1921 she donated the amount of 1000 dollars from the Polish diaspora in America, as it was initially assumed that this would be the basis for the Radium Institute [8].

Oncological diseases made up a significant issue from an epidemiological point of view for doctors in the mid-19th century; therefore at the turn of the 19th and 20th centuries, the first association which had as its objective cancer studies and treatment were created. [9]. The discovery of X-rays by Wilhelm Conrad Roentgen, and first of all, the discovery of radium by Maria and Peter Curie paved a new path in the fight against oncological diseases. Skłodowska-Curie laid the foundations for oncology as a science and a medical discipline [10].

In Poland, in 1906, upon the initiative of doctor Józef Jaworski and doctor Mikołaj Rejchman, the Committee for the Caner Study and Control was set up. Their efforts were concentrated mostly on statistical research, prophylaxis and attempts to encourage the medical milieus to undertake scientific research. It was in 1912 that the idea was put forward of organising a department for the study of cancer in Warsaw [11]. Yet, it was only after regaining independence that a chance would come to create structural solutions. In 1921, the Polish Committee for Fighting Cancer (PKdZR) was founded by Henryk Barylski, Czesław Jankowski, Stefan Sterling-Okuniewski and Bronisław Wejnert [9]. The main task of the committee was to organise the structures for cancer treatment and research. The committee gathered epidemiological data, carried out educational initiatives and dealt with health education, as well as organised outpatient clinics for cancer patients. Soon, regional committees were to be founded in Krakow, Łodz, Poznan, Vilnius and Lviv. In 1923, the first issue of the *Journal of the Polish Committee for Fighting Cancer* was published (*Nowotwory* continue that heritage) as one of the first periodicals in the world devoted solely to cancer treatment [12].

In 1924, the committee organised the First Polish Meeting for Fighting Cancer in Warsaw. During the meeting, some resolutions were passed, which now are regarded as the first Polish Cancer Control Program. This strategy defined three main objectives: scientific, clinical and epidemiological studies; dissemination of knowledge of cancers and health education; creation of oncological centres [13]. It was then that plans for the foundation of oncological centres in larger cities around the Poland of that time were laid down; the active process

of building the Radium Institute in Warsaw was begun. The centres existing up to that moment were widely dispersed and rather limited in size. Apart from a few university centres, also some smaller, either community or private hospitals were set up, they did not have any great success in radium therapy. According to estimate data, even before the creation of the Radium Institute, Poland had *circa* 3 grams of radium, yet the dispersion of this element and its quality, and foremost the lack of qualifications of the staff, paired with inadequate knowledge about radium's manner of action, lead to the fact that the treatment results were greatly unsatisfactory and purely incidental, whilst work with radium was also frequently hazardous for the doctors involved [8].

The opening of the Radium Institute in Warsaw – a modern institution combining academic and clinical activity – marked a ground-breaking moment in the history of Polish oncology. As designated, the institute promoted teamwork, whilst knowledge about cancers which previously had only a character of descriptive learning was transferred into modern clinical science, based on the knowledge of oncological processes and the command of treatment tactics and techniques [14].

During the visit which Maria Skłodowska-Curie paid to Warsaw in October 1921, the idea of creating an institute finally started to take shape. At the meeting with the representatives of women organisations, she said: *If you really want to give me proof of your friendship and respect, please see to the creation of the Radium Institute in Warsaw. This is a task for you as women since our experience so far shows that, especially in female patients, the treatment of malignant tumours with radium gives invaluable results* [15].

The scientist, not only gave the ideas but also started to act herself with full energy and determination, establishing contacts and writing numerous letters. It was in November that she wrote to Ignacy Paderewski: *I dare to ask you for the support of fundraising for a cause which I greatly desire to pursue. It is about the creation of a central Radium Institute in Warsaw which task would be to treat patients with radium and carry out scientific research related*… [16].

Since its very beginning, the Warsaw Institute was supposed to be a comprehensive institution, where patient treatment would be carried out together and in connection with scientific research. Skłodowska, on every occasion, would stress the double role of the future institute. The plans were getting their final shape at the moment when the institution in Paris was still struggling with a painful inadequacy e of the hospital section, so while planning its sister institution, Maria wanted to create a comprehensive centre in which the two areas of activity would make up an organic whole. Such a type of centre was a completely different and novel solution [17].

The creation of the Radium Institute

It is impossible to name all the distinguished persons involved in the organisation of the institute. The driving force behind contemporary social and scientific organisations, also extremely dynamic and determined female organisations and, finally, the ability to pursue such an important cause in spite of all divisions – these all make up an unprecedented example even today. The Institute would not have been created if it had not been for Maria's elder sister, doctor Bronisława Dłuska, and also her brother, doctor Józef Skłodowski had been involved in the creation of the Institute since its very beginning [3, 18, 19]. It was in December 1921 that he wrote to Maria stating that he *had submitted the project of an act of the Association of the Radium Institute, modelled on the statute Józef Mianowski Fund* [20]. The founding of the association under the honorary patronage of Curie-Skłodowska gave a formal framework to her dream, making it a point where there was no turning back.

In 1923 in France, the 25th anniversary of the discovery of radium was celebrated. On this occasion, on 26th December at Sorbonne University, an official celebration was held, whilst the French government awarded Maria with an extraordinary distinction – a lifetime grant of 40 000 francs per year. The Polish state could not afford such a gesture at that time. Subsequently, the Polish Committee for Fighting Cancer (PKdZR) made an appeal to Polish society to donate to the "National Gift for Maria Skłodowska-Curie", which was supposed to be the Radium Institute named after her [21].

In March 1924, the Committee of the Maria Skłodowska-Curie National Gift was created with the intention to found the Radium Institute in Warsaw. Its honorary presidency was entrusted to the President of Poland, Stanisław Wojciechowski, whilst the post of the President of the Management Board was conferred to the Speaker of the Senate, Wojciech Trąmpczyński; the Deputy President of the Committee was professor Antoni Ponikowski, the then rector of Warsaw Polytechnics and the secretary – Stefan Sterling-Okuniewski, who was the secretary of the Polish Committee for Fighting Cancer and current director of the committee's journal. The committee members also included members of the Board of Ministers, representatives of universities, scientific institutions and associations, and clergy of various denominations [3].

The institute creation was gaining momentum. The appeal garnered a wide and enthusiastic response. The University of Warsaw donated a plot of land at Wawelska street for the site. It was not only institutions and elites that responded to the call – a common cause and the prestige that Maria enjoyed united the society, irrespective of one's financial status and beliefs. It is remarkable that the stickers with an image of Skłodowska-Curie – which were the donation certificates with a nominal value of 10 groszes – were sold at the number exceeding one million and a half copies [3]. The committee was very active in publishing and advertising – brochures, Maria's portraits and postcards with donation certificates were sold. The branches of the committee were also active in other cities [22, 23].

And so, on 7th June 1925, the ceremony of placing the ground-breaking plaque for the construction of the Institute

was held with the participation of Maria Skłodowska-Curie, who came for this occasion from Paris; the President of the Republic of Poland, Stanisława Wojciechowski; representatives of the academic, political and cultural milieus and also residents of Warsaw who turned out in large numbers [24]. In 1926 construction started at full speed (fig. 1–3).

The Warsaw Institute was intended to be a sister institution of the Radium Institute in Paris. Its first architect was Tadeusz Zieliński, and, after his death in 1925, the work were continued by Zygmunt Wóycicki [3, 22]. At each stage, the project was consulted extensively with Maria Skłodowska-Curie and professor Claudius Regaud, a pioneer in radiotherapy and the head of the Pasteur Laboratory at the Paris Institute. In Warsaw, the undertaking was supervised by Maria's sister, doctor Bronisława Dłuska (fig. 4).

Skłodowska attached a lot of importance to the preparation of scientific workshops and looked over even the smallest details herself. However, with the course of time, in the face of chronic financial difficulties, it became clear that the scientific section of the institute would not be completed anytime soon [25].

Figure 1. The Radium Institute at Wawelska street in Warsaw on its inauguration day (from the collections of the National Digital Archives)

Figure 2. Maria Skłodowska-Curie and the President of Poland, Stanisław Wojciechowski (first from the right) during the ceremony of laying the cornerstone for the construction of the Radium Institute. Above Skłodowska-Curie, there are (from the left), the Rector of the University of Warsaw and the President of the Association of the Radium Institute – Professor Franciszek Krzyształowicz, doctor Bronisława Dłuska, doctor Kazimierz Dłuski and doctor Józef Skłodowski (from the collections of the National Digital Archives)

At the end of October 1929, Maria Skłodowska-Curie received from the hands of the President of the United States, Herbert Hoover, a symbolic check for 50 000 US dollars for the purchase of radium for the Institute in Warsaw. The money came from the fundraising actions among American women and the Polish diaspora. The *spiritus movens* of the entire undertaking was again William B. Meloney. The visit, however, was overshadowed by an event which impacted the fate of the entire world at that time – 24th October went down in history as "Black Friday": the Wall Street stock market crash unleashed the greatest economic crisis in the history of the world, spre-

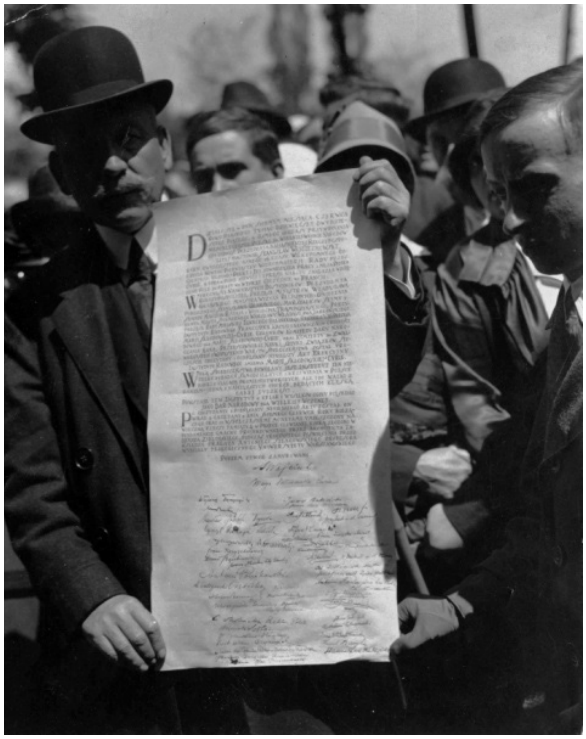

Figure 3. The founding act of the Radium Institute, 7th June 1925 (from the collections of the National Digital Archives)

Figure 4. Maria Skłodowska-Curie accompanied by President Ignacy Mościcki, Professor Stefan Pieńkowski (first from the right), doctor Bronisława Dłuska (first from the left) and Professor Franciszek Krzyształowicz (second from the left) while visiting the construction site of the Institute, 4th October 1928 (from the collections of the National Digital Archives)

ading immediately to Europe; in Poland, it also deteriorated an already difficult economic situation, leading to a significant slow-down in the collection of money for the completion of the institute. That said, the drive to obtain resources for the purchase of radium was a starting point for another social initiative : an illustrated book presenting the state of the construction of the institute [22]. A donation certificate could be bought for 100 zloties and thus the benefactor could get the rights for a memorial plaque in the future institute. The cause was supported by the Ladies Club at the Polish Committee for Fighting Cancer. Also the Committee of United Female Associations was set up for the completion of the Maria Skłodowska-Curie Radium Institute. Michalina Mościcka and Aleksandra Piłsudska took the honorary patronage over the committee (fig. 5) [26].

Thanks to the funds brought from the USA on 12th April 1930, Maria Skłodowska-Curie signed a contract for the supply of radium to Poland with Union Minière du Haut-Katanga (an English-Belgian mining company that were active in Africa on the territory of the current Republic of Kongo) and 833.23 mg of radium was purchased for 54 574 dollars and 90 cents. Maria also received some part of this element as a gift from the company. Thanks to this, Skłodowska provided 1033.21 mg of radium for the Institute, in the form of platinum tubes and needles, labelled later on as RMS (Radium of Maria Skłodowska) [8, 27, 28].

In the end, given the incessant financial shortages, it was necessary to take out a financial loan for completion of construction [1]. On 21st January 1931, the Polish Parliament adopted a resolution on the donation of a state-owned estate at Wawelska street, to the Association of the Radium Institute for the *completion of construction and the fastest launch of the institute*, whilst the justification of the resolution stated that, *the benefits for the state in starting the institute are extremely great* [29]. Thanks to this it was possible to make a mortgage out at the Insurance Board for Academic Staff [1]. The clinic was thus equipped, yet the resources did not suffice for the completion of the research buildings (fig. 6–8).

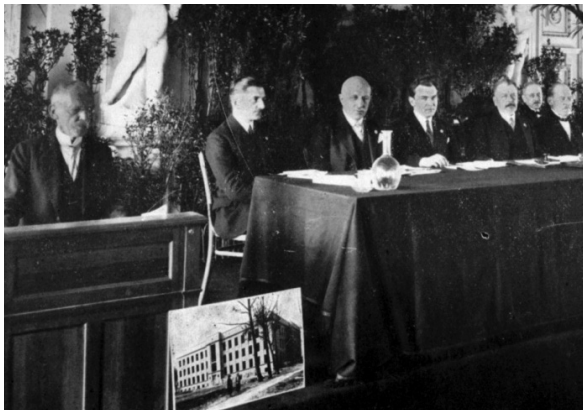

Figure 5. The opening ceremony of the Second Cancer Meeting on 23rd March 1929 – Professor Franciszek Krzyształowicz presents the report from the activity of the Committee of the Radium Institute and the account of the progress in the conduction (from the collections of the editing office of the Maria Sklodowska-Curie National Research Institute of Oncology [MSCNRIO])

The first patients were admitted to the institute in January 1932. Work in the first months of the year was extremely difficult. The committee funds were lacking and the institute was severely in debt. Between mid-January and the date of the official opening of the institute, only 40 patients were hospitalised.

Figure 6. The building of the clinic of the Radium Institute during the completion works, a view from the side of the planned garden (from the collections of the National Digital Archives)

Figure 7. The building of the scientific laboratories of the Radium Institute – finishing works (from the collections of the National Digital Archives)

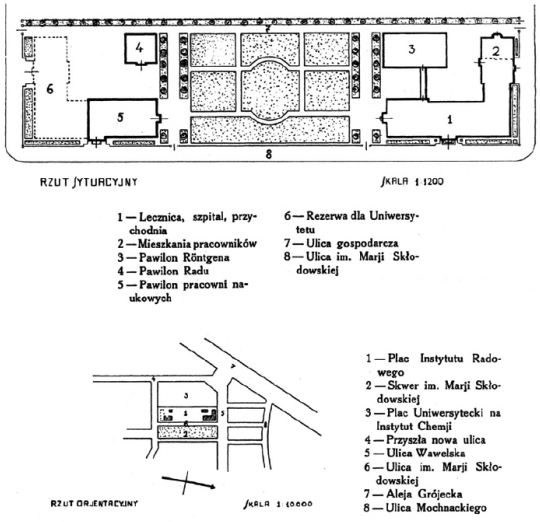

Figure 8. The views of the buildings of the Radium Institute as designed by Tadeusz Zieliński and Zygmunt Wóycicki – as in the brochure published in October 1929: *The State of the Construction of the Radium Institute*… [22]

Unfortunately, the official opening did not signify the end of the financial problems for the institute, which was supposed to be a self-sufficient centre which would earn money on treatment services provided, yet both the patients and the doctors were quite distrustful about the new methods of treatment. This is how the institute director, Franciszek Łukaszczyk, recollected the period: *It crossed my mind that Poland had been provided such an institution – at that time one of the few in the world – thanks to Maria Skłodowskia-Curie. Yet it was too early for the current state of medicine development in Poland and thus the institute was isolated and without the appropriate resources…* [1].

The beginnings of the Institute's activity

The opening ceremony of the Radium Institute was held on 29th May 1932 with the participation of Maria Skłodowska-Curie, The President of the Republic of Poland, Ignacy Mościcki, Prime Minister Aleksander Prystor and numerous representatives of the realms of science, politics and medicine (fig. 9–13). Skłodowska, when addressing the audience, said: *The Committee… took the right decision, I believe, to open the medical treatment department first in order to meet the obligation to offer high-quality therapy, which is ground-breaking and challenging, to Polish society. However, this therapy should always go hand in hand with research, without which no progress can be made. Therefore, I do hope that the launch of the research laboratories and workshops planned for the Institute, will take place shortly after the opening of the medical department…* [3].

Figure 9. January 1932 – the meeting with the representatives of the press immediately after the admission of the first patient to the Radium Institute – doctor Bronisława Dłuska (standing in the middle), Maria Pieńkowska (on the left), Lucyna Kotarbińska (on the right); doctor Józef Laskowski (the second from the right) and doctor Franciszek Łukaszczyk (the third from the right); (from the collections of the National Digital Archives)

Figure 10. The opening ceremony of the Radium Institute on 29th May 1932. The ceremony was honoured by the of the President of Poland, Ignacy Mościcki; the Prime Minister, Aleksander Prystor, the Speaker of the Senate, Władysław Raczkiewicz, the Minister of Foreign Affairs, August Zaleski; the Minister of Industry and Commerce, Ferdynand Zarzycki, the Minister of Communication, Alfons Kühn; the Minister of Post and Telegraph, Ignacy Boerner, the Ambassador of France, Jules Laroche (from the collections of the National Digital Archives)

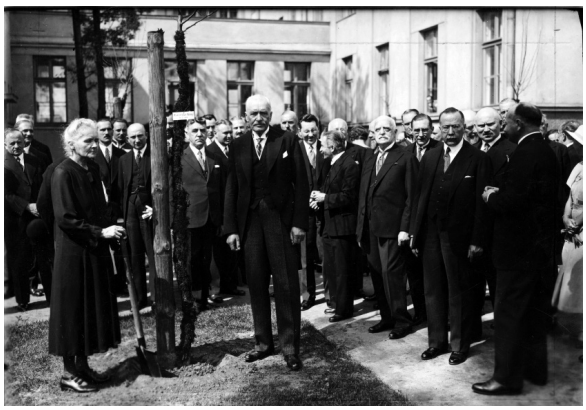

Figure 11. 29th May 1932 after the official opening of the Radium Institute, memorial trees were planted in the Institute's garden. In the front – Maria Skłodowska-Curie and the President of Poland Ignacy Mościcki (from the Collections of the Military History Office)

Figure 12. Doctor Franciszek Łukaszczyk in his office – the first Director and the Chief Doctor of the Radium Institute, 1936 (from the collections of the National Digital Archives)

Figure 13. The opening ceremony of the Radium Institute – from the left, there are standing, the Ambassador of France, Jules Laroche, Maria Skłodowska-Curie, doctor Franciszek Łukaszczyk and Professor Claudius Regaud (from the collections of the National Digital Archives)

This concern for research laboratories hindered Maria from basking in total enjoyment of the opening whilst her worries were not unjustified as the concept of a centre combining on equal terms, the research in the fields apparently remote from medicine with clinical activity was by all means a new thing [30].

The first director of the Institute, and, at the same time, the head of its clinical department was doctor Franciszek Łukaszczyk, who had been preparing for this role for many years, among others, under the supervision of Professor Regaud in Paris. The pathology laboratory was directed by doctor Józef Laskowski. During the first months of the Institute's activity, these were the only doctors in the Institute and were assisted by only one nurse. Soon the team was joined by doctor Halina Noblinówna. Despite his thorough training in foreign centres, young doctor Łukaszczyk saw many cases for the first time and had to think on his feet to find adequate solutions to the problems that appeared [1].

Sadly, Maria Skłodowska-Curie did not live to see the opening of the research laboratories. The physics laboratory was launched as late as 1936, with its head Cezary Pawłowski who was Skłodowska-Curie's student. While preparing for this position, he spent 4 years in the Paris laboratory. In October 1936, Irena Curie and Frederic Joliot-Curie came to Warsaw. They also visited the newly opened laboratory and, in recognition of its high level and meticulous organisation, they donated a precious electromagnet purchased with the money received from their Nobel Prize. In 1937, two other laboratories were opened in the physics laboratory: an X-ray showroom and a laboratory for measuring radioactive objects [30, 31]. Also in 1936, the biological laboratory was opened, which was directed by the talented and highly respected Zygmunt Zakrzewski [32].

In 1937, the number of hospital beds increased from 45 to 100. At that time there were 7 doctors employed: in addition to Franciszek Łukaszczyk, Józef Laskowski and Halina Noblinówna, the staff also comprised Adam Kukliński, Anna Madejczyk, Jerzy Szabunia and Józef Towpik. They all helped pave the way to previously unknown areas and created new standards. In the first years of the Institute's activity, mostly radiotherapy was used, and the relatively few surgeries that were undertaken were performed by surgeons from outside the Institute. An especially novel approach was initiated by Józef Laskowski, consisting of a close correlation between a microscopic image and clinical picture. Such an approach, combining histopathology and clinical radiotherapy, later on named the histo-clinical method, was highly innovative on a world scale. The collaboration between a pathologist and clinician allowed for tracing radiosensitivity and defining prognostic and predictive factors [33]. In addition, the creation of a modern department collecting medical documentation with archival data of typed patient histories where medical secretaries were employed was also a great achievement.

Having gone through difficult beginnings, the Institute started to develop dynamically. The number of patients was growing, results were improving, scientific laboratories started to operate and didactic activity was being organised. With great speed, original scientific papers were starting to be published (by 1939 more than 50 papers had been published) [1]. The number of beds in the clinical was increased to 120, and at the beginning of 1939, the average occupancy exceeded 90%. The average waiting period for a vacant bed was close to three weeks. On the eve of the war, the Institute was a fully organised and actively working treatment and academic centre (fig. 14–17).

The times of the occupation

The outbreak of the Second World War put a stop to the Institute's undertakings [34–36]. It was on 5th September 1939 that director Łukaszczyk decided to discontinue treatment with radium, taking it out of Warsaw and hiding it a summer cottage belonging to doctor Dionizy Zuberbier in Jozefow. This was a many-hour long journey during which the doctor was exposed to an massive dose of irradiation, as the agent was transported without the correct protection. This would not be the last time this happened. The story of radium and the role of professor Łukaszczyk provide a good story for a film script [1, 8, 34, 37–39]

After the capitulation of Warsaw, the consent for the restoration of treatment was obtained, thanks to the efforts and

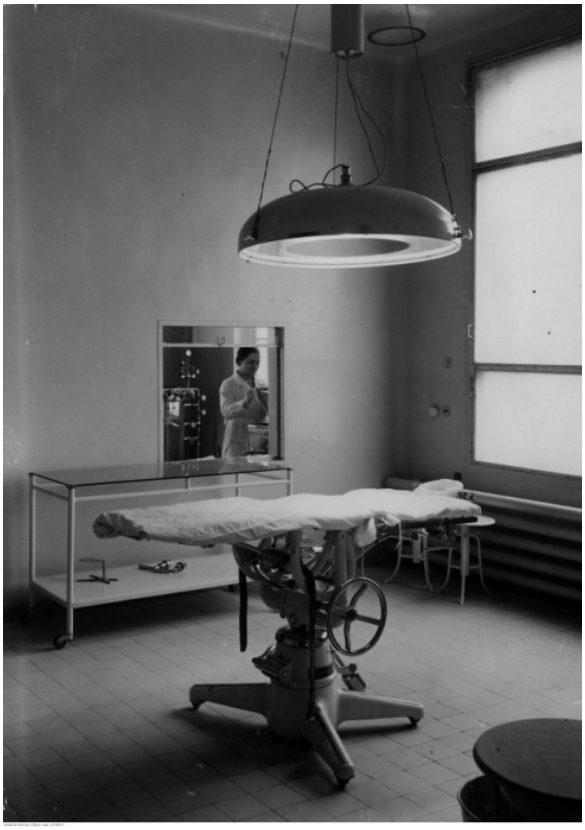

Figure 14. The operating theatre in the Radium Institute, 1936 (from the collections of the National Digital Archives)

Figure 15. The irradiation room at the Radium Institute, the late 1930s (from the collections of the National Digital Archives)

Figure 16. The memorial plaques commemorating the most generous benefactors of the Radium Institute placed in front of the main entrance, above the lift for the patients, 1936 (from the collections of the National Digital Archives)

Figure 17. The corridor on the ground floor in the main building of the Institute at Wawelska, 1936. On the wall on the right-hand side, there are plaques with the names of the Institute's benefactors (from the collections of the National Digital Archives)

Figure 18. The Radium Institute, with the name changed into the Municipal Cancer Hospital, in the period of the German occupation – the view from Wawelska street towards the West (from the collections of the Museum of Warsaw Uprising)

contacts of professor Łukaszczyk. The Institute was renamed to Municipal Cancer Hospital (fig. 18). Łukaszczyk brought the radium back to the Institute, but the element, kept in a safe, was confiscated by the Germans; however a part of the radium remained hidden in a secret place and in spite of the months-long investigation, the Gestapo were finally convinced that the radium had been taken out of Poland together with the valuable equipment of the operating theatre. The radium, saved from confiscation and hidden in the Institute, was used for the treatment of patients during the entire period of the Nazi occupation [1].

The Warsaw Uprising in 1944 brought complete annihilation to the Institute. At the end of July, many patients discharged themselves and the majority of doctors went to the sanitary points ascribed to them [34]. According to various accounts, at the Institute, there were about 80 patients remaining with a similar number of staff and their families. On 5th August 1944, the staff and the patients who were able to walk were forcibly removed. Other patients were murdered and the building was plundered and burnt by the soldiers of SS RONA. Only a few people survived the extermination of the Institute's staff [34]. These events span a period of almost 78 years, and until not

very long ago, these tragic happenings seemed both absurd in their cruelty and distant enough to be safe. Today, however, we see Ukrainian hospitals being fired at and war crimes committed by Russian soldiers on Ukrainian civilians; suddenly those images of the Institute from August 1944 turn out to be tragically contemporary and closer than ever.

On the 20th August 1944, director Łukaszczyk, having bribed German soldiers with his wife's bracelet, managed to reach the Institute in an armoured vehicle. He took the radium hidden there and brought it to Reguly, near Warsaw, and then to Poronin in the Polish mountains [8, 34, 38, 39].

The development of modern oncology

Most of the Institute was destroyed together with the equipment, including the priceless scientific documents. In spite of the immense damage and other urgent needs connected with rebuilding the entire country, it was in November 1945 that the decision to rebuild the Institute was taken by the government. At the end of the year the construction work started, including the development of the clinic's building and adding one more floor. In the year that followed the first patients were admitted, and one year later, the Institute, having already 240 beds, resumed its activity for good [40, 41]. Professor Franciszek Łukaszczyk became its director again, remaining in this post until his death in 1956. The reconstruction works were initially supervised by doctor Hanna Kołodziejska-Wertheim. At the end of 1945, she left for Washington to visit the seat of UNRRA (United Nations Relief and Rehabilitation Administration). Thanks to her efforts, a significant amount of radium, devices for X-ray therapy and teaching aids as well as the library collections were obtained [42, 43]. During that period, the reconstruction was supervised by doctor Tadeusz Koszarowski. The good political intentions and financial support of the state came as a great surprise, yet a key role was played by the enthusiasm and commitment of the Institute's staff [1].

Shortly after the war, the Institute was organised into three departments: radiotherapy, managed by Professor Franciszek Łukaszczyk; pathology, whose head was professor Józef Laskowski; surgery, managed by doctor Tadeusz Koszarowski, who had been at the Institute since 1941. Also the Radiology Department was created by doctor Janusz Buraczewski as its head. At the end of 1947, the Institute staff comprised also Zofia Chełchowska, Władysław Jasiński, Hanna Kołodziejska-Wertheim, Anna Madejczykowa, Irena Skowrońska, Jeremi Święcki and Ludwika Tarłowska (fig. 19–21) [43].

The first years after the war were devoted to organising and equipping the Institute, employing and training staff as well as drafting the plans for the years to follow. Three main directions of action were set: basic research, clinical studies and treatment activity as well as the organisation of cancer control [44].

In 1949 the Polish Anti-Cancer Society resumed its activity (later on changing its name to the Polish Society of Oncology)

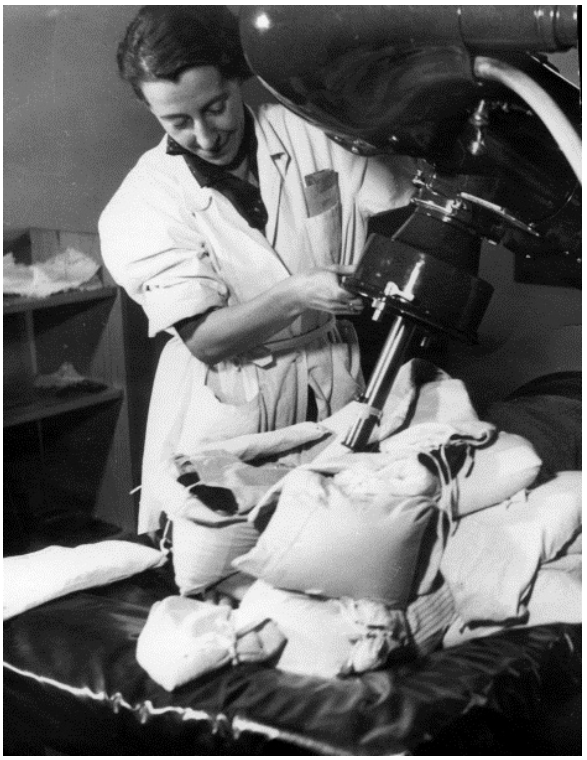

Figure 19. Doctor Hanna Kołodziejska-Wertheim at work, the 1950s (from the collections of the editing office of the MSCNRIO)

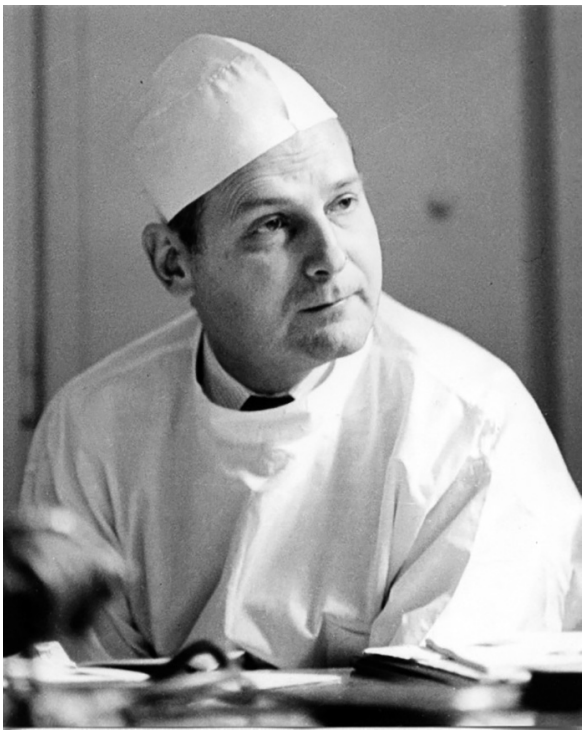

Figure 20. Professor Tadeusz Koszarowski (from the collections of the editing office of the MSCNRIO)

organising the Anti-Cancer Symposium, as first after the war. One year later, the Department of Cancer Biology, directed by doctor Stanisław Wisłocki was created and then the Medical Physics Department – again under the supervision of Professor Cezary Pawłowski.

Figure 21. The visit of the Queen of Belgium, Elisabeth (at the microscope) at the Institute of Oncology 1955. Visiting of the Department of Pathology. First from the left: Professor Józef Laskowski, above the Queen: doctor Ludwika Sikorowa and doctor Maria Dąbska – distinguished pathologists; both of them later on received the professor degree (from the collections of the editing office of the MSCNRIO)

Figure 22. The team of the Oncological Surgery, 1962. Standing from the left: doctor Marek Królikiewicz, doctor Jerzy Meyza, doctor Dorota Niemand (anaesthesiologist), Professor Tadeusz Koszarowski, doctor Hanna Werner-Brzezińska ("the Forewoman"), Maria Sowacka (secretary), doctor Tadeusz Lewiński, Danuta Krotkiewska (the scrub nurse and the chief of the operating theatre), doctor Albert Gerlach. Kneeling: doctor Andrzej Kułakowski and doctor Czesław Górski (from the collections of the editing office of the MSCNRIO)

In 1951, on the basis of the resolution of the Council of Ministers [45], the Radium Institute was combined with the Oncology Institute in Krakow and the National Cancer Institute in Gliwice, thus creating the Maria Skłodowska-Curie Institute of Oncology with the departments in Krakow and Gliwice having the status of Research Institute.

Poland at that time was developing a new model of health service which was socially oriented. At the Institute, new and intensive works were initiated concentrating on structural and systematic solutions, based on hard epidemiological data and the scientific models of oncological care. The creation of the National Cancer Register in 1952 played a key role in this process. An obligation to report cases of malignant tumours [47] and data collection in the register (although initially underestimated and incomplete) gave rise to planning real needs with regards to infrastructure, the basis and staff training. This provided the foundation for drafting the cancer treatment plan.

The definition of oncology, formulated in the 1950s by Professor Tadeusz Koszarowski, which specifies this discipline as a science of *aetiology, pathology, epidemiology, prevention and early detection of malignant tumours, combined treatment of cancer patients, palliative care and the organisation of cancer control* became the basis of treating oncology as a separate field of medicine, the formulation of the objectives of the Second Cancer Control Program and defining formal principles for gathering epidemiological data and approval of oncology as separate specialisation [10, 44].

In 1952 Franciszek Łukaszczyk, Józef Laskowski, Władysław Jasiński, Hanna Kołodziejska-Wertheim, Tadeusz Koszarowski, Jeremi Święcki and Ludwika Tarłowska developed the Second Cancer Control Program. The document included the plans for the development of scientific basic and clinical research, cancer epidemiology and prophylaxis and the creation of treatment base in oncological network [48].

One of the most important points of the Program was the initiation of the data collection about the malignant tumour incidence and mortality as well as of the epidemiological studies as the foundation of the modern organisation of cancer control. The Ministry of Healthcare and Social Protection issued an instruction for reporting the cases of malignant tumours to the register kept at the Warsaw Institute [47]. Within the Program also, the graduate and post-graduate training programmes were worked out, specialists were trained and multidirectional research was developed, also in collaboration with foreign centres. An intensive international exchange was carried out [48].

In 1953, at the Institute an Independent Surgical Department was created – under the supervision of Tadeusz Koszarowski [49], whilst one year later – the Department of Oncological Gynaecology managed by doctor Ludwika Tarłowska [50]. In 1957 the Isotope Laboratory, created by professor Władysław Jasiński was opened and, in 1965, doctor Janusz Szymendera set up the Radio-chemotherapy laboratory (fig. 22) [32].

In 1956, as a result of post-irradiation disease, professor Franciszek Łukaszczyk died and professor Józef Laskowski was appointed as the new director. In the years that followed, the Institute was managed by professor Władysław Jasiński (1961–1972), professor Tadeusz Koszarowski (1972–1985), professor Jan Steffen (1986–1991), professor Andrzej Kułakowski (1991–1998), professor Marek P. Nowacki (1999–2009), professor Maciej Krzakowski (2009–2011), professor Krzysztof Warzocha (2012–2015), and since 2016 – professor Jan Walewski.

New headquarters

Analysis of the epidemiology data suggested a dynamic growth in the number of oncological diseases of that time which means a necessity to expand the diagnostic and treatment base. In 1972, a decision was taken to enlarge the Institute providing it with a new seat in Ursynów, which was

Figure 23. The team of the Chemotherapy Department – at the front: doctor Józef Zborzil, to the right doctor Grzegorz Madej, from the left: doctor Maryna Rubach, doctor Feliksa Pieńkowska, doctor Jan Walewski, 1970s (from the collections of the editing office of the MSCNRIO)

Figure 24. The team of the Radiotherapy Department, 1977. Standing from the left: doctor Janusz Meder, doctor Danuta Gołębiowska, Professor Zofia Dańczak-Ginalska, doctor Zbigniew Malinowski, doctor Anna Skowrońska-Gardas, doctor Tadeusz Morysiński, doctor Gizela Nowak. At the front: doctor Teresa Więckowska-Starzyńska and doctor Anna Świerczewska-Strójwąs (from the collections of the editing office of the MSCNRIO)

supposed to be the central oncological hospital in Poland. The Institute's representative for the construction was Professor Tadeusz Koszarowski, who also took over the function of the Institute director [44, 48, 51].

At the end of the 1960s, at the Oncology Clinic on Wawelska, a Chemotherapy Team was created, and in 1974, the first Chemotherapy Clinic in Poland, which was subsequently managed for 20 years by doctor Józef Zborzil (fig. 23) [52, 53].

By the mid-1970s, the basic elements of the oncological network were created. Thanks to the data coming from the Central Cancer Register and from local registers, it was possible to monitor the efficiency of the adopted solutions and plan further development (fig. 24–25) [44].

Professor Tadeusz Koszarowski, together with his team, worked on developing the Third Cancer Control Program (governmental program No. 6 – *Cancer Control*). This program was pursued in 1976–1990 with the main objective being a change in the 5-year survival level from 25% to 50%. The program was co-ordinated and conducted by the Institute. At that time, 11 comprehensive cancer centres were organised with the number of beds increasing to 6000; moreover, in excess of 600 specialists in oncology were trained [44].

Professor Koszarowski worked on the cancer control program consisting of the creation of comprehensive cancer centres associating high class specialists in many fields and specialist equipment – the centres conducted diagnostics

Figure 25. Professor Tadeusz Koszarowski – the Head of the Institute in 1972–1985, with the team of his closest collaborators, 1976. Sitting from the lest: Professor Zofia Dańczak-Ginalska – the Head of the Team for New Technologies in Radiotherapy, Professor Maria Dąbska – the Head of the Department of Cancer Pathology, Professor Tadeusz Koszarowski, Professor Ludwika Tarłowska – the Head of the Gynaecological Oncology Clinic, Professor Janusz Buraczewski – the Head of the Department of Radiological Diagnostics. Standing from the left: Professor Janusz Szymendera – the head of the Department of Nuclear Medicine, engineer Jerzy Rybicki – Deputy Director for Administration and Economics of the Institute and Economic, doctor Ryszard Sosiński – Deputy Director for Organisational Affairs, Professor Andrzej Kułakowski – the Head of the Oncological Surgery Clinic and Deputy Director for Clinical Affairs, Professor Jan Steffen – the Head of the Department of Immunology and the Deputy Director for Research Organisation and Co-ordination, Professor Helena Gadomska – the Head of the Department of the Research Information and Documentation, Professor Olga Mioduszewska – the Head of the Independent Laboratory of Pathomorphological Special Technologies, Professor Zbigniew Wronkowski – the Head of the Department for the Organisation of Cancer Control and Tumour Epidemiology (from the collections of the editing office of the MSCNRIO)

Figure 26. Fields in Ursynów, where the Oncology Centre is to be constructed – a visit of the team of the Surgery Clinic, 1974 (from the collections of the editing office of the MSCNRIO)

Figure 27. Professor Tadeusz Koszarowski presents the concept and the design of the Oncology Centre to the state authorities, first from the left: Edward Gierek (from the collections of the editing office of the MSCNRIO)

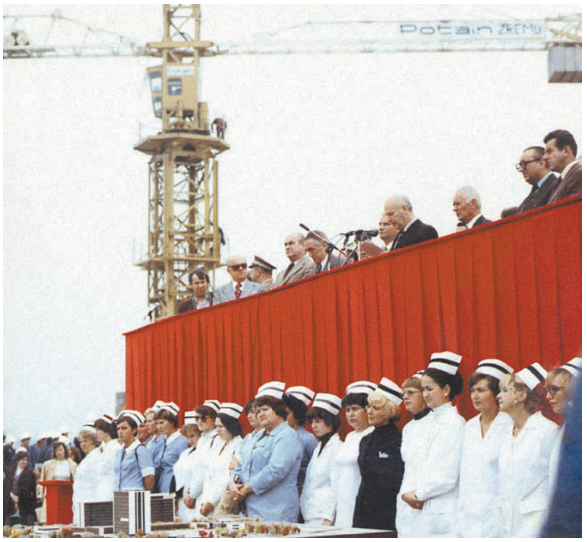

Figure 28. The ceremony of laying the cornerstone for the Oncology Centre in the fields of Ursynów, the speech of Professor Tadeusz Koszarowski, 19th July 1977 (from the collections of the editing office of the MSCNRIO)

Figure 29. The construction of the new seat of the Institute of Oncology in Ursynów, the late 1970s (from the collections of the editing office of the MSCNRIO)

and treatment as well as research and prophylaxis which was regarded as the basis for cancer control [48].

The largest investment of the PR-6 program was the construction of the new seat of the Institute of Oncology in Ursynów district in Warsaw (fig. 26–27). The promotor and real founder of the new seat was professor Koszarowski, who not only worked on the new concept, but also, thanks to his great diplomatic skills and charisma, was able to convince the current authorities to pursue this idea and win the support of numerous milieus – often with rather opposing ideologies. The social committee for the construction of the Oncology Centre was set up, including, apart from prominent representatives of the ruling party, members of the Polish Academy of Sciences, the clergy (Cardinal Stefan Wyszyński) and also the press, radio and television, trade unions and diverse medical groups [51].

And thus, on 19th July 1977, the founding bill was laid under the new seat which was an immense success given the politically complex and economically fraught period (fig. 28) [54]. However, the construction took almost 20 years and faced numerous obstacles. Even the Polish Film Chronicle which usually presented an optimistic image of the Polish reality of that period, provided such a comment: *The Warsaw Oncology Centre in Ursynów was supposed to grow fast and in a modern way. The dreams were supposed to come true thanks to a dedicated company, Budopol, created for this purpose; but then the whole amusement park with the Ferris wheel of material supplies, the roundabout of deadlines and the staff house of mirrors began* [55]. The next titles speak for themselves: *Delay* (1986), *Construction Crisis* (1987) or *Reverse Drive* (1989). It was only in the film from 1993 titled *From the Institute to the Centre,* did Professor Andrzej Kułakowski, the current director, proudly present the completed clinical building. The investment was completed as late as 1997 (fig. 29–31) [51, 54–62].

Figure 30. The construction of the new seat of the Institute of Oncology in Ursynów – the scientific building is constructed (from the collections of the editing office of the MSCNRIO)

The complex in Ursynów is now awaiting another development which is its urgent need, in spite of the fact that at the moment of its opening it was one of the most modern oncological centres in Europe [51, 62]. The concept of organ-related clinics was then many years ahead of the later concept of units of excellence which is today regarded as the optimum solution in the case of key cancers.

The completion of the Third Governmental Program of Cancer Control was followed by a period of stagnation [63]. There was no intention on the part of the decision makers to invest in oncology. During that period there were many cases of negligence and glaring underinvestment, paired with gradual wear and tear of the infrastructure and apparatus base in all oncological centres in Poland. In the following years there were attempts to implement the next Program of Cancer Control, yet each time the authorities refused. Nevertheless, on 22nd September 1999 the draft version of the Fourth National Program of Cancer Control was filed again in the health committees of the Polish Parliament and Senate and the desideratum was then sent to the government. In order to gain support and intensify actions, in December 1999, upon the initiative of professor Marek P. Nowacki and doctor Janusz Meder, support also by professor Tadeusz Koszarowski, the idea of the creation of the Polish Union of Oncology (PUO) was coined (fig. 32) [63]

Oncology Institute in the 21st century

In January 2000 the founding father of the PUO sent a letter to the President of Poland with a request to support their actions. The founding meeting was attended by the representatives of both chambers of the Polish Parliament (Seym and Senate), the Ministry of Health, directors of oncological centres, the head of academic chairs in medicine, national experts in oncology, haematology and related disciplines, the presidents of many medical scientific associations and patient societies [63].

On 3–4th February 2000 the World Summit Against Cancer for the New Millennium was held in Paris under the patronage of UNESCO. During the summit the Charter of Paris was drafted and signed not only by the prominent academics and oncology doctors, but also the President of France Jacques Chirac and the UNESCO Secretary General, Koichiro Matura, and, together with them – the representatives of governments, academic centres and NGOs from the entire world. The participants called upon the world leaders to support their joint efforts for the creation of the National Cancer Control program in each county and to respect the Paris Charter together. Among the postulates included in the Charter there were, among others, the protection and increase of the rights of a cancer patient, an increase of financial support for the purchase of infrastructure of international research (both basic and clinical), the elimination of differences in the standards and access to professional medical care and the implementation of the social policy which could promote cancer control by all the world countries. In the wake of these events, in June 2000, the Polish Cancer Control Summit was organised during which the Polish Oncology Union was officially set up with the main objective being to carry out intensive work for passing the parliamentary act on the National Program for Oncological Diseases Control (NPZChN) and providing financial resources for its execution. In the next years, several meetings took place with the participation of the management and scientific council of the Polish Oncology Union, held in the office of the Polish President and the Prime Minister in the Health Committees of the Polish Parliament and Senate; here the draft act was processed and prepared for legislation. Finally, after 6 years of intensive and tedious work, on 6th July 2005, at the plenary session of the Polish Parliament, the Act on the National Program for Oncological Diseases Control was unanimously passed with the President signing it on 20th July 2005 [63].

The most recent history of the Institute deserves a separate paper. Here we will only list the recent changes and key events from the perspective of its organisation and the role in the system of oncological care. The regulation of the Council of Ministers of 17th October 2019 gave the Institute the status of National Research Institute, defining its new and more extensive tasks [64]. The process of reorganisation is closely connected with the implementation of the National Oncology Network (KSO) and the adoption of the National Cancer Strategy (NSO) [65–67]. Under the new name – the Maria Sklodowska-Curie National Research Institute of Oncology, the Institute plays the coordination and monitoring role within the new strategy. The document worked out under the supervision of professor Piotr Rutkowski has the character of a complex cancer plan, setting out new directions for the development of the oncological care system, pointing to 5 strategic clinical areas of key significance for the improvement of the efficiency of cancer therapies and the adaptation of the system's solutions to meet the needs of the patients. Thanks to the introduction

Figure 31. The construction of the new seat of the Institute of Oncology in Ursynów was completed in 1997 (from the collections of the editing office of the MSCNRIO)

Figure 32. The meeting of the representatives of the Polish Oncology Union with the President of Poland, Aleksander Kwaśniewski, concerning the project of the National Program for Oncological Diseases Control; second from the left: Professor Tadeusz Koszarowski, further: Professor Kazimierz Roszkowski-Śliż and doctor Janusz Meder (from the collections of the editing office of the MSCNRIO)

of the new benchmarking methods and tools and financial frameworks, the strategy draws from the achievement of system solutions worked out for decades under the auspices of experts from the Institute and also from the thorough analysis of the needs of the system of cancer care worked out upon the initiation of the Polish Society of Oncology, Jacek Jassem by almost 200 specialists and scientific associations.

Among all the changes of key importance for the realisation of the strategic tasks, which are also closely related to the development of the Institute of Oncology – the role of the modernisation of the National Cancer Registry must be stressed (eKRN+ Project); for 50 years it has been the core of the structured cancer control actions. Last but not least, the Institute now enters a new decade at the moment when the works connected with the revitalisation of the hospital complex and the construction of the new clinic's building in Ursynów, are in progress which will significantly improve the conditions of patient treatment and work in the Institute. The beginnings of the work on these objectives were undertaken during especially difficult times: the pandemic posed new obstacles for oncology, uncovering weakness in the system and having a negative impact on the execution of plans. However, we are all in agreement in stating that such an intellectual potential, so meticulously worked out, together with the widely understood organisational and logistic infrastructure must be fully and consistently used in the timely pursuit of the tasks and goals defined in the National Cancer Strategy, which also fit within the framework of the European Beating Cancer Plan. Our hopes and determination are inextricably connected with opening up a new chapter in the history of the Institute with the support of the greatest decision-makers in Poland, including the President and Prime Minister.

Conclusions

The Institute of Oncology at Wawelska street was the cradle of modern specialisations and research fields in Polish oncology. It is impossible to name everyone who contributed to this development. The list presented here is by all means incomplete and selective, yet these names – of teachers and mentors of many future generations cannot be omitted.

The basic research was developed by: Zygmunt Zakrzewski, Stanisław Wisłocki, Kazimierz Dux, Adam Michałowski, Jan Steffen, Janusz Siedlecki, Przemysław Janik, Zygmunt Paszko,

Alina Czarnomska. Medical physics is represented by: Cezary Pawłowski, Barbara Gwiazdowska, Jerzy Tołwiński, Marian Dworakowski, Wojciech Bulski, Paweł Kukołowicz. Oncological pathology: Józef Laskowski, Ludwika Sikorowa, Maria Dąbska, Olga Mioduszewska, Anna Nasierowska-Guttmejer and Klara Zakrzewska. Epidemiology was developed thanks to: Zbigniew Wronkowski, Helena Gadomska and Witold Zatoński. The pioneers of nuclear medicine were Władysław Jasiński, Janusz Szymendera and Izabela Kozłowicz-Gudzińska. Radiotherapy was developed thanks to: Franciszek Łukaszczyk, Anna Madejczykowa, Hanna Kołodziejska-Wertheim, Władysław Jasiński, Jeremi Święcki, Danuta Gajl, Czesława Leszczyk, Joanna Makólska-Kowalska, Janina Schayer-Malinowska, Michał Wasilewski, Maria Wróblowa, Zofia Dańczak-Ginalska, Zbigniew Malinowski, Teresa Więckowska-Starzyńska, Władysław Nowakowski, Janusz Meder, Barbara Puchalska. The development of oncological surgery can be attributed to: Tadeusz Koszarowski, Hanna Werner-Brzezińska, Tadeusz Kołodziejski, Witold Rudowski, Andrzej Kułakowski, Czesław Górski, Tadeusz Lewiński, Jerzy Meyza, Włodzimierz Ruka, Grzegorz Luboiński, Marek P. Nowacki. Reconstructive surgery was developed by Andrzej Kułakowski, Edward Towpik and Sławomir Mazur. Ludwika Tarłowska initiated gynaecological oncology as a separate specialisation which was creatively developed then by Bożena Sablińska, Jerzy Haruppa, Jan Zieliński, Elżbieta Ploch and Zofia Kietlińska. Janusz Buraczewski laid the foundations of radio-diagnostics in oncology, developed later by Jadwiga Zomer-Drozda, and then – Marta Kaczurba and Janina Dziukowa. The foundations of chemotherapy and the first treatment standards in Poland can be attributed to: Anna Madejczykowa, Anna Żelechowska, Feliksa Pieńkowska, Józef Zborzil, Piotr Siedlecki, Maryna Rubach, Grzegorz Madej, Jan Walewski, Tadeusz Pieńkowski, whilst the core bases of oncological rehabilitation were created by Krystyna Mika and Hanna Tchórzewska-Korba [10, 28].

At the close of this, definitely incomplete outline of the history of the Institute, let us quote the words of professor Tadeusz Koszarowski, in which, as it seems, the idea planted more than 90 years ago by Maria Skłodowska-Curie, who determined the final shape of the Institute and the development of Polish oncology is rightly reflected: *Maria Skłodowska-Curie gave Polish society 1 gram of radium… Polish society, impoverished and destroyed by the war, reciprocated the gift of this Eminent Scholar by pursuing her "greatest dream" – the creation of the Radium Institute in Warsaw. This is a widely known and discussed fact. However, a much more precious, in fact priceless gift often goes unnoticed – this was her creative knowledge and the belief that the progress of learning and its application is not coined within the narrow limits of the science disciplines, but by means of combining and connecting them which leads to their mutual interpenetration* [68].

Conflict of interests: not reported

Janusz Meder
Maria Skłodowska-Curie National Research Institute of Oncology
Scientific Editor's Office
ul. Roentgena 5
02-781 Warszawa
e-mail: Janusz.Meder@pib-nio.pl

Received and accepted: 4 May 2022

References

1. Łukaszczyk F. Dwadzieścia pierwszych lat. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 56.
2. Szkic przemowy w zbiorach Bibliothèque nationale de France, NAF 18467, k. 153 (recto-verso); za: Korzeniowska D. Muzeum Marii Skłodowskiej-Curie w Warszawie Radium Lady. Kalendarium pierwszej podróży Marii Skłodowskiej-Curie do Stanów Zjednoczonych, 1921: 32. http://files.clickweb.home.pl/81/59/81596035-ed26-470a-9e68-94067687c620.pdf. (10.03.2022).
3. Sobieszczak-Marciniak M. Maria Skłodowska-Curie i powstanie Instytutu Radowego w Warszawie. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 17–28.
4. List Heleny Paderewskiej do Marii Skłodowskiej-Curie z 17 lipca 1919 roku. In: Kabzińska K, Piskurewicz J, Róziewicz J. ed. Korespondencja polska Marii Skłodowskiej-Curie (1881–1934). Instytut Historii Nauki PAN i Polskie Towarzystwo Chemiczne, Warszawa 1994: 136.
5. Pietrzkiewicz D. Przyczynek do biografii Ludwika Wertensteina. Nauka. 2022(1): 103–143.
6. Hurwic J. Nieznany list Marii Skłodowskiej-Curie. Kwartalnik Historii Nauki i Techniki. 1984; 29(3–4): 557–558.
7. Hurwic J. Pracownia Radiologiczna im. Mirosława Kernbauma przy Towarzystwie Naukowym Warszawskim. W 40. rocznicę śmierci Ludwika Wertensteina. Postępy Fizyki. 1986; 37(2): 151–168.
8. Gwiazdowska B, Tołwiński J, Bulski W. Kamieniem węgielnym był rad. Nowotwory. 2000; 5(4): 410–416.
9. Supady J. Organizacje i instytucje do walki z rakiem w Polsce w latach 1906–1939. Wydawnictwo Adi, Łodź 2003: 7.
10. Wronkowski Z, Towpik E. Instytut Radowy i Instytut Onkologii w Warszawie. In: Towpik E. ed. Centrum Onkologii Instytut im. Marii Skłodowskiej-Curie w Warszawie 1932–2002. Centrum Onkologii – Instytut, Warszawa 2002: 6–15.
11. Jaworski J. Przyszły zakład do badań nad rakiem w Warszawie wobec współczesnego stanu wiedzy w tej kwestii. Gazeta Lekarska. 1912; 32(49): 1368–1373.
12. Towpik E, Wysocki W. The Nowotwory journal over the last 95 years (1923–2018). Nowotwory. Journal of Oncology. 2018; 67(6): 321–335, doi: 10.5603/njo.2017.0054.
13. Uchwały pierwszego wszechpolskiego Zjazdu w sprawie walki z rakiem. Warszawskie Czasopismo Lekarskie. 1925(1): 36.
14. Kołodziejska H. Onkologia Polska na XXX-lecie Polskiej Rzeczpospolitej Ludowej. Nowotwory. 1974; 24(4): 3.
15. Maria Skłodowska-Curie i historia odkrycia radu. Wydawnictwo Komitetu Daru Narodowego dla Marji Skłodowskiej-Curie 1925: 20.
16. List Marii Skłodowskiej-Curie do Ignacego Paderewskiego z 27 listopada 1921 roku. In: Kabzińska K, Piskurewicz J, Róziewicz J. ed. Korespondencja polska Marii Skłodowskiej-Curie (1881–1934). Instytut Historii Nauki PAN i Polskie Towarzystwo Chemiczne, Warszawa 1994: 176.
17. Gwiazdowska B, Bulski W, Sobieszczak-Marciniak M. Maria Skłodowska-Curie. Znane i mało znane fakty z życia Uczonej, ciąg dalszy. Postępy Techniki Jądrowej. 2015; 58(1): 24–30.
18. Łukaszczyk F. Pamięci Dr Bronisławy Dłuskiej. Medycyna. 1939; 9: 361–362.
19. Towpik E, Dłuska B. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 223–230.
20. List Józefa Skłodowskiego do Marii Skłodowskiej-Curie, grudzień 1921. In: Kabzińska K, Piskurewicz J, Róziewicz J. ed. Korespondencja polska Marii Skłodowskiej-Curie (1881–1934). Instytut Historii Nauki PAN i Polskie Towarzystwo Chemiczne, Warszawa 1994: 176–178.
21. „Dar narodowy" dla p. Skłodowskiej-Curie. Kurier Warszawski. 1923(355): 11.

22. Stan budowy Instytutu Radowego dla walki z rakiem im. Marji Skłodowskiej-Curie w Warszawie, ul. Wawelska 3, jako Daru Narodowego od całej Polski dla wielkiej uczonej, Galewski i Dau Warszawa, październik 1929.
23. Pospieszny T, Wajs E. 89 rocznica otwarcia Instytutu Radowego w Warszawie. Piękniejsza Strona Nauki. http://piekniejszastronanauki.pl/mojem-najgoretszem-zyczeniem/ (30.03.2022).
24. Meder J, Towpik A. 95 lat od wmurowania aktu erekcyjnego pod budowę Instytutu Radowego w Warszawie. Biuletyn PTO Nowotwory. 2021; 6: 154–156.
25. List Marii Skłodowskiej-Curie do Czesława Białobrzeskiego z 19 grudnia 1929 roku. In: Kabzińska K, Piskurewicz J, Róziewicz J. ed. Korespondencja polska Marii Skłodowskiej-Curie (1881–1934). Instytut Historii Nauki PAN i Polskie Towarzystwo Chemiczne, Warszawa 1994: 353.
26. Odezwa Komitetu Organizacyj Kobiecych zjednoczonych dla wykończenia Instytutu Radowego im. Marii Skłodowskiej-Curie. Druk Olesiński i Merkel, Warszawa 1929.
27. Tołwiński J. Historia radu w Polsce. Nowotwory. 1992; 42: 131–137.
28. Towpik E. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012.
29. Towpik E. Ustawa z dnia 1931 r. o odstąpieniu nieruchomości państwowej w Warszawie Towarzystwu Instytutu Radowego im. Marii Skłodowskiej-Curie, za: Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 54–55.
30. Bulski W. Fizyka medyczna. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 125.
31. List Cezarego Pawłowskiego do Marii Skłodowskiej-Curie z 9 lutego 1934 roku. In: Korespondencja polska Marii Skłodowskiej-Curie (1881–1934). Instytut Historii Nauki PAN i Polskie Towarzystwo Chemiczne, Warszawa 1994: 416–419.
32. Siedlecki J. Historia badań podstawowych. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 137–150.
33. Fijuth J. Powstawanie dyscyplin onkologicznych i jednostek w Instytucie Onkologii – Radioterapia. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 109–118.
34. Tarłowska L, Towpik E. Okupacja i powstanie warszawskie. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 73–88.
35. Kołodziejska-Wertheim H. Zniszczenia wojenne i odbudowa – sprawozdanie przedstawione 8 października 1945 r. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 89–94.
36. Promieniowanie, reż. Irena Kamieńska, Wytwórnia Filmów Dokumentalnych Warszawa, 1982.
37. Madejczykowa A. Wspomnienia z pracy w Instytucie Radowym. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 297–300.
38. Chrzanowski A. Nieznane dzieje polskiego radu. Nowotwory. 1985; 35(3): 275–279.
39. Tołwiński J. Historia radu w Polsce. Nowotwory. 1992; 42: 131–137.
40. Walka z rakiem. Polska Kronika Filmowa 34/47.
41. O życie człowieka, reż. Roman Banach, Wytwórnia Filmów Oświatowych Łódź, 1955.
42. Kołodziejska-Wertheim H. Zniszczenia wojenne i odbudowa – sprawozdanie przedstawione 8 października 1945 r. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 89–94.
43. Kołodziejska-Wertheim H. Pracowałam w Instytucie Onkologii. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 301–307.
44. Koszarowski T. Udział Instytutu Onkologii im. Marii Skłodowskiej-Curie w rozwoju społecznej walki z chorobami nowotworowymi w Polsce w Latach 1945-1982. Nowotwory. 1983; 33(1): 7–12.
45. Rozporządzenie Rady Ministrów z dnia 24 marca 1951 r. w sprawie utworzenia Instytutu Onkologicznego im. Marii Curie-Skłodowskiej. Dz.U. 1951 nr 19 poz. 153.
46. Wojciechowska U. Historia rejestracji nowotworów złośliwych. In: Wojciechowska U, Didkowska J, Zatoński W. ed. Rejestracja nowotworów złośliwych. Zasady i metody. Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie, Warszawa 2007: 24.
47. Okólnik Ministerstwa Zdrowia Nr 2/51 w sprawie zgłaszania przypadków nowotworów złośliwych (Dz. U. Min. Zdr. z 1951 r. Nr 2, poz. 8).
48. Wronkowski Z. Osiemdziesiąt lat badań w zakresie epidemiologii nowotworów, organizacji walki z rakiem, profilaktyki i oświaty zdrowotnej w Warszawie. Nowotwory Journal of Oncology. 2012; 62: 473–476.
49. Kułakowski A. Historia Oddziału i Kliniki Chirurgii Onkologicznej w latach 1948-94. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 151–163.
50. Tarłowska L. Rozwój i działalność Kliniki Onkologii Ginekologicznej. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012: 180–189.
51. Koszarowski T. Dać świadectwo prawdzie. Historia tworzenia i budowy Centrum Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Społeczny Komitet Budowy Centrum Onkologii, Warszawa 1998.
52. Rubach M, Siedlecki P. Początki chemioterapii w Polsce: w 40. rocznicę powstania pierwszej w kraju Kliniki Chemioterapii w Instytucie Onkologii w Warszawie. Nowotwory. Journal of Oncology. 2015; 64(6): 544–550, doi: 10.5603/njo.2014.0097.
53. Rubach M, Siedlecki P. Chemioterapia. In: Towpik E. ed. Materiały do historii Instytutu Radowego i Instytutu Onkologii im. Marii Skłodowskiej-Curie w Warszawie. Polskie Towarzystwo Onkologiczne, Warszawa 2012, s, Warszawa 2012: 217–222.
54. Centrum Onkologii Polska Kronika Filmowa 5/79 wyd. A. https://35mm.online/vod/kroniki/polska-kronika-filmowa-79-05a.
55. Budowlana zapaść. Polska Kronika Filmowa 87/21. https://35mm.online/vod/kroniki/polska-kronika-filmowa-87-21.
56. Centrum Onkologii, Polska Kronika Filmowa 24/80 wyd. B. https://35mm.online/vod/kroniki/polska-kronika-filmowa-80-24b.
57. Polska Kronika Filmowa 80/03 wyd. B. https://35mm.online/vod/kroniki/polska-kronika-filmowa-80-03b.
58. Centrum Onkologii, Polska Kronika Filmowa 83/44. https://35mm.online/vod/kroniki/polska-kronika-filmowa-83-44.
59. Polska Kronika Filmowa 85/01. https://35mm.online/vod/kroniki/polska-kronika-filmowa-85-01.
60. Poślizg. Polska Kronika Filmowa 86/37. https://35mm.online/vod/kroniki/polska-kronika-filmowa-86-37.
61. Na wstecznym biegu. Polska Kronika Filmowa 89/37. https://35mm.online/vod/kroniki/polska-kronika-filmowa-89-37.
62. Z Instytutu do Centrum, Polska Kronika Filmowa 93/12. https://35mm.online/vod/kroniki/polska-kronika-filmowa-93-12.
63. Meder J. Rak głównym zabójcą ludzi w XXI wieku: Narodowy Program Zwalczania Chorób Nowotworowych. In: Potrykowska A, Strzelecki Z, Szymborski J, Witkowski J. ed. Zachorowalność i umieralność na nowotwory a sytuacja demograficzna Polski. Rządowa Rada Ludnościowa, Warszawa 2014: 50–85.
64. Rozporządzenie Rady Ministrów z dnia 17 października w sprawie reorganizacji Centrum Onkologii – Instytutu im. Marii Skłodowskiej-Curie w Warszawie oraz nadania Instytutowi statusu państwowego instytutu badawczego, 2019 r. Dz.U. poz. 2153.
65. Ustawa z dnia 26 kwietnia 2019 r. o Narodowej Strategii Onkologicznej Dz.U. 2019 r. poz. 969.
66. Uchwała nr 10 Rady Ministrów z dnia 4 lutego 2020 r. w sprawie przyjęcia programu wieloletniego pn. Narodowa Strategia Onkologiczna na lata 2020-2030 M.P. 2020 r. poz. 189.
67. Uchwała nr 11 Rady Ministrów z dnia 4 lutego 2020 r. uchylająca uchwałę w sprawie ustanowienia programu wieloletniego na lata 2016-2024 pod nazwą „Narodowy Program Zwalczania Chorób Nowotworowych" M.P. 2020 poz. 190.
68. Koszarowski T. Na początku by dar. In: Towpik E. ed. Instytut Radowy i Instytut Onkologii w Warszawie, w: Centrum Onkologii Instytut im. Marii Skłodowskiej-Curie w Warszawie 1932–2002. Centrum Onkologii – Instytut, Warszawa 2002: 5.

VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 155–160
DOI: 10.5603/NJO.2022.0026

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

The effectiveness of a live animal model in a laparoscopic partial nephrectomy for renal cancer training – a survey study

Oleksii Potapov[1], Francisco M. Sanchez Margallo[2], Andrzej L. Komorowski[3]

[1]*State Scientific Institution: Center for Innovative Medical Technologies of the National Academy of Sciences of Ukraine, Kiev, Ukraine*
[2]*Jesús Usón Minimally Invasive Surgery Centre, Caceres, Spain*
[3]*Department of Surgery, College of Medicine, University of Rzeszow, Rzeszow, Poland*

Introduction. A laparoscopic partial nephrectomy for kidney cancer is a technically demanding procedure. Among many training approaches a live animal model is considered to be one of the most promising.

Material and methods. During nine editions of a two day live animal laparoscopy course, nine urologists took part in exercises aimed at mastering a partial nephrectomy for kidney cancer. After finishing the courses, an online survey was sent to all participants in order to evaluate the practical implications of the training on a live animal model.

Results. Seven participants responded to the survey. Two attended one course, two attended two courses and three attended more than twice. The number of partial nephrectomies performed during the course ranged from 0 to 20. All participants declared good understanding of the knot formation and stated that they use their obtained knowledge on a regular basis. Six of seven participants would like to repeat the course. All participants would recommend this course to colleagues with no partial nephrectomy experience.

Discussion. A live animal laparoscopy course for experienced urologists can yield positive results in terms of technical abilities and the implementation of minimally invasive techniques into clinical practice. It seems that this type of advanced simulation is better for clinicians than residents. The high level of satisfaction and willingness to repeat the course seem to back up this hypothesis.

Conclusions. The live animal model seems to be an interesting tool in advanced training in minimally invasive partial nephrectomy for kidney cancer.

Key words: laparoscopy, partial nephrectomy, animal model, minimally invasive surgery

Introduction

A laparoscopic nephrectomy, simple or radical, has become the standard approach to nephrectomy as it has been shown to minimize morbidity without compromising the longer-term outcomes [1].

A laparoscopic partial nephrectomy is recommended for patients with tumors less than 7 cm in diameter, considering renal parenchyma spearing approach if only anatomically possible and oncologically accurate [2].

How to cite:

Potapov O, Sanchez Margallo FM, Komorowski AL. ***The effectiveness of a live animal model in a laparoscopic partial nephrectomy for renal cancer training – a survey study.*** *NOWOTWORY J Oncol* 2022; 72: 155–160.

It is well-established that oncologic safety and long-term results in patients undergoing a partial nephrectomy is superior to nephrectomy in carefully selected renal cancer patients [3]. With the advancement of modern diagnostic tools and screening programs, more and more patients can be scheduled for a minimally invasive surgical (MIS) partial nephrectomy approach. Despite the fact of the rapid introduction of the robotic technique, still the most common MIS approach to a partial nephrectomy is a laparoscopy.

In a study by Boga et al., no significant differences were observed in eGFR changes and post-operative new-onset chronic kidney disease 1 year after surgery ($p = 0.768$, $p = 0.614$, respectively) during the overall mean follow-up period of 36.07 ± 13.56 months ($p = 0.007$). During the follow-up period, there were no cancer-related death observed in both groups and non-cancer-specific survival was 93.5% and 94.4% in the laparoscopic and robotic groups, respectively ($p = 0.859$) [4]. The main problem inherent in the laparoscopy approach to a partial nephrectomy is the level of technical difficulty of the operation [5]. In order to adequately prepare surgeons for this demanding operation, different modalities were introduced into the training curriculum including silicone-based models [6]. Different animal models were proposed for the MIS training in urology [6]. Live anesthetized animals are a well established model for the laparoscopic training and obtaining complex skills by the minimally invasive surgeons [7, 8]

However, there is a lack of evaluation of feedback from the participants of the different training approaches and therefore it can be difficult to assess the value of this type of training. In this study, we analyzed the subjective impact of training in a laparoscopic partial nephrectomy using a live porcine model.

Material and methods

Study setting and design

A survey-based observational study was performed. The study participants were recruited from Polish urologists, who participated in two days hands-on training course in laparoscopic urology. Training was held in the Jesús Usón Minimally Invasive Surgery Centre, Cáceres, Spain. The program of the course contained lectures, dry lab training, tissue model and a live anesthetized animal model. There were nine editions of the course. All participants were actively practicing specialists in urology.

Tutors

The tutors who participated in the study (surgeons and veterinary surgeons) had experience in both theoretical activity and practical mentoring during animal MIS procedures, participating in at least five hands-on courses as mentors. The same lectures and basic training exercises were given to all participants. Advanced exercises were adapted to the previous experience of the participants and a tailored approach was chosen for the intracorporeal suturing exercise.

Exercises

Before proceeding to the animal model, the participants underwent a step-by-step training program, including lectures, practical skills teaching, and intracorporeal suturing. The suturing was done in the *ex-vivo*, a preserved porcine small intestine inside a plexiglass training box. The main focus was on the formation of the intracorporeal node at different angles and under stressful conditions.

Animal model

The porcine species is used as the experimental model for urological laparoscopy training because of its anatomical similarities in the position and structure of the kidneys to the human urinary tract. At the beginning of the procedure, the animal is positioned on the back for the first trocar introduction and obtaining a pneumoperitoneum with the assistance of the Veress needle. The features of the anatomy of the anterior abdominal wall of the pig can cause sliding of the trocar between the layers and cause insufflation outside the abdominal cavity. To allow for partial nephrectomy on both sides of the animal, we put the first 10 mm optical trocar 1 cm above the umbilical scar. Then pneumoperitoneum pressure is set to 12 mm Hg. All animals undergo standard pre-op and intraoperative medication.

Working ports positions are as follows: subcostal 10 mm trocar for the scissors, needle holder and energy source instruments for the right hand. For the left hand 5 mm trocar in the iliac fossa, to handle the dissector or grasping forceps. A 5 mm trocar is placed in the flank, for the forceps and the aspirator. After positioning of the trocars, the animal is rotated to the side in a lateral position with lumbar elevation for the viscera shifting and better renal exposure. The final position of the animal and the operating team is shown on figure 1.

A peritoneal excision is done from the posterior side at the height of the ureter and caudal pole of the kidney with the monopolar L-hook. Using the forceps or aspirator, the caudal pole of the kidney is retracted for the pedicle exposure and manipulations. The renal artery is then dissected, and a vessel silicone tourniquet is prepared to be applied, as shown in figure 2.

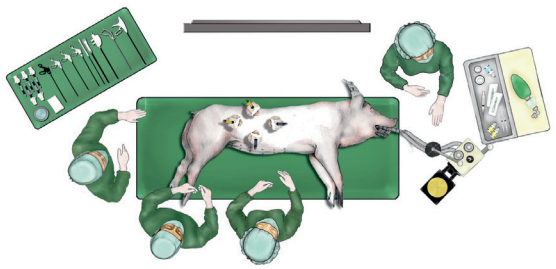

Figure 1. Position of the team and the animal (illustration from the *Manual de Formación en Cirugía Laparoscópica Paso a Paso*, Caceres 2013, with permission)

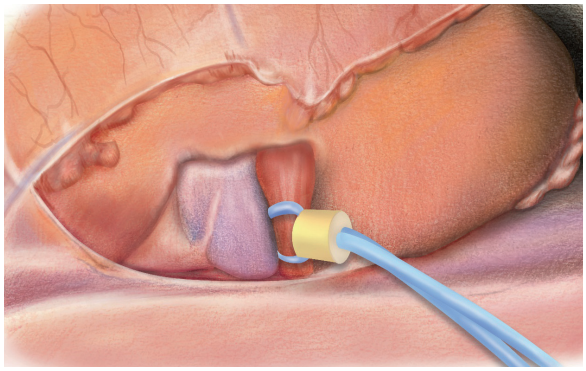

Figure 2. Silicone tourniquet application (illustration from the *Manual de Formación en Cirugía Laparoscópica Paso a Paso*, Caceres 2013, with permission)

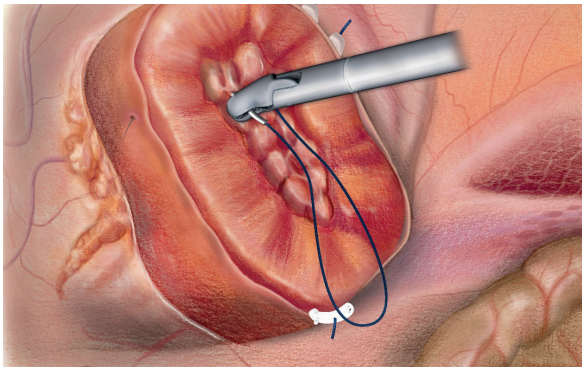

Figure 3. Final steps of the procedure (illustration from the *Manual de Formación en Cirugía Laparoscópica Paso a Paso*, Caceres 2013, with permission)

The renal vein is dissected to achieve confidence of vascular damage control by the participants. Once it is achieved, the operating surgeon marks the incision line with the monopolar coagulation. Afterwards two clips are applied on the tourniquet to obtain arterial occlusion and the timer is set. The parenchyma of the kidney is transected without energy use with the laparoscopic Metzenbaum scissors. Once the excision is completed, hemostasis of the bed is performed. Kidney reconstruction is performed with the 3–0 polyglactin absorbable sutures using hemostatic gauze, as shown in figure 3. Then tourniquet is removed by cutting one part of the loop.

After finishing a partial nephrectomy, three working ports are removed from the abdomen under direct vision and trocar wounds are sutured. Then, the animal is placed in the contralateral position by the technical team for the exposure of the second kidney and the position of working ports are inverted. During the change of position, an ex-suflation is performed, promoting the control of the hemostasis. The procedure site is examined after re-establishing the pneumoperitoneum.

Survey

The anonymous questionnaire was sent to participants at least 12 months after finishing the course. There were five demographical questions and 13 questions regarding the course and its effect on clinical practice. The detailed questionnaire can be seen in table I. The questionnaire was sent to the participants through the Google forms (Google LLC, 1600 amphitheatre parkway mountain view CA 94043).

Table I. List of questions regarding training in laparoscopic partial nephrectomy used in the survey

	Question	Answer
1	full name	
2	age	
3	position	resident
		medical doctor
		chief specialist/ chief of the department
		other
4	How many times have you been on our course in Caceres?	once
		two times
		more than two times
5	date of the training in Caceres (year, month)	
6	How many partial nephrectomies have you performed on a tissue model? (please mention the number)	
7	How many partial nephrectomies have you performed on a live animal model as an operating surgeon? (please mention the number)	
8	How many partial nephrectomies have you performed on a live animal model as an assisting surgeon? (please mention the number)	
9	How do you evaluate the training for partial nephrectomy in Caceres on animal tissue from 1 (completely useless) to 10 (the best I can imagine)?	completely useless the best I can imagine

Table I. cont. List of questions regarding training in laparoscopic partial nephrectomy used in the survey

	Question	Answer
10	Do you feel you were ready to perform laparoscopic partial nephrectomy in humans after attending training?	not ready
		prepared but definitely needing more training
		prepared but needed some assistance
		well prepared
11	Have you done partial laparoscopic nephrectomy after our course?	yes
		no
12	Did you have intracorporeal suturing skills and knot tying capabilities before taking part in the training course?	
		yes
		no
		other
13	Did you use your obtained knowledge, tips, and tricks in intracorporeal suturing and knot tying in the operating room after the training course?	
		yes
		no
14	Would you like to participate again in such a course?	yes
		no
		maybe
15	How many partial nephrectomies did you perform before the course? (please mention number)	
16	How many partial nephrectomies did you perform after the course? (please mention number)	
17	Would you recommend this course for colleagues with no partial nephrectomy experience?	yes
		no
18	Would you advocate this course for colleagues wanting to master partial nephrectomy technique?	yes
		no

Results

The questionnaire was sent to nine participants. Seven participants (77%) returned the filled form. All those that responded, responded to all questions in the questionnaire. The age of the participants was within the range 45–54 years (mean 49 years). All participants were male. Six participants were medical doctors, and one – a Chief specialist/ Chief of the department. Two attended training course in Caceres once, another two twice, and three participants participated more than twice. The number of partial nephrectomies that were done on the tissue model ranged from 0 (one result) to 20 (one result), the latter figure seems highly unlikely given the overall number of nephrectomies performed. Other participants mention 1 (one result), 2 (two results), and 3 (one result), this result seems more likely to be true. One participant forgot the exact number of procedures performed on the model, mentioning one or two attempts. The number of operations performed on the live animal model as an operating and assisting surgeon are presented in table II.

Five participants declared that before attending the training course they did not have a clear understanding of intracorporeal knots formation in laparoscopic surgery. After the course, all seven participants declared a good understanding of the sequence of knot formation and the steps required to increase quality and performance in intracorporeal knot tying.

All seven participants mentioned that they use their obtained knowledge, tips, and tricks in intracorporeal suturing and knot tying in the operating room after the training cour-

Table II. Number of cases performed on a live anesthetized animal model

How many partial nephrectomies have you performed on a live animal model as an operating surgeon?	How many partial nephrectomies have you performed on a live animal model as an assisting surgeon?
1	1
0	0
1 or 2	1 or 2
2	3
0	1
10	10
2	3

se on a regular basis. The number of procedures performed by the participants in their home hospitals are presented in figures 4 and 5.

Six of seven participants declared their wish to return for this type of training course in the future. Seven participants agreed on the statement to recommend this course to colleagues with no partial nephrectomy experience. Six of the seven participants agreed to advocate this course for colleagues willing to master partial nephrectomy laparoscopic technique.

Discussion

Minimally invasive surgery permeates all branches of surgery urology included. It is common to study the basics of minimally invasive surgery during residency, but there are no clearly established mandatory programs that would guarantee a high-quality result and implementation of minimally invasive operations into clinical practice for more senior surgeons. There is also still a large number of surgeons who completed their training long before the widespread introduction of minimally invasive technologies. Overall, the literature describes a large number of studies on the skills of residents after completing short-term courses, but little attention is paid to courses for more senior colleagues.

Among the population of young specialists, hands-on training is quite popular. Some studies show great satisfaction of participants with all of them willing to recommend hands--on training to other residents, considering it an important stepping stone in their career [10]. Some authors showed improvement, not only in the task performance by residents and students, but even an increased interest in their surgical specialty due to this minimally invasive course [11].

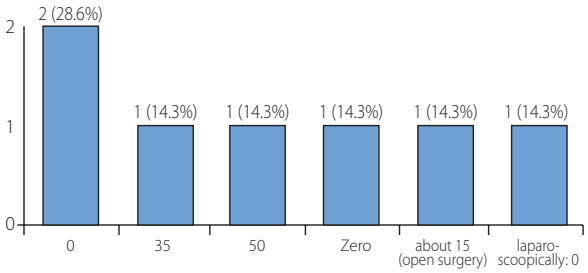

Figure 4. Number of partial nephrectomies performed before attending the course

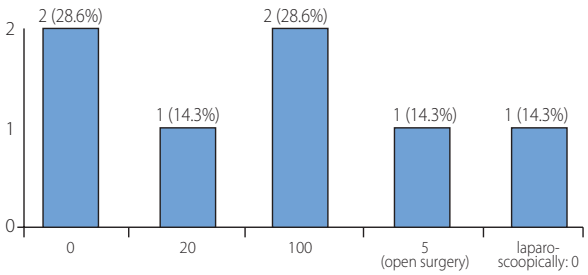

Figure 5. Number of partial nephrectomies performed after attending the course

Unlike residents, senior specialists could implement new surgical interventions immediately after completing a training course without delay. At the beginning of the learning curve, this could be a negative factor for the quality of performance. If this statement is indeed true, the training of senior specialists should become a priority in the structure of postgraduate education.

In a urology setting, one of the most common indications for the minimally invasive approach is nephron sparing surgery [12]. Laparoscopic partial nephrectomy is recommended for patients diagnosed with kidney tumors less than 7 cm in diameter. The anatomical location of the tumor has got to be taken into account as well [2].

The laparoscopic partial nephrectomy is highly demanding in terms of surgical performance [5]. To obtain the required technical skills, many training approaches can be proposed including live animal models [6]. While evaluation of the learned skills is fairly common, the real impact of such courses on clinical practice is unknown. In this paper we tried to determine whether live animal model training had any impact on clinical practice of urologists specializing in urologic oncology. While data obtained in our survey is limited, it seems to back up the statement that an animal model in training for laparoscopic partial nephrectomy for kidney cancer is well received by experienced clinicians. It seems that the implementation of short duration intensive training can be beneficial in starting minimally invasive programs at urology departments.

One of the most praised elements of the course was intracorporeal knot tying. It is clear that intracorporeal suturing should be included in all minimally invasive training programs, including partial nephrectomy training courses. This is especially true when we realize that laparoscopic suturing and knot tying are technically challenging and failure to tie a knot can lead to conversion to open procedure [13]. Despite the low number of participants, we can observe positive responses and the potentially positive impact on clinical practice of short-term training courses, the importance of which for experienced professionals is underestimated.

Conclusions

The live animal model seems to be an interesting tool in advanced training in minimally invasive partial nephrectomy for kidney cancer – specially for established clinician urologists.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license

reference code: 001/20/Cert granted by *The Ethics Committee in Animal Experimentation of the "Jesús Usón" Minimally Invasive Surgery Center*, in compliance with existing laws for the use of experimental animals (Royal Decree 53/2013, of February 1st) for the care and use of animals.

Conflict of interest: none declared

Andrzej L. Komorowski
University of Rzeszow
College of Medicine
Department of Surgery
ul. Kopisto 2A
35-315 Rzeszów, Poland
e-mail: z5komoro@cyf-kr.edu.pl

Received: 27 Feb 2022
Accepted: 18 Mar 2022

References

1. Berger A, Brandina R, Atalla MA, et al. Laparoscopic radical nephrectomy for renal cell carcinoma: oncological outcomes at 10 years or more. J Urol. 2009; 182(5): 2172–2176, doi: 10.1016/j.juro.2009.07.047, indexed in Pubmed: 19758651.
2. Lee RA, Strauss D, Kutikov A. Role of minimally invasive partial nephrectomy in the management of renal mass. Transl Androl Urol. 2020; 9(6): 3140–3148, doi: 10.21037/tau.2019.12.24, indexed in Pubmed: 33457286.
3. Srivastava A, Ficarra V, Kutikov A. The Alphabet Soup of Modern Nephrometry Systems. Eur Urol Oncol. 2018; 1(5): 435–436, doi: 10.1016/j.euo.2018.08.026, indexed in Pubmed: 31158084.
4. Boga MS, Sönmez MG, Karamık K, et al. Long-term outcomes of minimally invasive surgeries in partial nephrectomy. Robot or laparoscopy? Int J Clin Pract. 2021; 75(2): e13757, doi: 10.1111/ijcp.13757, indexed in Pubmed: 33058376.
5. Polok M, Dzielendziak A, Apoznanski W, et al. Laparoscopic Heminephrectomy for Duplex Kidney in Children-The Learning Curve. Front Pediatr. 2019; 7: 117, doi: 10.3389/fped.2019.00117, indexed in Pubmed: 31001503.
6. Golab A, Smektala T, Kaczmarek K, et al. Laparoscopic Partial Nephrectomy Supported by Training Involving Personalized Silicone Replica Poured in Three-Dimensional Printed Casting Mold. J Laparoendosc Adv Surg Tech A. 2017; 27(4): 420–422, doi: 10.1089/lap.2016.0596, indexed in Pubmed: 28061038.
7. Ganpule A, Chhabra JS, Desai M. Chicken and porcine models for training in laparoscopy and robotics. Curr Opin Urol. 2015; 25(2): 158–162, doi: 10.1097/MOU.0000000000000139, indexed in Pubmed: 25581541.
8. McDougall EM, Clayman RV, Chandhoke PS, et al. Laparoscopic partial nephrectomy in the pig model. J Urol. 1993; 149(6): 1633–1636, doi: 10.1016/s0022-5347(17)36465-0, indexed in Pubmed: 8501822.
9. Komorowski AL, Mituś JW, Sanchez Hurtado MA, et al. Porcine Model In The Laparoscopic Liver Surgery Training. Pol Przegl Chir. 2015; 87(8): 425–428, doi: 10.1515/pjs-2015-0083, indexed in Pubmed: 26495920.
10. Kerbage Y, Rouillès J, Estrade JP, et al. Surgical training through simulation dedicated to French Ob-gyn residents. Evaluation and satisfaction. J Gynecol Obstet Hum Reprod. 2021; 50(7): 102076, doi: 10.1016/j.jogoh.2021.102076, indexed in Pubmed: 33515852.
11. Seo HoS, Eom YH, Kim MKi, et al. A one-day surgical-skill training course for medical students' improved surgical skills and increased interest in surgery as a career. BMC Med Educ. 2017; 17(1): 265, doi: 10.1186/s12909-017-1106-x, indexed in Pubmed: 29282043.
12. Stajno P, Wiechno P, Demkow T. Urologia onkologiczna — co zmieniło się w ciągu ostatnich 25 lat? Nowotwory J Oncol. 2016; 66(3): 238–244, doi: 10.5603/njo.2016.0040.
13. Khawaja AR, Ali S, Dar Y, et al. Outcome of laparoscopic nephron sparing surgery using a Satinsky clamp for hilar control: a trusted tool (SKIMS experience). Curr Urol. 2021; 15(3): 172–175, doi: 10.1097/CU9.0000000000000022, indexed in Pubmed: 34552458.

VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 161–166
DOI: 10.5603/NJO.a2022.0010

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

The prognostic value of RDW, NLR and PLR in sequential radio-chemotherapy for advanced lung cancer

Iwona Jabłońska[1], Marcin Miszczyk[1], Marcin Goławski[2], Iwona Dębosz-Suwińska[3], Rafał Suwiński[4]

[1]*III[rd] Radiotherapy and Chemotherapy Clinic and Teaching Hospital, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[2]*Department of Biophysics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland*
[3]*Department of Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[4]*II[nd] Radiotherapy and Chemotherapy Clinic and Teaching Hospital, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*

Introduction. Inflammation plays an important role in carcinogenesis, therefore morphology-based inflammatory indices could be prognostic factors in lung cancer patients. This study aimed to analyze if red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are associated with patients' prognosis in non-small cell lung cancer (NSCLC) patients.

Material and methods. The study population included 110 patients treated with definitive sequential radio-chemotherapy for stage IIIA–IIIB NSCLC. The data were retrospectively analyzed using the receiver operating characteristic (ROC) method, Kaplan-Meier estimator, log-rank testing, and Cox proportional hazards regression model.

Results. The ROC analysis has shown that the optimal cut-off values were 14% for RDW, 2.1 for NLR, and 120 for PLR, with area under the curve (AUC) of 0.606, 0.509, and 0.564 respectively. The overall survival was significantly higher in patients with RDW ≤ 14% with a median survival of 31.2 months compared to 20.2 months for patients with RDW > 14%. RDW was an independent prognostic factor in multivariate analysis.

Conclusions. RDW can provide additional information in assessing patients' prognosis, but it is necessary to consider its modest sensitivity and specificity. NLR and PLR were not found to be independent prognostic factors.

Key words: lung cancer, red cell distribution width, RDW

Introduction

Lung cancer is the most common cause of cancer-related death among men and the second most frequent among women with as many as 1.76 million deaths worldwide annually [1]. The disease is frequently diagnosed at an advanced stage, which is associated with a poor prognosis. Approximately 84% of lung cancers are non-small cell lung cancers (NSCLC) characterized by a 5-year overall survival rate of 24%, which is significantly higher than 6% for small cell lung cancer (SCLC) [2, 3].

Inflammation plays a significant role in cancer development and is regarded as the 7th hallmark of cancer [4]. Inflammatory cells release molecules to the tumor microenvironment, including growth factors that stimulate proliferation and survival factors that limit apoptosis. Furthermore, these

How to cite:

Jabłońska I, Miszczyk M, Goławski M, Dębosz-Suwińska I, Suwiński R. ***The prognostic value of RDW, NLR and PLR in sequential radio-chemotherapy for advanced lung cancer.*** *NOWOTWORY J Oncol* 2022; 72: 161–166.

molecules include proangiogenic factors and extracellular matrix-modifying enzymes, which facilitate angiogenesis, invasion, and metastasis [5].

Multiple studies indicate that blood morphology indices, such as red blood cell distribution width (RDW) [6–13], neutrophil-to-lymphocyte ratio (NLR) [14–19], and platelet-to-lymphocyte ratio (PLR) [6, 19–21], may be prognostic factors in cancer patients. Such indices could be particularly useful for clinicians given that the majority are based on routinely performed laboratory tests.

RDW indicates the variability of red blood cell volume, and it is commonly used to distinguish the etiology of anemia [22]. Higher RDW values reflect a larger variation of erythrocyte volume, which can be associated with chronic inflammation [23] and oxidative stress [24]. Likewise, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been reported as inflammation biomarkers [19, 25]. In our study, we analyzed whether parameters such as RDW, NLR, and PLR could be useful in assessing prognosis in patients treated with definitive sequential radio-chemotherapy for stage IIIA–IIIB NSCLC.

Material and methods

This retrospective analysis was based on a group of 110 patients treated for NSCLC at a single institution between January 2009 and December 2017. The following inclusion criteria were used:

- inoperable stage IIIA or IIIB NSCLC (according to the 7th edition of AJCC/UICC TNM Classification of Malignant Tumors),
- radical sequential radiotherapy and chemotherapy as the primary method of treatment.

Patients with a diagnosis of a secondary malignant neoplasm, ongoing autoimmune disease, or chronic steroid uptake were excluded from the study group.

The data were collected from patients' medical history and the Polish National Cancer Registry. Out of the initial database of 176 patients, 64 cases had to be excluded due to missing data (36.8%). The final cohort included 110 patients. The RDW was available in 81 cases (73.6%), NLR and PLR in 110 cases (100%). The indices were calculated based on laboratory tests performed before the first dose of chemotherapy (median delay of 1 day, IQR 0–10).

The vast majority of patients (97; 88.2%) received chemotherapy based on cisplatin and vinorelbine. Remaining patients

Table I. Patients' characteristics

	Whole group	RDW ≤14%	RDW >14%
	n = 110	n = 58	n = 23
age	61.8 years (57.1–66.4)	61.8 years (57.1–66.4)	62.8 years (54–66.4)
sex:			
• male	82 (74.5%)	44 (75.9%)	16 (69.6%)
• female	28 (25.5%)	14 (24.1%)	7 (30.4%)
history of smoking:			
• non-smoker	13 (11.8%)	10 (17.2%)	1 (4.3%)
• active or former smoker	95 (86.4%)	48 (82.8%)	20 (86.9%)
• pack-years	33.0 (20–42)	30 (0–64.5)	32.5 (0–58.5)
blood panel:			
• WBC	8.6 (7.1–10.1)	8.2 (6.8–9.7)	8.8 (7.3–10.5)
• RBC	4.6 (4.3–4.9)	4.7 (4.4–4.9)	4.5 (3.9–4.9)
• HGB	13.6 (12.6–14.5)	13.9 (13.4–14.7)	12.3 (11.2–13.7)
• RDW	13.4 (12.9–14.1)	13.1 (12.7–13.6)	15.0 (14.3–16.9)
• NLR	2.8 (2.1–3.9)	2.5 (2.0–3.4)	2.6 (1.9–3.6)
• PLR	145.1 (107.8–232.9)	147.4 (107.3–200.6)	132.9 (107.8–232.9)
stage:			
• IIIA	73 (66.4%)	40 (69%)	10 (43.5%)
• IIIB	37 (33.6%)	18 (31%)	13 (56.5%)
type:			
• adenocarcinoma	17 (15.5%)	11 (19.0%)	5 (21.7%)
• squamous cell carcinoma	69 (62.7%)	37 (63.8%)	12 (52.2%)
• large cell	5 (4.5%)	2 (3.4%)	2 (8.7%)
• NOS (not otherwise specified)	19 (17.3%)	8 (13.8%)	4 (17.4%)
Zubrod score:			
• 0	35 (31.8%)	23 (39.7%)	6 (26.09%)
• 1	73 (66.4%)	34 (58.6%)	16 (69.56%)
• 2	2 (1.8%)	1 (1.7%)	1 (4.35%)
GTV (cc):			
• primary	34.2 (16.0–56.3)	27.8 (4.3–203.2)	43.2 (6.4–471.0)
• nodal	2.85 (0.0–8.9)	2.65 (0.0–37.1)	5.8 (0.0–15.9)

The data is presented as median value and interquartile range or number and percentage for binary variables.
WBC – white blood cell count; RBC – red blood cell count; HGB – hemoglobin concentration; RDW – red blood cell distribution width; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; GTV – gross tumor volume

received gemcitabine and carboplatin (5; 4.5%), cisplatin and etoposide (5; 4.5%), carboplatin and vinorelbine (2; 1.8%), or pemetrexed and cisplatin (1; 0.9%). The median radiotherapy dose was 67.2 Gy (IQR 66.51–69.2). The majority of the patients received radiotherapy doses ranging between 60 and 70 Gy (93.6%). The remaining patients had their total dose reduced due to treatment complications. Patients' characteristics are presented in table I.

The receiver operating characteristic (ROC), Kaplan-Meier estimator, log-rank testing, and Cox proportional hazards regression model were used for the analysis. Median OS was chosen as a cut-off point for the ROC analysis. The univariate Cox analysis was performed using known clinical factors. Statistically significant cofactors (p-value < 0.05) were included in the multivariable analysis (MVA, tab. II). Due to the inclusion of corresponding variables, the MVA was performed twice, using RDW, NLR, and PLR as continuous and binary indices. The Spearman Rank Correlation test was used to assess the correlation between the RDW or primary gross tumor value (GTVp) and hemoglobin concentration (HGB). The statistical analysis was performed using the STATISTICA 13.3 by TIBCO Software Inc.

Results

The median overall survival (OS) was 27 months; 17 (15.5%) patients were alive at the time of the analysis.

The ROC analysis (fig. 1) showed that RDW had the highest discriminatory value for overall survival (AUC = 0.606; 95% CI: 0.479–0.733). PLR (AUC = 0.564; 95% CI: 0.452–0.675) and NLR (AUC = 0.509; 95% CI: 0.398–0.619) had lower discriminatory values.

In the univariate Cox regression model, RDW as a continuous value and histopathological diagnosis of squamous cell carcinoma were associated with increased mortality risk as well

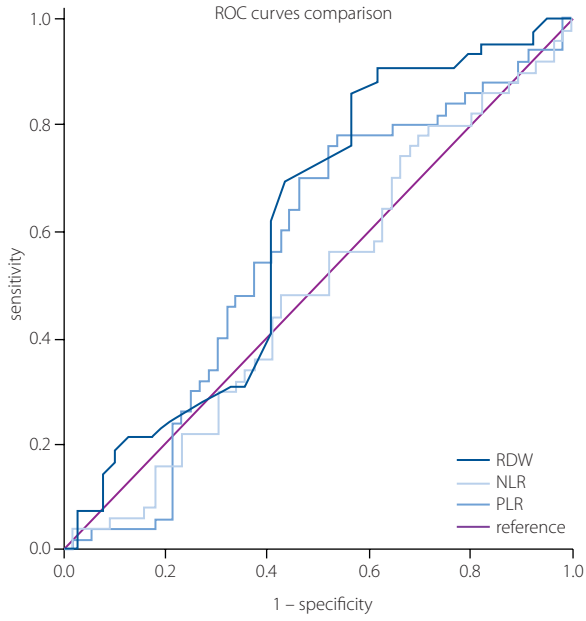

Figure 1. ROC analysis based on RDW, PLR, and NLR for OS in patients treated with sequential radio-chemotherapy for advanced inoperable NSCLC

Table II. Univariate and multivariate COX regression analysis

	Univariate analysis	
	HR (95% CI)	p-value
sex (male)	1.080 (0.654–1.784)	0.765
smoking	0.816 (0.815–3.509)	0.158
pack-years	0.999 (0.989–1.009)	0.802
RDW	1.227 (1.054–1.430)	0.008
RDW (>14%)	2.434 (1.420–4.173)	0.001
NLR (>2.1)	0.547 (0.336–0.889)	0.015
PLR (>120)	0.592 (0.377–0.928)	0.022
hemoglobin	0.937 (0.807–1.088)	0.395
neutrophil count	1.029 (0.956–1.107)	0.446
platelet count	1 (0.999–1.001)	0.926
lymphocyte count	1.28 (0.916–1.799)	0.154
TNM stage (IIIB *vs.* IIB–IIIA)	1.216 (0.774–1.912)	0.396
type – squamous cell carcinoma	1.619 (1.038–2.524)	0.034
type – adenocarcinoma	0.535 (0.258–1.110)	0.093
type – NOS	0.727 (0.438–1.109)	0.217
Zubrod (1–2 *vs.* 0)	1.496 (0.927–2.415)	0.099
primary GTV (per cc)	1.004 (1.002–1.007)	0.0006
nodal GTV (per cc)	1.000 (0.986–1.014)	0.997
total GTV (per cc)	1.003 (1.001–1.006)	0.002
Multivariate analysis		
RDW, NLR and PLR as continuous variables		
RDW	1.179 (1–1.39)	0.049
type – squamous cell carcinoma	1.558 (0.997–2.43)	0.051
primary GTV (per cc)	1.003 (1.000–1.006)	0.009
RDW, NLR and PLR as binary variables separated by Youden index value		
RDW (>14%)	2.048 (1.155–3.632)	0.014
NLR (>2.1)	0.584 (0.33–1.033)	0.065
PLR (>120)	0.648 (0.378–1.111)	0.115
type – squamous cell carcinoma	1.717 (1.093–2.695)	0.019
primary GTV (per cc)	1.004 (1.002–1.007)	<0.001

RDW – red blood cell distribution width; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; TNM – stage according to AJCC/UICC TNM Classification of Malignant Tumors; NOS – not otherwise specified; GTV – gross tumor volume

as RDW, NLR, and PLR presented as binary values categorized by Youden index value (tab. II). In the MVA, squamous cell carcinoma (SCC) histopathology became nearly statistically significant (p = 0.051), while GTVp and RDW remained inde-

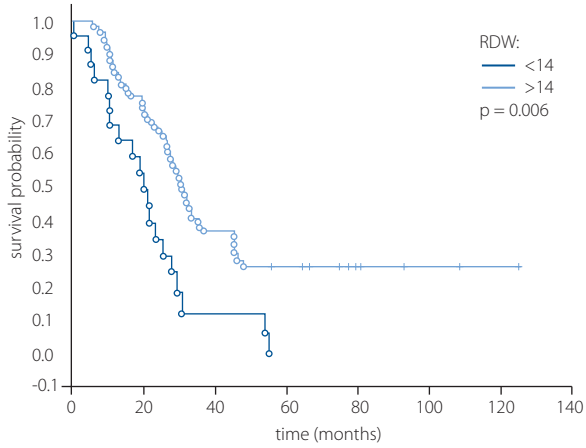

Figure 2. Overall survival stratified by RDW in patients treated with sequential radio-chemotherapy for advanced inoperable NSCLC

pendent prognostic factors. When presenting blood indices as binary variables, RDW, SCC histopathology, and primary GTV remained independent prognostic factors, while NLR and PLR were non-significant (tab. II).

The overall survival was significantly higher in patients with RDW ≤ 14%, with a median survival of 31.2 months compared to 20.2 months for patients with RDW > 14% (fig. 2, p = 0.006).

Discussion

Inflammation plays an important role in tumor development, including angiogenesis, tumor invasion, and metastasis. Many molecules released by the inflammatory cells to the tumor environment promote cancer development [5, 26]. Elevated expression of various inflammatory biomarkers, including interleukin-10 (IL-10) and transforming growth factor (TGF-β), were found to be associated with poor survival in patients with NSCLC [27, 29].

The correlation between C-reactive protein, erythrocyte sedimentation rate (ESR), and RDW was reported by Lippi et al. in 2009 [23]. In another study, by Allen et al. reported a correlation of RDW and different inflammatory biomarkers; it was suggested that RDW may reflect pathologic processes, such as inflammatory stress and impaired iron metabolism [30]. Since RDW can be considered a marker of chronic inflammation, its elevated value may be associated with poor survival in patients.

In this study, overall survival (OS) was significantly lower in patients with higher RDW as well as higher PLR and NLR, when the latter two were expressed as binary values. Furthermore, as shown in table I, patients with RDW > 14% had lower HGB and RBC than those with RDW ≤ 14%, higher median GTVp, and more frequently stage IIIB disease. Additionally, there was a statistically significant correlation between HGB and RDW (p = 0.002). However, the HGB was not significantly associated with survival (tab. II), while RDW was found to be an independent prognostic factor.

Many authors reported that elevated RDW values are associated with an advanced cancer stage in NSCLC [7, 31, 32]. In our study, we have shown that RDW can also provide additional prognostic insights in patients presenting advanced disease (IIIA–IIIB). Chen et al. found that among 245 NSCLC patients, RDW ≥ 13.25 was significantly correlated with cancer stage III–IV [31]. In a study conducted by Song et al. RDW > 12.95 was strongly associated with the IIIB and IV stage of NSCLC [32]. Koma et al. conducted a study to assess the association between RDW levels and prognosis in 332 patients with NSCLC (stages I–IV) [7]. In the last study, the authors divided patients into two groups: the early (stage I–II) and advanced cancer stage (stage III–IV). In the early stage group, higher RDW levels (>15%) were associated with prognosis, but such association was not found in the advanced stage group [7]. The RDW was also found as potentially helpful in screening, as RDW varies significantly between healthy adults and NSCLC patients [31, 32].

In this analysis, in contrast to other studies, we analyzed RDW both as a continuous and binary variable. The conversion of continuous variables into binary variables can lead to overfitting and lack of reproducibility of results, especially considering the relatively low AUC values for each investigated index (0.606, 0.564, and 0.509 respectively). While setting a cut-off value can produce statistically significant results, those values vary in different studies. Koma et al. established a cut-off value of 15% [7]. Toyokawa et al. used 14.5% as a cut-off value, which they described as "the upper limit of the hospital laboratory normal range" [33]. Ichinose et al. used a cut-off value of 13.8 [34]. Some authors used quartiles or tertiles to divide patients into groups, such as Kiriu et al. [35] or Warwick et al. [36]. In our study, we have shown that RDW remains a significant prognostic factor even as a continuous variable, and although defining a single cut-off value remains controversial, higher RDW values are universally associated with poorer prognosis in NSCLC patients.

The strength of our study lies in the analysis of RDW influence on prognosis in patients limited to stage III NSCLC, decreasing the influence of cancer stage on prognosis, and the use of RDW as both a continuous and binary index in COX regression analysis, which is less prone to overfitting. We acknowledge the study limitations, including the small group size, retrospective design, and limited clinical data available. Additionally, concurrent radio-chemotherapy and immunotherapy with durvalumab are currently considered to be the standard of care for advanced NSCLC patients, superseding sequential radio-chemotherapy. However, due to the recent introduction of durvalumab to clinical practice [37–39], there is limited follow-up data available. Moreover, sequential radio--chemotherapy remains in use for patients with contraindications for concurrent therapy [39, 40].

Conclusions

The introduction of RDW to the initial patient assessment might improve the prognostic accuracy, as RDW was determined to be an independent prognostic factor for the OS in non-operative stage IIIA and IIIB NSCLC, albeit with limited specificity and sensitivity. Both NLR and PLR were not found to be statistically significant prognostic factors in our analysis.

Conflict of interest: none declared

Marcin Goławski
Medical University of Silesia
Department of Biophysics, Faculty of Medical Sciences in Zabrze
ul. Jordana 19
41-808 Zabrze, Poland
e-mail: martin.golawski@gmail.com

Received: 19 Nov 2021
Accepted: 2 Feb 2022

References

1. Cancer [Internet]. Geneva: World Health Organisation; 3 Mar 2021. https://www.who.int/news-room/fact-sheets/detail/cancer (19.03.2021).
2. Cancer A–Z [Internet]. Atlanta: American Cancer Society; c2021. Lung cancer: key statistics for lung cancer; c2021. https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html (20.03.2021).
3. Cancer A–Z [Internet]. Atlanta: American Cancer Society; c2021. Lung cancer: early detection, diagnosis and staging: lung cancer survival rates; c2021. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html?fbclid=IwAR1XssnYQXP7B_51krxuQPwi_3BCS8x3bmBCZWJ0fiXCjNUQ9QeDUyGjHNY (20.03.2021).
4. Colotta F, Allavena P, Sica A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009; 30(7): 1073–1081, doi: 10.1093/carcin/bgp127, indexed in Pubmed: 19468060.
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674, doi: 10.1016/j.cell.2011.02.013, indexed in Pubmed: 21376230.
6. Łochowski M, Chałubińska-Fendler J, et al. Łochowska Prognostic value of red blood cell distribution width-standard deviation (RDW-SD) in patients operated on due to non-small cell lung cancer. J Thorac Dis. 2020; 12: 773–781, doi: 10.21037/jtd.2019.12.94.
7. Koma Y, Onishi A, Matsuoka H, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. PLoS One. 2013; 8: e80240, doi: 10.1371/journal.pone.0080240.
8. Miszczyk M, Jabłońska I, Magrowski Ł, et al. The association between RDW and survival of patients with squamous cell carcinoma of the tongue. Simple, cheap and convenient? Rep Pract Oncol Radiother. 2020; 25(4): 494–499, doi: 10.1016/j.rpor.2020.03.026, indexed in Pubmed: 32477015.
9. Li J, Yang X, Ma J, et al. Relationship of red blood cell distribution width with cancer mortality in hospital. Biomed Res Int. 2018: 8914617, doi: 10.1155/2018/8914617.
10. Riedl J, Posch F, Königsbrügge O, et al. Red cell distribution width and other red blood cell parameters in patients with cancer: association with risk of venous thromboembolism and mortality. PLoS ONE. 2014; 9: e111440, doi: 10.1371/journal.pone.0111440.
11. Wang Y, Zhou Y, Zhou K, et al. Prognostic value of pre-treatment red blood cell distribution width in lung cancer: a meta-analysis. Biomarkers. 2020; 25: 241–247, doi: 10.1080/1354750X.2020.1731763.
12. Wang PF, Song SY, Guo H, et al. Prognostic role of pretreatment red blood cell distribution width in patients with cancer: A meta-analysis of 49 studies. J Cancer. 2019; 10: 4305–4317, doi: 10.7150/jca.31598.
13. Hirahara N, Tajima Y, Fuji Y, et al. Comprehensive analysis of red blood cell distribution width as a preoperative prognostic predictor in gastric cancer. Anticancer Res. 2019; 39: 3121–3130, doi: 10.21873/anticanres.13448.
14. Walsh SR, Cook EJ, Goulder F, et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005; 91(3): 181–184, doi: 10.1002/jso.20329, indexed in Pubmed: 16118772.
15. Pryt M, Kalwas M, Nejc D, et al. Can we predict lymph node metastasis by using preoperative markers in gastric cancer patients? Nowotwory J Oncolology. 2019; 69(1): 7–11, doi: 10.5603/njo.2019.0002.
16. Gomez D, Farid S, Malik HZ, et al. Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. World J Surg. 2008; 32(8): 1757–1762, doi: 10.1007/s00268-008-9552-6, indexed in Pubmed: 18340479.
17. Halazun KJ, Aldoori A, Malik HZ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol. 2008; 34(1): 55–60, doi: 10.1016/j.ejso.2007.02.014, indexed in Pubmed: 17448623.
18. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014; 106(6): dju124, doi: 10.1093/jnci/dju124, indexed in Pubmed: 24875653.
19. Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer. 2011; 47(17): 2633–2641, doi: 10.1016/j.ejca.2011.03.028, indexed in Pubmed: 21724383.
20. Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg. 2009; 197(4): 466–472, doi: 10.1016/j.amjsurg.2007.12.057, indexed in Pubmed: 18639229.
21. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014; 23(7): 1204–1212, doi: 10.1158/1055-9965.EPI-14-0146, indexed in Pubmed: 24793958.
22. Sultana GS, Haque SA, Sultana T, et al. Value of red cell distribution width (RDW) and RBC indices in the detection of iron deficiency anemia. Mymensingh Med J. 2013; 22: 370–376.
23. Lippi G, Targher G, Montagnana M, et al. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009; 133: 628–32, doi: 10.5858/133.4.628.
24. Bujak K, Wasilewski J, Osadnik T, et al. The prognostic role of red blood cell distribution width in coronary artery disease: a review of the pathophysiology. Dis Markers. 2015; 2015: 1–12, doi: 10.1155/2015/824624.
25. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001; 102(1): 5–14, indexed in Pubmed: 11723675.
26. Gomes M, Teixeira AL, Coelho A, et al. The role of inflammation in lung cancer. Adv Exp Med Biol. 2014; 816: 1–23, doi: 10.1007/978-3-0348-0837-8_1, indexed in Pubmed: 24818717.
27. Li J, Shen C, Wang X, et al. Prognostic value of TGF-β in lung cancer: systematic review and meta-analysis. BMC Cancer. 2019; 19(1): 691, doi: 10.1186/s12885-019-5917-5, indexed in Pubmed: 31307405.
28. Zeni E, Mazzetti L, Miotto D, et al. Macrophage expression of interleukin-10 is a prognostic factor in nonsmall cell lung cancer. Eur Respir J. 2007; 30(4): 627–632, doi: 10.1183/09031936.00129306, indexed in Pubmed: 17537769.
29. De Vita F, Orditura M, Galizia G, et al. Serum interleukin-10 levels as a prognostic factor in advanced non-small cell lung cancer patients. Chest. 2000; 117(2): 365–373, doi: 10.1378/chest.117.2.365, indexed in Pubmed: 10669676.
30. Allen LA, Felker GM, Mehra MR, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010; 16: 230–238, doi: 10.1016/j.cardfail.2009.11.003.
31. Chen J, Wu J, Lv X, et al. The value of red blood cell distribution width, neutrophil-to-lymphocyte ratio, and hemoglobin-to-red blood cell distribution width ratio in the progression of non-small cell lung cancer. PLoS One. 2020; 15: e0237947, doi: 10.1371/journal.pone.0237947.
32. Song B, Shi P, Xiao J, et al. Utility of red cell distribution width as a diagnostic and prognostic marker in non-small cell lung cancer. Sci Rep. 2020; 10: 15717, doi: 10.1038/s41598-020-72585-4.
33. Toyokawa G, Shoji F, Yamazaki K, et al. Significance of the red blood cell distribution width in resected pathologic stage I nonsmall cell lung cancer. Semin Thorac Cardiovasc Surg. 2020; 32: 1036–1045, doi: 10.1053/j.semtcvs.2019.04.011.
34. Ichinose J, Murakawa T, Kawashima M, et al. Prognostic significance of red cell distribution width in elderly patients undergoing resection for non-small cell lung cancer. J Thorac Dis. 2016; 8: 3658–3666, doi: 10.21037/jtd.2016.12.44.

35. Kiriu T, Yamamoto M, Nagano T, et al. Prognostic value of red blood cell distribution width in non-small cell lung cancer treated with anti--Programmed Cell Death-1 antibody. In Vivo (Highlands). 2019; 33: 213–220, doi: 10.21873/invivo.11462.
36. Warwick R, Mediratta N, Shackcloth M, et al. Preoperative red cell distribution width in patients undergoing pulmonary resections for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2013; 45: 108–113, doi: 10.1093/ejcts/ezt275.
37. Łaczmańska I, Dębicka I, Gil J, et al. Medycyna personalizowana w raku płuca. Nowotwory J Oncolology. 2021; 71(2): 122–128, doi: 10.5603/njo.2021.0026.
38. Imfinzi [Internet]. Amsterdam: European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi (21.01.2022).
39. Krzakowski M, Jassem J, Antczak A, et al. Cancer of the lung, pleura and mediastinum. Oncol Clin Pract. 2019; 15(1), doi: 10.5603/OCP.2018.0056.
40. NCCN Guidelines Version 1.2022 Non-Small Cell Lung Cancer [Internet]. Plymouth Meeting: National Comprehensive Cancer Network; 7 Dec 2021. https://www.nccn.org/guidelines/guidelines-detail?category-=1&id=1450 (19.03.2021).

VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 167–173
DOI: 10.5603/NJO.a2022.0022

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Assessment of the effectiveness of clinical PSA concentration measurements in early prostate cancer detection

Tomasz Tatara[1, 2], Wojciech Miazga[2], Jakub Świtalski[2, 3], Katarzyna Wnuk[2, 4], Magdalena Jabłońska[2, 5], Adrian Matera[2], Dagmara Karauda[2], Agnieszka Zagrobelna[2], Sylwia Jopek[3]

[1]*Department of Public Health, Faculty of Health Sciences, Medical University of Warsaw, Warsaw, Poland*
[2]*Department of Health Policy Programs, Department of Health Technology Assessment, Agency for Health Technology Assessment and Tariff System, Warsaw, Poland*
[3]*Department of Health Economics and Medical Law, Faculty of Health Sciences, Medical University of Warsaw, Warsaw, Poland*
[4]*Department of Epidemiology and Primary Cancer Prevention, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[5]*Department of Prevention of Environmental Hazards, Allergology and Immunology, Faculty of Health Sciences, Medical University of Warsaw, Warsaw, Poland*

Introduction. Prostate cancer is a malignant neoplasm originating primarily in the peripheral zone of the prostate gland. A patient's survival depends largely on the stage of the disease and the treatment method used, which is why early detection of the tumour plays an important role. One of the methods used for screening for prostate cancer is the measurement of prostate specific antigen (PSA) concentration.

Material and methods. The analysis was based on the results of the research found in the systematic review. The following sources of medical information were searched for secondary research: Medline (*via* PubMed), Embase (*via* Ovid), The Cochrane Library. The time range has been set to articles published between July 2011 and July 2021.

Results. The inclusion criteria for a systematic review of the clinical effectiveness of PSA measurements in the early detection of prostate cancer were met by 5 secondary scientific evidence articles. Most of the evidence found showed an increase in the detection of prostate cancer after PSA testing. In case of stage III or IV tumours and the metastatic prostate cancer (CaP) variant, a statistically significant reduction in tumour detection was demonstrated. Most of the scientific evidence indicates a statistically insignificant effect of PSA screening on the risk of death due to CaP (with a diagnostic threshold of ≥4 ng/ml).

Conclusions. Screening in the opportunistic variant aimed at prostate cancer with the use of PSA concentration is justified in men between 50 and 69 years of age, and in men <50 years of age should they have additional risk factors. Conversely, it seems unjustified to conduct population-based screening for prostate cancer.

Key words: prostate cancer, prostate-specific antigen, early detection of cancer

How to cite:

Tatara T, Miazga W, Świtalski J, Wnuk K, Jabłońska M, Matera A, Karauda D, Zagrobelna A, Jopek S. ***Assessment of the effectiveness of clinical PSA concentration measurements in early prostate cancer detection.*** *NOWOTWORY J Oncol* 2022; 72: 167–173.

Introduction

Prostate cancer (CaP) is a malignant neoplasm originating in the peripheral zone of the prostate gland. Almost 95% of CaP cases are adenocarcinomas, with changes occurring within the apical part of the peripheral zone of the prostate which are often of a multifocal nature [1]. It is also important that at an early stage of development CaP may cause no symptoms, or manifest symptoms specific to benign prostatic hyperplasia. As a result, early detection and application of preventive measures may be difficult. At a later stage of local development, this neoplasm may affect surrounding organs, such as seminal vesicles, bladder neck or ureteral openings, leading to erectile dysfunction, hydronephrosis and far-reaching renal failure. This neoplasm often exhibits metastatic features, involving the obturator lymph nodes and those located below the bifurcation of the common iliac vessels. In the final stage of development, CaP may also affect distant organs, such as the brain, lungs, or liver [2].

According to the literature, there are 3 main risk factors for prostate cancer [3]:

- age – this applies especially to men over 50,
- race/ethnicity – this applies especially to representatives of the Negroid race,
- genetic factors – that is, the presence of CaP cases in the family history, especially first-degree relatives (grandfather, father, brother). The risk in such case is often two or three times greater than in cases without familial history of CaP.

Some publications suggest that other risk factors are obesity, previous urinary tract infections and high consumption of saturated fatty acids, although the data is not conclusive [4].

Prostate cancer is the second most common cancer in the male population and the third in terms of all cancers in the world (1.41 million new cases in 2020; age-standardized incidence rate (world) – 30.7/100 000) [5]. In Europe, the incidence is approximately 148.1/100 000 [6], while the frequency of CaP in Poland is at the level of 117.9/100 000 people (standardization by revised European Standard Population ESP2013) [7]. According to the data stored in the Institute for Health Metrics and Evaluation database, the highest incidence values are observed in the age group of 70–74 (2,517.68/100 000), with a gradual increase visible already in the age group 50–54 (547.9/100 000) [8]. Prostate cancer was the fifth leading cause of cancer death among men in the world in 2020 (375 000 deaths; age-standardized mortality rate (world) – 7.7/100 000). However, it should be emphasized that mortality rates for CaP have decreased in many high-income countries since the mid-1990s, including those in Northern and Western Europe, but during the same period, rates increased in most countries in Central and Eastern Europe (also in Poland) [5]. This neoplasm accounts for 13.14% of malignant neoplasm incidence in the male population [9].

Survival depends largely on the stage of the disease and the applied treatment method; hence early tumour detection is crucial [10]. One of the methods used to screen for CaP is the measurement of the concentration of the prostate specific antigen (PSA) [11]. This test involves taking a venous blood sample from which the serum PSA concentration is then calculated. Depending on the result obtained, it is possible to identify men who are likely to develop prostate cancer. However, this tool is not a CaP-specific measurement. An increase in PSA concentration may occur with age (higher PSA values in men >40 years of age), in case of benign prostatic hyperplasia, due to physical activity, or because of a history of urinary tract infections [12]. It is possible to measure free PSA (fPSA), total PSA (tPSA) or intact PSA (iPSA) or using specific measurement protocols such as Prostate Health Index (PHI) or 4KScore, which include more than one PSA variant [13].

Objective

The clinical effectiveness of PSA concentration measurement in the early detection of prostate cancer.

Material and method

The clinical analysis was based on the research results found in the systematic review performed according to the following protocol:

- defining the inclusion criteria for publications to be included in the analysis,
- development/verification of a search strategy for scientific reports,
- searching medical information sources/updating results from medical information sources,
- acquiring full texts of scientific reports potentially useful in clinical analysis,
- selection of studies based on the criteria of inclusion in the analysis,
- analysis of the research data,
- statistical and clinical significance analysis of the results obtained from studies included in the analysis.

Searching for clinical trials was based on a detailed systematic review protocol developed in accordance with the Cochrane Collaboration guidelines before starting this research [14]. The protocol consisted of criteria for including studies in the review, the search strategy, the method of selecting studies, and the planned methodology for conducting data analysis and synthesis.

The analysis was performed on clinical trials that met the criteria for:

- population: general male population,
- interventions: measuring PSA concentration,
- alternative technologies (comparators): not limited,
- methodologies: meta-analyses of randomized trials; systematic reviews of randomized trials; meta-analysis of observational studies; systematic reviews of observational studies,

- endpoints: evaluation of the clinical effectiveness of PSA testing.

The following sources of medical information were searched for secondary research: Medline (*via* PubMed), Embase (*via* Ovid), The Cochrane Library. The last search of the databases was performed on July 27, 2021.

At all stages of the systematic review, the selection of studies was completed by two analysts working independently (MJ and AM). Inconsistencies were resolved by consensus with the participation of a third independent analyst (WM).

The quality of the secondary studies included in the analysis was assessed by verifying the key domains of the AMSTAR2 tool for critical evaluation of systematic reviews. This tool enables selection. To obtain the highest rating, the published research must score positively on every assessed aspect. Even single negative score in a critical domain results in lowering article value to low, and two or more negative scores lower the evaluation value to critically low.

Secondary research presented the results of the statistical analysis carried out by the authors of the studies (they are based on primary data and therefore constitute a reliable source of information). No meta-analysis was performed, and the results of each publication were presented separately.

Results

The inclusion criteria for a systematic review of the clinical effectiveness of PSA measurement in the early detection of prostate cancer were met by the following scientific evidence (n = 5; Paschen 2021, Fenton 2018, Ilic 2018, Rahal 2016, Lumen 2012):

- Paschen 2021 – meta-analysis based on 11 randomized controlled trials (RCTs), which systematically assessed the benefits and harms of population-based screening using the measurement of PSA concentration (quality: low) [15],
- Fenton 2018 – meta-analysis based on 3 RCTs and 5 observational (cohort) studies presenting systematic review of the screening evidence using PSA measurement performed; the results related to prophylaxis were not meta-analysed (quality: high) [16],
- Ilic 2018 – meta-analysis based on 5 RCTs, determining the effectiveness and safety of PSA concentration measurement as a screening test for CaP (quality: low) [17],
- Rahal 2016 – meta-analysis based on 11 RCTs, in which a quantitative review of the available screening studies using PSA concentration measurement (quality: low) was performed [18],
- Lumen 2012 – meta-analysis based on 8 RCTs, assessing the impact of population screening using PSA concentration measurement on CaP detection, stage and severity, and mortality (quality: critically low) [19].

The results of the included studies are presented below.

Effectiveness

Prostate cancer detectability and PSA diagnostic precision

As part of the Ilic 2018 meta-analysis, based on 4 RCTs, a statistically significant effect of screening utilising PSA concentration measurement on a 23% increase in CaP detection, regardless of the stage of cancer advancement had been shown (incidence risk ratio [IRR], 1.23; 95% confidence interval [CI]: 1.03–1.48). Moreover, a meta-analysis based on 3 RCTs showed that the PSA screening test had a statistically significant influence on the increase in the detection of stage I and II prostate cancer by 39% (relative risk [RR], 1.39; 95% CI: 1.09–1.79). In the case of stage III or IV neoplasms, a statistically significant reduction in detection had been demonstrated (RR, 0.85; 95% CI: 0.72–0.99). Individual results included the PSA diagnostic threshold of ≥3 ng/ml [17].

As part of the Fenton 2018 meta-analysis, the authors summarized data on the effectiveness of PSA concentration measurement in detecting CaP. The conclusions of the analysis were based on 3 large primary studies (CAP 2018 [20], PLCO 2017 [21, 22], ERSCP 2014 [23, 24]). The British CAP 2018 (The Cluster Randomized Trial of PSA Testing for Prostate Cancer) showed a statistically significant effect of screening with PSA concentration measurement on an increase in CaP detection by 19% (RR, 1.19; 95% CI: 1.14–1.25). Similar results were obtained in the American study PLCO 2017 (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial), which showed a statistically significant increase in CaP detection by 12% (RR, 1.12; 95% CI: 1.07–1.17), while the European Randomized Study of Screening for Prostate Cancer (ERSPC 2014) showed the highest effectiveness of population screening using PSA – a 59% increase in CaP detection in the population of European men was observed (RR, 1.57; 95% CI: 1.51–1.62). In case of the metastatic CaP variant – a statistically significant reduction in the detection of this type of cancer was demonstrated (RR, 0.70; 95% CI: 0.60–0.82) [16].

In Lumen 2012, the authors referred to 7 large studies taking into account population screening using PSA measurements. A meta-analysis based on 7 RCTs showed a statistically significant effect of population screening compared to non-screened subjects on increasing CaP detection by 55% (RR, 1.55; 95% CI: 1.17–2.06). The diagnostic threshold of PSA concentration in the studies included in the meta-analysis ranged between 2.5 and 10 ng/ml [19].

The characteristics and results of individual studies included in the review are presented in table I.

Death due to CaP

As part of the Paschen 2021 meta-analysis based on 4 RCTs, a statistically significant reduction in the risk of death due to CAP was demonstrated when participating in the screening using PSA concentration measurement with a diagnostic threshold <4 ng/ml (IRR, 0.68; 95% CI: 0.51–0.89) and a statistically insignificant reduction of said risk when establishing

Table I. Characteristics and individual test results concerning CaP detection

Author/ year	N research	Population, n	PSA diagnostic threshold (ng/ml)	End point	RR/IRR result (95% CI)
Ilic 2018 (MA)	4 RCT	males aged 50–74, 675 232	≥3.0	CaP incidence rate	IRR = 1.23 (1.03–1.48)
	3 RCT	men aged 50–74, 647 751		detectability of CaP in stage I or II	RR = 1.39 (1.09–1.79)
	3 RCT	men aged 50–74, 647 751		detectability of CaP in stage III or VI	RR = 0.85 (0.72–0.99)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 50–69, 408 825	3.0	CaP detectability	RR = 1.19 (1.14–1.25)
	1 RCT (PLCO 2017)	men aged 55–74, 76 683	4.0		RR = 1.12 (1.07–1.17)
	1 RCT (ERSPC 2014)	men aged 50–74, 181 999	2.5–4.0		RR = 1.57 (1.51–1.62)
				detectability of the metastatic variant of the CaP	RR = 0.70 (0.60–0.82)
Lumen 2012 (MA)	7 RCT	men aged 45–74, 525 108	2.5–10.0	CaP detectability	RR = 1.55 (1.17–2.06)

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio; IRR – incidence risk ratio

a PSA test threshold of ≥4 ng/ml (IRR, 0.95; 95% CI: 0.86–1.05). In addition, a meta-analysis based on 11 RCTs showed that screening using PSA concentration measurement statistically significantly reduces the number of deaths due to CaP over a 16-year perspective by 3 deaths/1000 people (3; 95% CI: 1–5 /1000) and reduces the number of CaP progressions to the metastatic variant in the next 12 years by 3/1000 people (3; 95% CI: 2–4/1000) [15].

The 2018 Ilic meta-analysis based on 4 RCTs did not show a statistically significant effect of screening with PSA concentration measurement on CaP mortality (IRR, 0.96; 95% CI: 0.85–1.08) [17].

The 2018 Fenton meta-analysis considered the conclusions of the 3 RCT evaluation. Two studies (CAP 2018, PLCO 2017) showed no statistically significant effect of PSA screening on the risk of death due to CaP (RR, 0.96; 95% CI: 0.85–1.08; RR, 1.04; 95% CI: 0.87–1.24). In turn, the third study (ERSPC 2014) showed a statistically significant effect of PSA screening on the risk of death from CaP (RR, 0.79; 95% CI: 0.69–0.91) [16].

As part of the Rahal 2016 meta-analysis, the authors took into account 11 RCTs, finding no statistically significant effect of screening using PSA concentration measurement on CaP mortality (RR, 0.89; 95% CI: 0.76–1.04) [18].

The Lumen 2012 meta-analysis based on 7 RCTs did not show a statistically significant effect of population screening using PSA concentration measurement on the reduction of the risk of death due to CaP (RR, 0.88; 95% CI: 0.72–1.06). However, based on 4 RCTs, using the adjusted analysis (studies with: follow-up >8 years; PSA test in the control group <33.3%; compliance in the screening group >75%), a statistically significant effect of

Table II. Characteristics and individual test results concerning death due to CaP

Author/ year	N research	Population, n	PSA diagnostic threshold (ng/ml)	End point	RR/IRR result (95% CI)
Paschen 2021 (MA)	4 RCT	men aged 55–70, 66 832	<4	death due to CaP	IRR = 0.68 (0.51–0.89)*
	4 RCT	men aged 55–70, 199 085	≥4		IRR = 0.95 (0.86–1.05)
Ilic 2018 (MA)	4 RCT	men over 18 years of age with or without lower urinary tract symptoms that would suggest the presence of prostate cancer, 718 258	≥3.0		IRR = 0.96 (0.85–1.08)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 55–74, 418 732	3.0		RR = 0.96 (0.85–1.08)
	1 RCT (PLCO 2017)	men aged 55–74, 84 748	4.0		RR = 1.04 (0.87–1.24)
	1 RCT (ERSPC 2014)	men aged 55–74, 175 758	2.5–4.0		RR = 0.79 (0.69–0.91)*
Rahal 2016 (MA)	11 RCT	men aged 55–69, 302 497	–		RR = 0.89 (0.76–1.04)
Lumen 2012 (MA)	7 RCT	men aged 45–74, 571 594	–		RR = 0.88 (0.72–1.06)

* a statistically significant results
MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio; IRR – incidence risk ratio

population screening using PSA concentration measurement on reduction of the risk of death due to CaP by 24% (RR, 0.76; 95% CI: 0.58–0.98) [19]. The characteristics and results of individual studies included in the review are presented in table II.

Overall mortality

As part of the Ilic 2018 meta-analysis based on 4 RCTs, no statistically significant effect of screening using PSA concentration measurements on overall mortality was demonstrated (IRR, 0.99; 95% CI: 0.98–1.01) [17].

In the Fenton 2018 meta-analysis, none of the 3 RCTs included (CAP 2018, PLCO 2017, ERSPC 2014) showed a statistically significant effect of PSA screening on overall mortality (RR, 0.99; 95% CI: 0.94–1.03; RR, 0.98; 95% CI: 0.95–1.00; RR, 1.00; 95% CI: 0.98–1.02) [16]. The characteristics and results of individual studies included in the review are presented in table III.

Number needed to invite

The Fenton 2018 meta-analysis showed that it was necessary to invite 154 men to the CAP 2018 study (95% CI: 128–192), 84 men to the PLCO 2017 study (95% CI: 59–144) and 26 men to the ERSPC 2014 study (95% CI: 24–29) to diagnose one additional case of CAP in men [16]. The characteristics and results of the Fenton 2018 study regarding number needed to invite (NNI) are presented in table IV.

Safety

Some of the found scientific publications (n = 4) refer to the results of the ERSCP, PLCO and/or CAP studies, which analysed the effectiveness of population screening for CaP and the side effects resulting from this type of screening (Paschen 2021, Fenton 2018, Ilic 2018, Lumen 2012). Based on the above-mentioned study, the authors analysed: the frequency of false-positive results, the rate of over-detection, as well as the percentage and consequences of prostate biopsies based on the PSA result [15–17, 19].

False Positive Results

In PLCO 2017, 10.4% of men had at least 1 false positive PSA test result of all participants who underwent at least 1 PSA test in the first 4 (out of 6 cycles) screening tests (n/N = 3387/32 567). In turn, in the ERSPC 2014 study, 17.8% of men received at least 1 false positive PSA test result among all participants who were tested at least once in one of the 5 centres (n/N = 10 965/61 604).

Over-detection

Depending on the method of measuring over-detection, the percentage of over-detection ranged from 16.4 to 20.7% in the PLCO 2017 study and from 33.2 to 50.4% in the ERSPC 2014 study. In the CaP 2018 study, the over-detection rate was 40.7%

Biopsy based on PSA result

In the PLCO 2017 study, 12.6% of men underwent at least 1 biopsy (6295 biopsies in total) in all PLCO screening cycles (16.4 biopsies/ 100 men assigned to screening). Of the men subjected to biopsy, 2% experienced complications such as infection, bleeding, or difficulty urinating (n/N = 97/4861).

Table III. Characteristics and individual test results concerning all-cause mortality

Author/ year	N research	Population, n	End point	RR/IRR result (95% CI)
Ilic 2018 (MA)	4 RCT	men over 18 years of age with or without lower urinary tract symptoms that would suggest the presence of prostate cancer, 718 258	general mortality	IRR = 0.99 (0.98–1.01)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 55–74, 418 732		RR = 0.99 (0.94–1.03)
	1 RCT (PLCO 2017)	men aged 55–74, 84 748		RR = 0.98 (0.95–1.00)
	1 RCT (ERSPC 2014)	men aged 55–74, 175 758		RR = 1.00 (0.98–1.02)

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio; IRR – incidence risk ratio

Table IV. Fenton 2018 results for number needed to invite (NNI)

Author/year	N research	Population, n	End point	NNI score (95% CI)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 55–74, 418 732	NNI	NNI = 154 (128–192)
	1 RCT (PLCO 2017)	men aged 55–74, 84 748		NNI = 84 (59–144)
	1 RCT (ERSPC 2014)	men aged 55–74, 175 758		NNI = 26 (24–29)

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; NNI – number needed to invite

In the ERSPC 2014 study, the biopsy rate among men randomized for screening was 27.7 biopsies/100 men. In CaP 2018, 7.3% of participants (n/N = 71/977) and 5.5% of participants (n/N = 54/981) experienced moderate or severe pain and moderate or severe fever within one month of biopsy, respectively.

In the PLCO 2017, ERSPC 2014 and CaP 2018 studies, prostate cancer, based on the performed biopsy, was not confirmed in 67.7%, 75.8% and 60.6% of the participants of the respective studies. Moreover, there was no statistically significant relationship between the biopsy performed and the reduction of the risk of death (ERSPC 2014, PLCO 2017).

Discussion

Based on the results of the research found in the systematic review, the clinical effectiveness of PSA testing in the early detection of prostate cancer was assessed.

The results of most of the evidence found indicate an increase in the detection of CaP by screening with PSA measurement [16, 17, 19]. In the case of stage III or IV tumours [17] and the metastatic CaP variant [16], a statistically significant reduction in tumour detection was demonstrated. Some of the evidence found indicates the occurrence of adverse effects resulting from screening based on the PSA test [15–17, 19]. Most of the scientific evidence indicates a statistically insignificant effect of PSA screening on the risk of death due to CaP [15, 16, 19] – at the diagnostic threshold of ≥4 ng/ml.

For the purposes of discussion, the current clinical practice guidelines for PSA testing were reviewed. The most important conclusions of the recommendations are presented below.

The recommendations of the Polish Society of Clinical Oncology from 2013 [25] indicate that the population screening for the diagnosis of CaP at an early stage (clinically asymptomatic) is based on the determination of serum PSA levels. The target PSA concentration values for the presence of CaP are 4.0 ng/ml. However, even in the case of lower PSA values, it is not possible to completely exclude the probable presence of this tumour. It should be noted that the Paschen 2021 meta-analysis showed a statistically significant reduction in the risk of death due to CaP with a diagnostic threshold of <4 ng/ml.

The Polish Society of Urology in 2011 [26] indicated that despite the lower risk of death due to CaP, screening tests using the PSA measurement determine a high probability of false positive results.

The American Cancer Society (ACS 2021) [12] recommends that men should be given the opportunity to make an informed decision about undergoing screening for CaP, with the support of their physician. After being informed about the possibility of screening, adjusted to age of the patient, men who wish to undergo screening tests should have their blood tested for the presence of a prostate specific antigen.

The National Comprehensive Cancer Network (NCCN 2021) [13] emphasizes the role of patient education in recognizing and distinguishing the symptoms of lower urinary tract diseases caused by benign prostatic hyperplasia. Measurement of the concentration of prostate-specific antigens should be offered to men aged 45–75 years who have received all the necessary information about the test and are in good health. Recommendations based on expert consensus suggest that PSA measurement should be offered to men over 75 years of age without or with a small number of comorbidities. In addition, it is not recommended to measure men who will not benefit from having prostate cancer detected (PSA testing should only be offered to men with a life expectancy ≥10 years).

The European Society for Medical Oncology (ESMO 2020) [27] does not recommend PSA-based screening. The organisation emphasises that measuring PSA levels contributes to the reduction of mortality, but the disadvantage is over-detection and unnecessary treatment of men with false-positive results. In addition, the recommendations indicate that an early PSA measurement may be offered to men over 50 and over 40 with a family history of CaP, African-Americans of more than 45 years of age, and carriers of the *BRCA1/2* mutation above 40 years of age.

According to the US Preventive Services Task Force Recommendation Statement (USPSTF 2018) [28], the decision to conduct PSA testing in men aged 55–69 should be made individually. Experts emphasize that the benefits of screening PSA tests are small, while the harm is significant, such as frequent over-detection, unnecessary treatment or false positive results determining the need for further diagnostics. In addition, it has been shown that screening based on PSA levels for men >70 years is not recommended.

Limitations

In this review only publications in English are included. The search has been limited to publications from the last 10 years (July 27, 2011–July 27, 2021). The studies included in the secondary scientific evidence found covered a diverse population in terms of ethnicity and geography. Also evidence were characterized by high heterogeneity (including various methods of presenting the analysed data).

Conclusions

The authors of included studies indicated an increase in the detection of CaP during PSA screening tests, with no effect on the reduction of the risk of death due to prostate cancer. Screening in the opportunistic variant aimed at prostate cancer with the use of PSA concentration is justified in men between 50 and 69 years of age, and in men above 50 years of age with additional risk factors.

It seems unreasonable to conduct population screening based on the measurement of PSA concentration due to frequent over-detection, unnecessary treatment or false-positive results necessitating further diagnosis.

Conflict of interest: none declared

Jakub Świtalski
Medical University of Warsaw
Faculty of Health Sciences
Department of Health Economics and Medical Law
ul. Ciołka 27
01-445 Warszawa, Poland
e-mail: jakub.switalski@wum.edu.pl

Received: 19 Jan 2022
Accepted: 22 Feb 2022

References

1. Krzemieniecki K, Krzakowski M. Selected issues of clinical oncology. In: Polesek M. ed. Interna Szczeklik. LSC Communications Europe Sp. zoo, Kraków 2017: 2330–2332.
2. Stelmach A, Potemski P. Neoplasms of the urogenital system. In: Krzakowski K, Warzocha K. ed. Recommendations for diagnostic and therapeutic treatment in malignant neoplasms - 2013. Via Medica, Gdańsk 2013: 335–351.
3. Cuzick J, Thorat M, Andriole G, et al. Prevention and early detection of prostate cancer. Lancet Oncol. 2014; 15(11): e484–e492, doi: 10.1016/s1470-2045(14)70211-6, indexed in Pubmed: 25281467.
4. The prostate gland. National Cancer Registry. http://onkologia.org.pl/rak-gruczolu-krokowego/ (12.2021).
5. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
6. European Cancer Information System. European Commission. https://ecis.jrc.ec.europa.eu/explorer.php?$0-0$1-AEE$4-1$3-All$6-0,85$5-2020,2020$7-7$2-All$CEstByCancer$X0_8-3$CEstRelativeCanc$X1_8-3$X1_9-AE27$CEstBySexByCancer$X2_8-3$X2_-1-1 (02.2022).
7. Didkowska J, Wojciechowska U, Olasek P, et al. Malignant neoplasms in Poland in 2019. http://onkologia.org.pl/wp-content/uploads/Nowotwory_2019.pdf (02.2022).
8. Institute for Health Metrics and Evaluation, GBD Results Tool: Prostate Cancer. https://vizhub.healthdata.org/gbdcompare/ (12.2021).
9. On-line reports database. National Cancer Registry. http://onkologia.org.pl/rak-gruczolu-krokowego/ (02.2022).
10. Krzysztofiak T, Majewski W. The efficacy of radical radiotherapy for patients with primarily diagnosed prostate cancer with metastases to regional lymph nodes. Nowotowry J Oncol. 2018; 68(5-6): 253–258, doi: 10.5603/NJO.2018.0040.
11. Krzemieniecki K, Krzakowski M. Selected issues of clinical oncology. In: Polesek M. ed. Interna Szczeklik. LSC Communications Europe Sp. zoo, Kraków 2017: 2330–2332.
12. American Cancer Society Recommendations for Prostate Cancer Early Detection 2021. American Cancer Society. https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/acs-recommendations.html (12.2021).
13. Carroll PR, Parsons JK, Box G, et al. NCCN Guidelines Version 1.2021. Prostate Cancer Early Detection. https://www.cancer.org/cancer/prostate-cancer/detection-diagnosisstaging/acs-recommendations.html (12.2021).
14. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration in London 2011.
15. Paschen U, Sturtz S, Fleer D, et al. Assessment of prostate-specific antigen screening: an evidence-based report by the German Institute for Quality and Efficiency in Health Care. BJU Int. 2022; 129(3): 280–289, doi: 10.1111/bju.15444, indexed in Pubmed: 33961337.
16. Fenton JJ, Weyrich MS, Durbin S, et al. Prostate-Specific Antigen-Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018; 319(18): 1914–1931, doi: 10.1001/jama.2018.3712, indexed in Pubmed: 29801018.
17. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ. 2018; 362: k3519, doi: 10.1136/bmj.k3519, indexed in Pubmed: 30185521.
18. Rahal AK, Badgett RG, Hoffman RM. Screening Coverage Needed to Reduce Mortality from Prostate Cancer: A Living Systematic Review. PLoS One. 2016; 11(4): e0153417, doi: 10.1371/journal.pone.0153417, indexed in Pubmed: 27070904.
19. Lumen N, Fonteyne V, De Meerleert G, et al. Population screening for prostate cancer: an overview of available studies and meta-analysis. Int J Urol. 2012; 19(2): 100–108, doi: 10.1111/j.1442-2042.2011.02912.x, indexed in Pubmed: 22103653.
20. Martin R, Donovan J, Turner E, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality. JAMA. 2018; 319(9): 883–895, doi: 10.1001/jama.2018.0154, indexed in Pubmed: 29509864.
21. Andriole GL, Crawford ED, Grubb RL, et al. PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009; 360(13): 1310–1319, doi: 10.1056/NEJMoa0810696, indexed in Pubmed: 19297565.
22. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017; 123(4): 592–599, doi: 10.1002/cncr.30474, indexed in Pubmed: 27911486.
23. Schröder FH, Hugosson J, Roobol MJ, et al. ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009; 360(13): 1320–1328, doi: 10.1056/NEJMoa0810084, indexed in Pubmed: 19297566.
24. Schröder F, Hugosson J, Roobol M, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014; 384(9959): 2027–2035, doi: 10.1016/s0140-6736(14)60525-0, indexed in Pubmed: 25108889.
25. Stelmach A, Potemski P, Borówka A, et al. Neoplasms of the genitourinary system. http://www.onkologia.zalecenia.med.pl/pdf/zalecenia_PTOK_tom1_07_Nowotwory_ukladu_moczowo-plciowego_20130301.pdf (12.2021).
26. Heindenreich A., Bolla M., Joniau S. et al. Guidelines for the management of patients with prostate cancer. https://pturol.org.pl/Image/files/Guidelines%20WYTYCZNE%20rak%20stercza.pdf (12.2021).
27. Parker C, Castro E, Fizazi K, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020; 31(9): 1119–1134, doi: 10.1016/j.annonc.2020.06.011, indexed in Pubmed: 32593798.
28. Grossman DC, Curry SJ, Owens DK, et al. US Preventive Services Task Force. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018; 319(18): 1901–1913, doi: 10.1001/jama.2018.3710, indexed in Pubmed: 29801017.

VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 174–183
DOI: 10.5603/NJO.a2022.0024

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Immunological aspects of heat shock protein functions and their significance in the development of cancer vaccines

Iryna Boliukh[1], Agnieszka Rombel-Bryzek[1], Barbara Radecka[2, 3]

[1]*Department of Clinical Biochemistry and Laboratory Diagnostics, Institute of Medical Sciences, University of Opole, Opole, Poland*
[2]*Department of Oncology, Institute of Medical Sciences, University of Opole, Opole, Poland*
[3]*Department of Clinical Oncology, Tadeusz Koszarowski Cancer Centre in Opole, Opole, Poland*

The primary function of intracellular heat shock proteins (HSPs) is to protect the cell by suppressing the effects of various stress factors by either refolding misfolded proteins or blocking apoptosis. After neoplastic transformation, cells overexpress HSPs, which act as factors promoting the neoplastic process by stabilizing proteins responsible for carcinogenesis, however, HSPs can be released into the extracellular environment where they act as important modulators of the immune response. In a tumor microenvironment, extracellular HSPs are able to induce a pro- or anti-neoplastic response, using various mechanisms of affecting immune cells, The study of the role of extracellular HSPs in immunomodulation processes is a very important direction in the search for new methods of cancer treatment. This review summarizes reports on the use of HSPs in immunotherapeutic cancer strategies, in particular in cancer vaccine design.

Key words: heat shock proteins, cancer immunotherapy, vaccine

Introduction

The research conducted so far confirms the importance of heat shock proteins (HSPs) in such oncological processes as cell proliferation, infiltration and metastasis. Heat shock proteins are receiving increased attention as potential therapeutic targets. The success of anti-cancer treatment depends on the level of the body's immune protection. Heat shock proteins affect the balance between protective and destructive immune responses in the tumor microenvironment, hence the concept of using HSPs in cancer immunotherapy and designing cancer vaccines.

The innate and adaptive immune system is essential for the effective recognition and removal of neoplastic cells in the process of immune surveillance. Many previous studies have demonstrated the importance of natural killer (NK) cells, natural killer T-cells (NKT), eosinophils, αb and γδ T- and B-lymphocytes in immune surveillance [1, 2]. Studies on animal models have shown that mice deprived of any of the above-mentioned immune cell populations showed an increased susceptibility to methylcholanthrene-induced sarcomas [1].

Chemical mediators such as IFN 1, IFN-γ, IL-12, and TNF-α are equally important. In patients with immunosuppression caused by, for example, acquired immunodeficiency syndrome (AIDS), transplantation or even old age, cancer incidence is several times higher than in patients with normal immunity [3]. Kaposi's sarcoma (KS) is a neoplasm that defines the diagnosis of AIDS, as the likelihood of developing KS in people with AIDS is 175–400 times higher. Before the AIDS epidemic, the incidence of this type of sarcoma was

How to cite:

Boliukh I, Rombel-Bryzek A, Radecka B. ***Immunological aspects of heat shock protein functions and their significance in the development of cancer vaccines.*** *NOWOTWORY J Oncol* 2022; 72: 174–183.

not higher than two per million people. The second most frequently diagnosed AIDS-related cancer is non-Hodgkin's lymphoma, which is 73 times more common in these patients than in the average population [4].

The role of HSPs in immune processes associated with cancer

Tumor recognition by the immune system is based on the expression of mutant proteins and tissue-specific antigens by the neoplastic cells, as well as overexpression of tumor-associated antigens (TAAs). One of the key factors enabling the development of a neoplastic process in the body is the tumor's ability to avoid immunological detection. This effect is achieved through:

- suppression of the major histocompatibility complex (MHC) class I expression on the neoplastic cell surface
- loss or alteration of TAA expression by neoplastic cells
- inhibition of the mechanisms of cancer cell-specific antigen recognition
- local expression of inhibitory immune molecules such as transforming growth factor (TGF) – β and Fas-ligand [5].

Given this, it is clear why scientists are interested in increasing the potential and specificity of the anti-cancer immune response.

The development of the neoplastic process is accompanied by changes in the structure and function of protein complexes and individual molecules. Protein functions are determined by its conformation (spatial structure), which depends on the functioning of heat shock proteins – molecular chaperones or stress proteins – highly conserved specialized proteins responsible for the correct folding of proteins and preventing their unwanted aggregation. HSPs help transport proteins into the cells across the membranes. HSP-molecular chaperones interact with proteins in equal amounts (stoichiometrically), therefore a huge amount of HSPs are synthesized at the time of cellular stress, forming complexes with cellular proteins. In the process of neoplastic transformation, the cell experiences oxidative stress and nutrient deficiency. We observe high expression of mutated cancer-specific proteins that have a destructive effect on the processes of cell proliferation, growth and death. This leads to high expression of HSPs [6]. Thus, intracellular HSPs play the role of cancer promoters, stabilizing the altered conformation of mutant proteins responsible for carcinogenesis [7].

Stress conditions in a tumor lead to necrotic lysis of neoplastic cells accompanied by the release of HSP-peptide complexes (HSP complexes with cellular proteins) into extracellular space. Detection of HSPs in the extracellular environment suggests that HSPs perform functions other than just that of intracellular chaperones. A large number of immune cells concentrate around the site of necrosis. It has been noticed that HSP-peptide complexes, including complexes with neoplastic peptides, can be taken up by antigen presenting cells (APC) through endocytosis [8]. The absorption of the HSP70-peptide complex by APC with the participation of LOX-1, FEEL-1 and SREC-1 receptors was reported [9]. Absorbed peptides are processed by APC and participate in antigen cross-presentation. After processing, antigenic epitopes in the form of complexes with MHC class I and II are presented to T lymphocytes [10]. This results in the activation of cytotoxic T lymphocytes (CTL), which induces a cytotoxic response, and of helper T cells (Th), which, in turn, activate B lymphocytes to induce humoral response.

HSPs can be released into the extracellular space not only during necrotic disintegration, but can also be secreted in the form of extracellular milieu HSP (EX-HSP), membrane-associated HSP (mHSP) and extracellular vesicle HSP (EV-HSP) [11]. Extracellular HSPs interact with immune cells, and these interactions may have suppressive or stimulating effects [12]. The general conclusion that can be drawn from the data presented so far is that the effect of HSPs on tumor growth depends on the mechanism of their release into the extracellular space. HSPs released into the extracellular space by tumor cells in result of cellular exocytosis may have an immunosuppressive effect. They lead to immune tolerance and anergy of immune cells, creating a favorable microenvironment for invasive growth and proliferation of neoplastic cells [13, 14].

HSP60 secreted as extracellular milieu (EX-HSP60) shows immunosuppressive properties, especially in relation to CTL, participating in the increase of CD4(+), CD25 and Foxp3 cell population. It also stimulates mononuclear cells to induce the production of anti-inflammatory cytokines such as IL-10 and IL-6 by CD4(+) T lymphocytes. CD4(+) T lymphocytes stimulated in this way demonstrate immunosuppressive properties [15, 16]. It has also been established that HSP60, acting through the TLR4 receptor, stimulates B lymphocytes to secrete IL-10 and IL-6 and also stimulates the proliferation of B-lymphocytes, which acquire the ability to stimulate T lymphocytes to secrete IL-10 and TNF-α [17]. HSP60 may also induce the production of TNF-α by macrophages, promote metastatic processes through the interaction with β-catenin and enhance the transcriptional activity of cells [18].

HSP27 secreted into the extracellular space induces the differentiation of monocytes into immunotolerant macrophages. The latter produce anti-inflammatory mediators, thrombospontin-1 and IL-10, which can induce the anergy of T lymphocytes. Macrophages also demonstrate pro-angiogenic activity and participate in the formation of new blood vessels, which is one of the conditions for tumor progression [6].

Extracellular HSP70 (EX-HSP70) inhibits TNF-α-induced IL-6, IL-8 and MCP-1 production, and also inhibits the maturation of dendritic cells (DC) and cytokine secretion [19]. Furthermore, EX-HSP70 can reduce the T lymphocyte response independently of the stimulatory effect of DCs.

In most cases, extracellular vesicle HSP (EV-HSP) also exerts immunosuppressive effects. EV-HSP72 stimulates myeloid-

derived suppressor cells (MDSC) and induces their suppressive activity dependent on the Stat3 pathway [13]. The immunosuppressive activity of MDSC is manifested by the secretion of IL-10, the involvement of regulatory T lymphocytes (Treg) and inhibition of CD4(+) and CD8(+) T lymphocytes.

However, the presence of HSPs in the extracellular space, especially as a result of necrotic or apoptotic tumor cell death, including destruction induced by chemotherapy or radiation therapy, may result in pro-inflammatory activation of immunocytes in both the tumor microenvironment and the entire immune system, thereby inhibiting tumor growth and metastasis. Acting as endogenous signaling factors, HSPs facilitate the functional maturation of APCs – dendritic cells and macrophages – which enhance the expression of MHC molecules and activate adaptive immune responses.

It should be pointed out that the role of EV-HSP in immunological processes is ambiguous, as they may also exhibit immunostimulatory properties (e.g. EV-HSP70 may induce chemotaxis of NK cells and enhance their cytolytic function) [20]. The immunostimulatory effect was also observed in relation to mHSP, for example mHSP70, which is able to activate the production of TNF-α by macrophages and the cytolytic activity of NK [21].

The immunostimulatory properties of HSP have been studied to establish their possible use in the development of anti-cancer therapies. The first publications describing HSPs as immune regulatory molecules appeared in the 1980s. It was shown that gp96 is a carrier of TAA acting as a TAA transporter [22]. The gp96 protein in combination with tumor antigens can stimulate immune response against the tumor cells it has been isolated from. A similar ability to enhance anti-tumor immunity has been demonstrated for HSP70 and HSP90 combined with tumor peptides [23].

Several examples of the immunostimulatory effects of HSPs have been described. Extracellular HSP70 activates NK and, in particular through the CD94 receptor, stimulates their proliferation and specific migration [24, 25]. HSPs located on the surface of neoplastic cells increase their sensitivity to NK. Increased lysis of cells under the influence of NK was observed in osteosarcoma and breast cancer expressing HSP70 on the cell membrane surface [27]. When interacting with CD91, CD14, TLR4 receptors on the surface of APC, HSPs are able to induce the production of pro-inflammatory cytokines (IL-1, IL-6, IL-12, TNF). Moreover, HSPs as molecular chaperones, are capable of binding TAA and these complexes may be presented by APCs, including DCs, through MHC I and II molecules. This leads to the anti-tumor activation of CD8(+) and CD4(+) T lymphocytes, stimulation of macrophages and NK cells, as well as activation of B lymphocytes [27]. HSPs are able to stimulate the maturation and migration of DCs. In this case, they can act "independently" without forming complexes with peptides or using ATP energy, i.e., acting not only as a chaperon but also having a cytokine-like function [28, 29].

Receptor-mediated HSPs have been observed to stimulate the maturation of CD11c + DCs that enhance MHC class II expression. In addition to increased MHC class II expression, HSP-activated DCs have been found to exhibit increased CD86 expression and TNF-α and IL-12 production [30]. Moreover, nitric oxide is released by dendritic cells and macrophages during the stimulation of HSPs, namely gp96 and HSP70, which in turn leads to a cytolytic or cytostatic effect on neoplastic cells *in vivo* [31]. Chemoattraction of DC and T lymphocytes in tumors following the exposure to hyperthermia leads to the release of HSP70. It was found that DCs are activated upon contact with HSP70 released from tumor cells and that this activation is dependent on TLR4 [32]. This demonstrates the ability of endogenous heat shock proteins to stimulate DCs *via* TLR4.

As chaperones, HSPs can bind to specific receptors on DCs, contributing to the cross-presentation of their peptides [33]. Typically, the antigen interaction with APC, especially DCs, leads to its presentation in the complex with MHC class II and its subsequent recognition by helper T lymphocytes (CD4(+)) in lymph nodes. The mechanism of antigen cross-presentation lies in the ability of DCs to process and present the antigen by means of MHC class I molecules. The MHC I-antigen complex is recognized by the CD8(+) T lymphocyte receptor and activates these cells to differentiate into mature cytotoxic T lymphocytes. HSPs have the ability to bind to antigenic peptides present on tumor cells and stabilize their conformation by forming permanent complexes with them (HSP-TAA).

SRECI and LOX-1 are the two most important DC receptors that allow the cross-presentation of HSP-TAA complexes. SRECI binds to a wide variety of HSPs (HSP60, HSP70, HSP90, HSP110, gp96 and GRP170), while LOX-1 binds mainly to HSP60 and HSP70 [34]. The interaction of the HSP-TAA and MHC class I complex with the immature CD8(+) T lymphocyte receptor leads to the activation of the latter. Activated CD8(+) T lymphocytes acquire cytotoxic properties, and therefore may induce apoptosis of tumor cells in which the aforementioned HSP-TAA complexes have been formed. Cross-presentation of peptides plays an important role in immune surveillance as the bound peptide is not only protected from degradation but the efficiency of cross-presentation in DCs is also higher. Moreover, some neoplastic cells express very little neoantigens, which limits the possibility of their presentation. Thus, cross-presentation of the HSP-peptide complex widens the range of complexes available as targets for the immune system (fig. 1).

There is also a known phenomenon of the reduction of surface molecules of the MHC class I presentation pathway in neoplastic cells, which can be used as a protective mechanism in tumor proliferation. It has been demonstrated to restore the presentation of MHC class I molecules on the cell surface after transfection with human HSP70. B16 melanoma cells with primary presentation deficiency have thus become available for recognition by CTL.

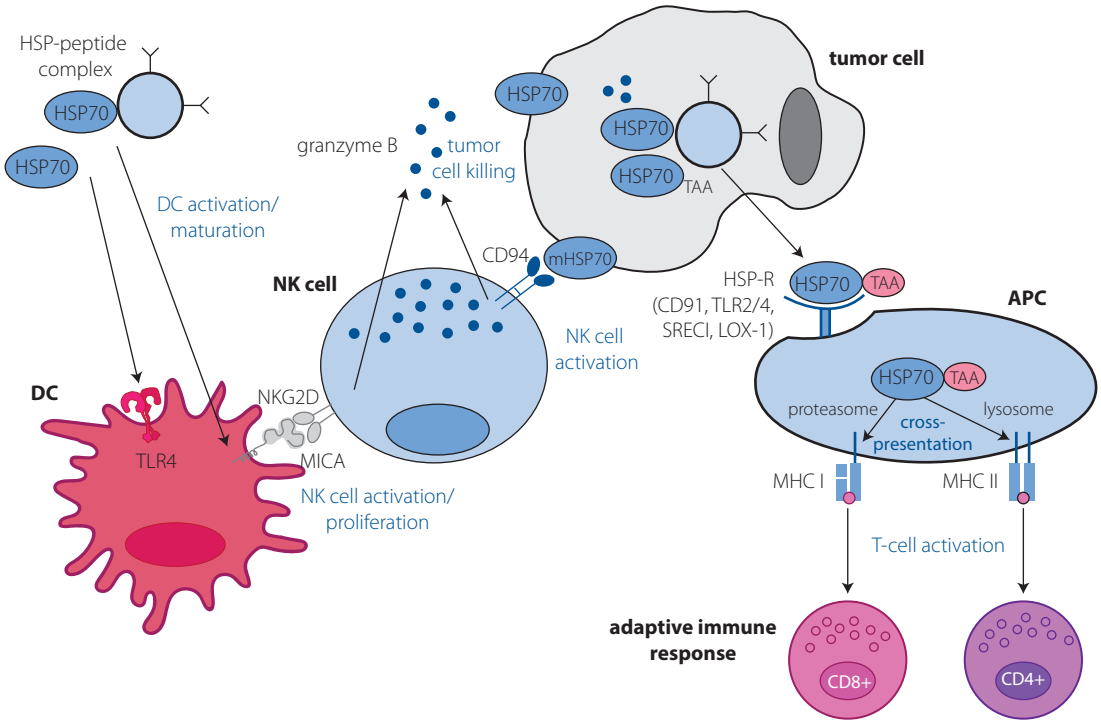

Figure 1. Antitumor immunomodulatory role of extracellular HSP70 (EX-HSP70) – [35] with modification

EX-HSP70 complexes with TAAs allowing them to be taken up by APC *via* CD91 (or other uptake receptors). EX-HSP70 provides a cross-presentation of TAA on MHC class I or II molecules, and promotes a signal cascade that activates CD8(+) and CD4(+) T lymphocytes. mHSP70 provides specific stimulation of NK-cells through the CD94 receptor. EX-HSP70 stimulates NK cells indirectly through the MICA receptor on NK cells, which binds to the NKG2D activation receptor. Activated NK cells increase the release of granzyme B, which triggers the process of perforin-independent apoptosis of cells by binding to the neoplastic mHSP70. Through binding to the TLR4 receptor of dendritic cells, EX-HSP70 stimulates their maturation and increases the expression of MICA, which, in this case, is a ligand for NKG2D

We can therefore say that the HSP-TAA complex contains not only a tumor associated antigen capable of stimulating specific immune response, but also an immunoadjuvant (in this case HSP) which is responsible for stimulating nonspecific immunity. This makes the HSP-TAA complexes very promising objects for their use in the design of cancer vaccines [5]. Moreover, cross-presentation of antigens in a complex with HSP derived from a tumor of a certain haplotype, has the ability to initiate CTL upon administration of the second haplotype to the recipient [36]. This broadens the arsenal of possible tools in the technology of designing immunological cancer treatments.

Immunological cancer treatment strategies

The search for methods of enhancing the immune response to TAA is a very dynamic area of contemporary research in oncology. The immunotherapeutic strategies developed so far can be divided into non-specific and specific. The main goal of the former is the nonspecific activation of immune responses by means of cytokines such as IL-2 [37–39], or by means of immune checkpoint inhibitors – anti-CTLA4 or anti-PD-1 drugs. Specific immunotherapy strategies can be classified as passive and active. Passive immunotherapy includes the use of:

- monoclonal antibodies against neoplastic antigens, e.g., trastuzumab [40],
- adaptive cell therapy, i.e., the transfer of *ex vivo* activated tumor infiltrated lymphocytes (TILs), and chimeric antigen receptors (CARs) [41, 42].

Cancer vaccines provide an example of active immunotherapy [43]. The main strategy of cancer vaccine design is to identify immune response targets (TAAs), to create immunogenic forms and conditions for the recognition of such antigens, and to induce proliferation and increase the activity of immunocompetent cells. Cancer vaccines can be divided into three main groups:

- cell vaccines based on the use of the whole or lysed autologous or allogeneic tumor cells and DCs modified by various *in vitro* or *in vivo* methods,
- peptide vaccines based on the identified tumor antigens; they are autologous, recombinant or synthetic vaccines based on peptides, heat shock proteins,
- genetic vaccines – this method consists in introducing DNA sequences coding for the tumor antigen to the patient.

All of these strategies have been and continue to be extensively researched and have their advantages and disadvantages. The effectiveness of the treatment depends not

only on the specific medicinal preparation but also on the method of administration, dose, number of repeats as well as the nature of the TAA itself. The strategy for using cellular vaccines is to administer autologous APC preparations that act as immune activators through antigen presentation by MHC class I and II. Dendritic vaccines provide an example of this type of therapy. During treatment with dendritic cells, monocytes are removed from the patient's blood, forced to differentiate into dendritic cells that "get acquainted" with the antigens isolated from that patient's tumor, and are then introduced into the body. Dendritic cells present TAA to cytotoxic T lymphocytes and activate them to fight cancer. Increased interest in these type of vaccines appeared after the approval of the first active cancer vaccine "Sipuleucel-T" in the treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer [44]. Other approaches in cell vaccine design involve the use of whole tumor cells of autologous or heterologous origin that are pre-devitalized. In the future, they will act as immunogenic targets to stimulate specific and innate anti-tumor immunity. This vaccine provides the immune system with all potential tumor antigens in every individual patient. Another advantage of this approach is that tumor antigens and their epitopes and presentation methods do not require identification. However, these vaccines suffer from a number of disadvantages, including the difficulty of obtaining enough tumor tissue for sustained therapy and the tolerance to the patient's "own" tumor antigens of patient's immune system.

Another type of cancer vaccine consists in protein or peptide vaccines, based on the use of native antigens or specific antigen epitopes, the introduction of which stimulates an immune system response in the form of a cascade of reactions, which leads to the targeted lysis of tumor cells. These proteins/peptides induce T lymphocytes by their presentation in a complex with MHC class II. The use of peptide vaccines in oncological patients is able to activate a specific anti-tumor immune response and is not accompanied by symptoms of toxicity. The disadvantage of this type of vaccine is the lack of the possibility of significant CTL stimulation. Therefore, many protein vaccine design strategies use adjuvants to enhance the immunostimulatory properties of these vaccines.

The basic principle of using genetic vaccines is to introduce mRNA or DNA sequence coding for the neoplastic antigen to the patient [45]. The sequence is placed in a plasmid and controlled by a promoter. When the vaccine is administered, the body cells that have absorbed the DNA synthesize the encoded protein. Then it is transported to the nearest lymph node, where it induces a specific immune response [46]. There are several options for the delivery of genetic vaccines. Viral vector-based cancer vaccines are considered a subtype of genetic vaccines. Viral vectors such as adenoviruses [47], pox or avipox viruses [48], some *herpes* viruses, and the like are used to create viral cancer vaccines. The virus in the vaccine is attenuated and contains a nucleotide sequence encoding the tumor antigen. The advantages of these vaccines include high transgene expression in infected cells, high immunostimulatory capacity and relative ease of production [49]. A drawback of using viral vectors is their ability to elicit an antiviral immune response to the vector. Similar advantages and disadvantages exist when using bacterial vectors, in particular in the case of intracellular bacteria *Listeria monocytogenes* [50]. This type of vaccine allows the attraction of the endogenous presentation of the encoded antigens by MHC class I. Stimulation of the CTL *via* the endogenous presentation pathway is a very desirable feature of active anti-cancer therapy since a stable CTL response is essential for anti-tumor immunity. HSPs are used as antigens, chaperones or adjuvants of DNA or peptide based vaccines [51]. It has been demonstrated that specific immunostimulation is induced for a wide range of antigens (including HER2/neu, mucin-1, E7, AFP, MAGE-3, gag, survivin and PSCA) with HSP70-mediated DNA vaccines [52–54].

Despite the significant anti-tumor activity of various immunotherapeutic strategies demonstrated in preclinical studies, the efficacy required in the drug registration processes has not been obtained. Research is still ongoing. The involvement of immunologically active HSPs is one of the investigated cancer immunotherapy strategies.

Design and application of vaccines based on HSP

Research on the use of anti-cancer properties of HSPs began in the mid-1980s [55]. The first trials involved vaccinating mice with attenuated tumor cells [56]. This enabled immune reaction against live cancer cells, but only in relation to allogeneic neoplasms. In the next stage, researchers started searching for molecules in neoplastic cells that may be responsible for the development of immunity. Tumor cell lysates were biochemically fractionated and the individual fractions were tested for their ability to vaccinate mice and generate an immune response against live tumor cells of the same type. It was shown that the fractions capable of inducing an immune response contained HSPs [57, 58]. HSPs obtained from autologous tumor tissue turned out to be associated with tumor-specific antigens, forming the so-called "antigenic imprint" of the tumor. The immunoadjuvant properties of HSPs are based on two mechanisms – the ability to induce an adaptive cytotoxic response of T lymphocytes to TAA in combination with HSPs and non-specific stimulation of immune cells. The development of HSP-based cancer vaccines is based on four main assumptions:

- HSPs obtained from other organisms act as classical foreign antigens, eliciting an immune response against their non-conservative epitopes,
- HSPs are able to elicit an immune response in the case of autologous administration in the absence of tolerance of the host's immune system to them,

- HSPs can cause the development of an immune response against a specific protein in the presence of cross-reactivity between HSPs and the protein,
- HSP-TAA are able to stimulate a specific immune response against the antigens included in the complex, while an immune response to HSPs will not develop.

The last of the described mechanisms determines the direction of the development of HSP-based vaccines that can be used in the prevention and treatment of various conditions, including infectious and neoplastic diseases[59]. Such vaccines were initially demonstrated to be effective in animals (e.g., in the treatment of liver cancer in rats [57]), and in the mid-1990s, studies of HSP-based vaccines were initiated in cancer patients.

The active ingredient in such vaccines is not a single HSP, but HSP-TAA complexes. There are two variants of such vaccines: recombinant cancer vaccines obtained by *ex vivo* formation of a complex using HSP and/or recombinant peptides, and cancer vaccines obtained by isolating HSP-TAA from a patient's tumor tissue that contains a specific tumor antigen set. The use of linked HSP-TAA complexes in the development of vaccines increases the ability of APCs to present TAA through MHC class I and II with subsequent activation of CD8(+) and CD4(+) T lymphocytes.

The ability of HSP or HSP-TAA complexes to induce antitumor immunity is dose dependent. Low doses of HSP-TAA complexes are effective in stimulating an anti-tumor immune response, while high doses do not, and may even be immunosuppressive. High doses of gp96-peptide complexes induce immunological tolerance, hence the attempts to use them in the treatment of autoimmune diseases [60, 61].

Currently, HSPs are being studied as immunostimulatory molecules in various therapeutic models. The promising results have been obtained in animal models of tumor growth. Extracellular HSP70 derived from the L1210 leukemia cell was used to immunize DBA/2 mice. The specific activation of CTL was found, which inhibited the growth of the implanted tumor [62]. These results have been confirmed in animal models of colon cancer and melanoma. An increased expression of HSP70 in the exosomes of the hyperthermically treated tumor cells was detected. The immune response in animals with cancer after the introduction of HSP70-enriched allogeneic exosomes was significantly higher than when using exosomes derived from cells without prior hyperthermia. As a result, increased IgG2a and IFN-γ production and tumor regression were observed [63].

In a study in the J558 myeloma model, the effectiveness of stimulating an anti-tumor immune response with exosomal forms of HSP70 was tested. The J558 myeloma cell line that produced the transgenic form of membranę-bound HSP70 in the exosome (mHSP70-EV) was developed, and the efficacy of these exosomes was tested compared to the exosomes from heat-shocked tumour cells expressing cytoplasmic HSP70. Exosomes released from these cells were used to immunize mice. mHSP70-EV significantly stimulated cytotoxic CD4(+) type 1 (Th1) and CD8(+) T lymphocytes, specifically activated NK cells, which significantly exceeded the effects of HSP70-EV [64].

The ability of NK cells to specific activation and damage mHSP70-positive tumor cells has also been demonstrated in animal models of lung cancer and glioblastoma. Combination therapy consisting of NK cells activated ex vivo with the natural HSP70 peptide (TKD) and a low dose of IL-2 (TKD/IL-2) was demonstrated. The adaptive transfer of TKD/IL-2 *ex vivo* activated murine NK cells resulted in inhibition of tumor growth and improved survival of the animals. This regimen therapy was well-tolerated. The antitumor activity was associated with a massive infiltration with CD8(+) T and NK cells in both tumor models and a decreased in PD-1 expression in immune effector cells [65].

Recent reports concern the use of immunotherapy using recombinant HSP70 in CT-26 Colon cancer and B16 melanoma models. The introduction of recombinant HSP70 to the tumor cel stimulates the transport of endogenous HSP70 to the extracellular space of the tumor, leading to a rapid activation of the immune response. The immunomodulatory effect of HSP70-bearing exosomes was manifested by CD8(+) activation, the accumulation of antitumor cytokines and the activation of NK cells, which had a positive effect on the reduction in tumor growth rate and elevation of life span in mice [66].

Furthermore, HSP70 enriched exosome derived from immune cells may also be of interest in anticancer immunotherapy. Scientists investigated the therapeutic effect of macrophage-derived HSP70 enriched exosome in the WEHI-164 fibrasarcoma model both *in vitro* and *in vivo*. Heat shock has been shown to increase the expression of membrane-bound HSP70 in macrophage-derived exosomes. In addition, the immunization of animals with these exosomes reduces the number of tumor cells, indicating a potential immunoadjuvant role of HSP70 in cancer immunotherapy [67].

In all the above-mentioned studies, the researchers showed that HSPs play an important role in anticancer immunity. At present, achievements in the field of HSP-based oncoimmunology are widely integrated into the phase of clinical trials. A study of the safety and efficacy of the antitumor vaccine based on the HSP-96 peptide complex (HSPPC-96), prepared from tumor specimens of patients with metastatic melanomas, was conducted. Activation of the immune response to HSP-96 related peptides was observed in patients receiving the vaccine weekly for 4 consecutive weeks. The overall survival of patients who showed an immune response was 82%. Moreover, the toxicity of the vaccine was very low [68]. Other studies confirm the effectiveness of the HSP-96 vaccination. Phase I and II clinical trials were conducted to investigate the efficacy of the HSPPC-96 vaccine in patients with recurrent glioblastoma multiforme. The study involved 41 patients. The primary endpoint was overall survival of 6 months. Studies have confirmed that the HSPPC-96 vaccine is safe and deserves further research [69].

Studies have shown that Vitespen, an autologous tumor derived heat shock protein gp96 peptide complex vaccine, has shown positive results in phase III clinical trials in patients with melanoma and renal cell carcinoma. It has been observed that Vitespen elicits a major MHC I mediated immune response in many types of cancer, as well as a clinical response in patients with early stage disease. In addition, the vaccine has a relatively low incidence of side effects [70, 71]. Another study investigated the safety, immunogenicity and clinical efficacy of an autologous vaccine of leukocyte-derived HSP70 peptide complexes in patients with chronic myeloid leukemia. Treatment with the vaccine was performed in conjunction with imatinib mesylate. Clinical responses were observed in 13 of 20 patients and were significantly correlated with the activation of immune responses, including an increase in the frequency of CML-specific IFN-γ producing cells and IFN-γ secreting NK cells. In addition, there were no side effects, indicating the safety of this vaccine [72].

Encouraging results from the phase II vaccine trials, based on a heat shock protein fused to sequences from the oncogenic E7 protein of HPV-16 in woman with high-grade cervical intraepithelial neoplasia was obtained. Four injections of HPV-16 HSP E7 fusion protein were given 3 weeks apart. Complete regression of intraepithelial neoplasia was observed in 35% of women and was correlated with the immune response [73].

DNA-HSP65, a DNA vaccine encoding the 65 kDa heat shock protein *Mycobacterium leprae* (HSP65), was tested in phase I clinical trials of hsp65 DNA in patients with advanced head and neck cancer. 42% of patients showed disease stability or regression following immunization. DNA-HSP65 induced some degree of immunostimulation with no evidence of pathological autoimmunity [74].

Was reported of a phase I clinical trials to evaluate the safety and immunogenicity of a therapeutic human papillomavirus administered to women with HPV-16 + cervical intraepithelial neoplasia (CIN)2/3. In the above study it was applied HPV-16 DNA vaccine [a plasmid expressing a Sig-E7-detox]-heat shock protein 70 fusion protein. Complete histologic regression occurred in 33% individuals. This vaccine was safe and well tolerated [75].

In this study, researchers examined a vaccination strategy using dendritic cells (DC) loaded with apoptotic and necrotic cell bodies derived from autologous tumors. Using this approach, clinical and immunologic responses were achieved in 33% patients with relapsed indolent non-Hodgkin's lymphoma (NHL). The achievement of clinical and immunological response was significantly associated with the degree of surface expression of calreticulin and HSP90 in DC antigenic cargo [76].

Other authors in phase I clinical trials tested a strategy for treating patients with of colon and lung cancer patients, with *ex vivo* heat shock protein 70-peptide-activated, autologous natural killer cells. After stimulation, the activity of NK cells against HSP70 membrane-positive colon carcinoma cells was enhanced in 10 of 12 patients [77].

Activation of CTL against neoplastic cells has been demonstrated through administering dendritic cells transfected with HSP70 mRNA (HSP70-DC) to patients with hepatocellular carcinoma associated with hepatitis C virus [78]. HSP105 peptide vaccines used in patients with colorectal cancer and esophageal cancer showed the ability to induce an immune response in phase I studies [79]. Cellular vaccines, the effect of which is related to overexpression of HSP70, have shown immunostimulatory effects in models of glioblastoma and ovarian carcinoma [80, 81]. Preparations designed with the use of pure HSP70 protein turned out to be active when tested in the B16 glioma and melanoma model [82]. Recombinant chaperones are an alternative source of HSPs for the development of cancer vaccines based on immunogenic peptides. When delivered to the tumor, recombinant HSP70 increases the sensitivity of cancer cells to the cytolytic activity of lymphocytes, reduces the level of immunosuppressive T regulatory cells and lowers the production of IL-10 [83]. The use of HSP70-TAA complexes has an immunostimulatory effect in models of leukemia, lung and ovarian cancer [84]. In addition, HSP70 in complex with antigenic peptides such as the Melan-A, MAGE-A1, tetanus toxin and influenza HA protein has been used to stimulate an antigen-specific immune response [85].

Attempts are also being made to combine HSP70-based vaccines with other anti-cancer drugs, such as immune checkpoint inhibitors, which researchers believe may improve efficacy. Intratumoral HSP70 injections have also been used in conjunction with local hyperthermia, irradiation or cationic magnetite liposomes [86, 87].

Conclusions

In recent years, the potential of HSP as an immunotherapeutic tool has been gaining more and more recognition. The influence of HSPs on the functioning of the immune system, manifested in particular by the activation of dendritic cells, increased activity of T lymphocytes, NK cells and increased antigenic presentation of TAA, allows the use of these proteins as therapeutic targets in oncology, including the development of cancer vaccines. A number of studies have demonstrated the anti-cancer efficacy of HSP-based vaccines, setting directions for further research. It should be noted that the safety and efficacy of cancer vaccines also depend on the route of administration, dose and vaccination schedule. Combining vaccines with other treatments can improve their effectiveness.

Conflict of interest: none declared

Iryna Boliukh
University of Opole
Institute of Medical Sciences
Department of Clinical Biochemistry and Laboratory Diagnostics
ul. Oleska 48
45-052 Opole, Poland
e-mail: iryna.boliukh@uni.opole.pl

Received: 18 Jan 2022
Accepted: 5 Apr 2022

References

1. Smyth MJ, Crowe NY, Godfrey DI. NK cells and NKT cells collaborate in host protection from methylcholanthrene-induced fibrosarcoma. Int Immunol. 2001; 13(4): 459–463, doi: 10.1093/intimm/13.4.459, indexed in Pubmed: 11282985.
2. Simson L, Ellyard JI, Dent LA, et al. Regulation of carcinogenesis by IL-5 and CCL11: a potential role for eosinophils in tumor immune surveillance. J Immunol. 2007; 178(7): 4222–4229, doi: 10.4049/jimmunol.178.7.4222, indexed in Pubmed: 17371978.
3. Derhovanessian E, Solana R, Larbi A, et al. Immunity, ageing and cancer. Immun Ageing. 2008; 5: 11, doi: 10.1186/1742-4933-5-11, indexed in Pubmed: 18816370.
4. Frisch M, Biggar RJ, Engels EA, et al. AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. JAMA. 2001; 285(13): 1736–1745, doi: 10.1001/jama.285.13.1736, indexed in Pubmed: 11277828.
5. Das JK, Xiong X, Ren X, et al. Heat Shock Proteins in Cancer Immunotherapy. J Oncol. 2019; 2019: 3267207, doi: 10.1155/2019/3267207, indexed in Pubmed: 31885572.
6. Banerjee S, Lin CFL, Skinner KA, et al. Heat shock protein 27 differentiates tolerogenic macrophages that may support human breast cancer progression. Cancer Res. 2011; 71(2): 318–327, doi: 10.1158/0008-5472.CAN-10-1778, indexed in Pubmed: 21224361.
7. Calderwood SK, Gong J. Heat Shock Proteins Promote Cancer: It's a Protection Racket. Trends Biochem Sci. 2016; 41(4): 311–323, doi: 10.1016/j.tibs.2016.01.003, indexed in Pubmed: 26874923.
8. Thériault JR, Adachi H, Calderwood SK. Role of scavenger receptors in the binding and internalization of heat shock protein 70. J Immunol. 2006; 177(12): 8604–8611, doi: 10.4049/jimmunol.177.12.8604, indexed in Pubmed: 17142759.
9. Delneste Y, Magistrelli G, Gauchat JF, et al. Involvement of LOX-1 in Dendritic Cell-Mediated Antigen Cross-Presentation. Immunity. 2002; 17(3): 353–362, doi: 10.1016/s1074-7613(02)00388-6, indexed in Pubmed: 12354387.
10. Stocki P, Morris NJ, Preisinger C, et al. Identification of potential HLA class I and class II epitope precursors associated with heat shock protein 70 (HSPA). Cell Stress Chaperones. 2010; 15(5): 729–741, doi: 10.1007/s12192-010-0184-z, indexed in Pubmed: 20358320.
11. Mambula SS, Calderwood SK. Heat shock protein 70 is secreted from tumor cells by a nonclassical pathway involving lysosomal endosomes. J Immunol. 2006; 177(11): 7849–7857, doi: 10.4049/jimmunol.177.11.7849, indexed in Pubmed: 17114456.
12. Pockley AG, Muthana M, Calderwood SK. The dual immunoregulatory roles of stress proteins. Trends Biochem Sci. 2008; 33(2): 71–79, doi: 10.1016/j.tibs.2007.10.005, indexed in Pubmed: 18182297.
13. Chalmin F, Ladoire S, Mignot G, et al. Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. J Clin Invest. 2010; 120(2): 457–471, doi: 10.1172/JCI40483, indexed in Pubmed: 20093776.
14. Borges TJ, Wieten L, van Herwijnen MJC, et al. The anti-inflammatory mechanisms of Hsp70. Front Immunol. 2012; 3: 95, doi: 10.3389/fimmu.2012.00095, indexed in Pubmed: 22566973.
15. de Kleer I, Vercoulen Y, Klein M, et al. CD30 discriminates heat shock protein 60-induced FOXP3+ CD4+ T cells with a regulatory phenotype. J Immunol. 2010; 185(4): 2071–2079, doi: 10.4049/jimmunol.0901901, indexed in Pubmed: 20631311.
16. Aalberse JA, Kapitein B, de Roock S, et al. Cord blood CD4+ T cells respond to self heat shock protein 60 (HSP60). PLoS One. 2011; 6(9): e24119, doi: 10.1371/journal.pone.0024119, indexed in Pubmed: 21931651.
17. Cohen-Sfady M, Nussbaum G, Pevsner-Fischer M, et al. Heat shock protein 60 activates B cells via the TLR4-MyD88 pathway. J Immunol. 2005; 175(6): 3594–3602, doi: 10.4049/jimmunol.175.6.3594, indexed in Pubmed: 16148103.
18. Tsai YP, Yang MH, Huang CH, et al. Interaction between HSP60 and beta-catenin promotes metastasis. Carcinogenesis. 2009; 30(6): 1049–1057, doi: 10.1093/carcin/bgp087, indexed in Pubmed: 19369584.
19. Stocki P, Wang XN, Dickinson AM. Inducible heat shock protein 70 reduces T cell responses and stimulatory capacity of monocyte-derived dendritic cells. J Biol Chem. 2012; 287(15): 12387–12394, doi: 10.1074/jbc.M111.307579, indexed in Pubmed: 22334699.
20. Gastpar R, Gehrmann M, Bausero MA, et al. Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells. Cancer Res. 2005; 65(12): 5238–5247, doi: 10.1158/0008-5472.CAN-04-3804, indexed in Pubmed: 15958569.
21. Gehrmann M, Marienhagen J, Eichholtz-Wirth H, et al. Dual function of membrane-bound heat shock protein 70 (Hsp70), Bag-4, and Hsp40: protection against radiation-induced effects and target structure for natural killer cells. Cell Death Differ. 2005; 12(1): 38–51, doi: 10.1038/sj.cdd.4401510, indexed in Pubmed: 15592361.
22. Maki RG, Old LJ, Srivastava PK. Human homologue of murine tumor rejection antigen gp96: 5'-regulatory and coding regions and relationship to stress-induced proteins. Proc Natl Acad Sci U S A. 1990; 87(15): 5658–5662, doi: 10.1073/pnas.87.15.5658, indexed in Pubmed: 2377606.
23. Udono H, Srivastava PK. Heat shock protein 70-associated peptides elicit specific cancer immunity. J Exp Med. 1993; 178(4): 1391–1396, doi: 10.1084/jem.178.4.1391, indexed in Pubmed: 8376942.
24. Multhoff G. Activation of natural killer cells by heat shock protein 70. 2002. Int J Hyperthermia. 2009; 25(3): 169–175, doi: 10.1080/02656730902902001, indexed in Pubmed: 19437234.
25. Gross C, Hansch D, Gastpar R, et al. Interaction of heat shock protein 70 peptide with NK cells involves the NK receptor CD94. Biol Chem. 2003; 384(2): 267–279, doi: 10.1515/BC.2003.030, indexed in Pubmed: 12675520.
26. Multhoff G. Heat shock protein 70 (Hsp70) stimulates proliferation and cytolytic activity of natural killer cells. Exp Hematol. 1999; 27(11): 1627–1636, doi: 10.1016/s0301-472x(99)00104-6, indexed in Pubmed: 10560910.
27. Tsan MF, Gao B. Cytokine function of heat shock proteins. Am J Physiol Cell Physiol. 2004; 286(4): C739–C744, doi: 10.1152/ajpcell.00364.2003, indexed in Pubmed: 15001423.
28. McNulty S, Colaco CA, Blandford LE, et al. Heat-shock proteins as dendritic cell-targeting vaccines--getting warmer. Immunology. 2013; 139(4): 407–415, doi: 10.1111/imm.12104, indexed in Pubmed: 23551234.
29. Asea A, Kraeft SK, Kurt-Jones EA, et al. HSP70 stimulates cytokine production through a CD14-dependant pathway, demonstrating its dual role as a chaperone and cytokine. Nat Med. 2000; 6(4): 435–442, doi: 10.1038/74697, indexed in Pubmed: 10742151.
30. Singh-Jasuja H, Scherer H, Hilf N, et al. The heat shock protein gp96 induces maturation of dendritic cells and down-regulation of its receptor. Eur J Immunol. 2000; 30(8): 2211–2215, doi: 10.1002/1521-4141(2000)30:8<2211::aid-immu2211>3.0.co;2-0, indexed in Pubmed: 10940912.
31. Panjwani NN, Popova L, Srivastava PK. Heat shock proteins gp96 and hsp70 activate the release of nitric oxide by APCs. J Immunol. 2002; 168(6): 2997–3003, doi: 10.4049/jimmunol.168.6.2997, indexed in Pubmed: 11884472.
32. Chen T, Guo J, Han C, et al. Heat shock protein 70, released from heat-stressed tumor cells, initiates antitumor immunity by inducing tumor cell chemokine production and activating dendritic cells via TLR4 pathway. J Immunol. 2009; 182(3): 1449–1459, doi: 10.4049/jimmunol.182.3.1449, indexed in Pubmed: 19155492.
33. Murshid A, Gong J, Stevenson MA, et al. Heat shock proteins and cancer vaccines: developments in the past decade and chaperoning in the decade to come. Expert Rev Vaccines. 2011; 10(11): 1553–1568, doi: 10.1586/erv.11.124, indexed in Pubmed: 22043955.
34. Murshid A, Theriault J, Gong J, et al. Investigating receptors for extracellular heat shock proteins. Methods Mol Biol. 2011; 787: 289–302, doi: 10.1007/978-1-61779-295-3_22, indexed in Pubmed: 21898244.
35. Linder M, Pogge von Strandmann E. The Role of Extracellular HSP70 in the Function of Tumor-Associated Immune Cells. Cancers (Basel). 2021; 13(18), doi: 10.3390/cancers13184721, indexed in Pubmed: 34572948.
36. Castelli C, Ciupitu AM, Rini F, et al. Human heat shock protein 70 peptide complexes specifically activate antimelanoma T cells. Cancer Res. 2001; 61(1): 222–227, indexed in Pubmed: 11196165.
37. Antony GK, Dudek AZ. Interleukin 2 in cancer therapy. Curr Med Chem. 2010; 17(29): 3297–3302, doi: 10.2174/092986710793176410, indexed in Pubmed: 20712575.
38. Parker BS, Rautela J, Hertzog PJ. Antitumour actions of interferons: implications for cancer therapy. Nat Rev Cancer. 2016; 16(3): 131–144, doi: 10.1038/nrc.2016.14, indexed in Pubmed: 26911188.
39. Metcalf D. The colony-stimulating factors and cancer. Nat Rev Cancer. 2010; 10(6): 425–434, doi: 10.1038/nrc2843, indexed in Pubmed: 20495576.
40. Goldenberg M. Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, a novel agent for the treatment of metastatic breast cancer. Clin Ther. 1999; 21(2): 309–318, doi: 10.1016/s0149-2918(00)88288-0, indexed in Pubmed: 10211534.

41. June CH. Adoptive T cell therapy for cancer in the clinic. J Clin Invest. 2007; 117(6): 1466–1476, doi: 10.1172/JCI32446, indexed in Pubmed: 17549249.
42. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? BMC Med. 2016; 14: 73, doi: 10.1186/s12916-016-0623-5, indexed in Pubmed: 27151159.
43. Palucka K, Banchereau J. Dendritic-cell-based therapeutic cancer vaccines. Immunity. 2013; 39(1): 38–48, doi: 10.1016/j.immuni.2013.07.004, indexed in Pubmed: 23890062.
44. Plosker GL. Sipuleucel-T in metastatic castration-resistant prostate cancer: profile report. BioDrugs. 2011; 25(4): 255–256, doi: 10.2165/11207140-000000000-00000, indexed in Pubmed: 21815700.
45. Yu M, Finn OJ. DNA vaccines for cancer too. Cancer Immunol Immunother. 2006; 55(2): 119–130, doi: 10.1007/s00262-005-0008-7, indexed in Pubmed: 16032397.
46. Zahm CD, Colluru VT, McNeel DG. DNA vaccines for prostate cancer. Pharmacol Ther. 2017; 174: 27–42, doi: 10.1016/j.pharmthera.2017.02.016, indexed in Pubmed: 28185916.
47. Snook AE, Baybutt TR, Hyslop T, et al. Preclinical Evaluation of a Replication-Deficient Recombinant Adenovirus Serotype 5 Vaccine Expressing Guanylate Cyclase C and the PADRE T-helper Epitope. Hum Gene Ther Methods. 2016; 27(6): 238–250, doi: 10.1089/hgtb.2016.114, indexed in Pubmed: 27903079.
48. Madan RA, Bilusic M, Heery C, et al. Clinical evaluation of TRICOM vector therapeutic cancer vaccines. Semin Oncol. 2012; 39(3): 296–304, doi: 10.1053/j.seminoncol.2012.02.010, indexed in Pubmed: 22595052.
49. Larocca C, Schlom J. Viral vector-based therapeutic cancer vaccines. Cancer J. 2011; 17(5): 359–371, doi: 10.1097/PPO.0b013e3182325e63, indexed in Pubmed: 21952287.
50. Tangney M, Gahan CGM. Listeria monocytogenes as a vector for anti-cancer therapies. Curr Gene Ther. 2010; 10(1): 46–55, doi: 10.2174/156652310790945539, indexed in Pubmed: 20158470.
51. Bolhassani A, Rafati S. Heat-shock proteins as powerful weapons in vaccine development. Expert Rev Vaccines. 2008; 7(8): 1185–1199, doi: 10.1586/14760584.7.8.1185, indexed in Pubmed: 18844593.
52. Pakravan N, Soudi S, Hassan ZM. N-terminally fusion of Her2/neu to HSP70 decreases efficiency of Her2/neu DNA vaccine. Cell Stress Chaperones. 2010; 15(5): 631–638, doi: 10.1007/s12192-010-0175-0, indexed in Pubmed: 20224916.
53. Garrod TJ, Grubor-Bauk B, Gargett T, et al. DNA vaccines encoding membrane-bound or secreted forms of heat shock protein 70 exhibit improved potency. Eur J Immunol. 2014; 44(7): 1992–2002, doi: 10.1002/eji.201343983, indexed in Pubmed: 24723366.
54. Wang L, Rollins L, Gu Q, et al. A Mage3/Heat Shock Protein70 DNA vaccine induces both innate and adaptive immune responses for the antitumor activity. Vaccine. 2009; 28(2): 561–570, doi: 10.1016/j.vaccine.2009.09.119, indexed in Pubmed: 19835823.
55. Delpino A, Falcioni R, Ferrini U. Modulation of Heat Shock Protein Synthesis in Two Human Melanoma Cell Lines. Tumori. 1984; 70(5): 393–398, indexed in Pubmed: 6506223.
56. Gross L. Intradermal immunization of C3H mice against a sarcoma that originated in an animal of the same line. Cancer Res. 1943: 323–326.
57. Srivastava PK, Das MR. The serologically unique cell surface antigen of Zajdela ascitic hepatoma is also its tumor-associated transplantation antigen. Int J Cancer. 1984; 33(3): 417–422, doi: 10.1002/ijc.2910330321, indexed in Pubmed: 6698641.
58. Ullrich SJ, Robinson EA, Law LW, et al. A mouse tumor-specific transplantation antigen is a heat shock-related protein. Proc Natl Acad Sci U S A. 1986; 83(10): 3121–3125, doi: 10.1073/pnas.83.10.3121, indexed in Pubmed: 3458168.
59. Baldin AV, Zamyatnin AA, Bazhin AV, et al. Advances in the Development of Anticancer HSP-based Vaccines. Curr Med Chem. 2019; 26(3): 427–445, doi: 10.2174/0929867325666180129100015, indexed in Pubmed: 29376489.
60. Chandawarkar RY, Wagh MS, Kovalchin JT, et al. Immune modulation with high-dose heat-shock protein gp96: therapy of murine autoimmune diabetes and encephalomyelitis. Int Immunol. 2004; 16(4): 615–624, doi: 10.1093/intimm/dxh063, indexed in Pubmed: 15039392.
61. Binder RJ, Zhou YuJ, Messmer MN, et al. CD91-Dependent Modulation of Immune Responses by Heat Shock Proteins: A Role in Autoimmunity. Autoimmune Dis. 2012; 2012: 863041, doi: 10.1155/2012/863041, indexed in Pubmed: 23209886.
62. Bu N, Li QL, Feng Qi, et al. Immune protection effect of exosomes against attack of L1210 tumor cells. Leuk Lymphoma. 2006; 47(5): 913–918, doi: 10.1080/10428190500376191, indexed in Pubmed: 16753878.
63. Cho Ja, Lee YS, Kim SH, et al. MHC independent anti-tumor immune responses induced by Hsp70-enriched exosomes generate tumor regression in murine models. Cancer Lett. 2009; 275(2): 256–265, doi: 10.1016/j.canlet.2008.10.021, indexed in Pubmed: 19036499.
64. Xie Y, Bai Ou, Zhang H, et al. Membrane-bound HSP70-engineered myeloma cell-derived exosomes stimulate more efficient CD8(+) CTL- and NK-mediated antitumour immunity than exosomes released from heat-shocked tumour cells expressing cytoplasmic HSP70. J Cell Mol Med. 2010; 14(11): 2655–2666, doi: 10.1111/j.1582-4934.2009.00851.x, indexed in Pubmed: 19627400.
65. Shevtsov M, Pitkin E, Ischenko A, et al. Hsp70-Activated NK Cells in Combination With PD-1 Inhibition Significantly Increase Overall Survival in Preclinical Models of Glioblastoma and Lung Cancer. Front Immunol. 2019; 10: 454, doi: 10.3389/fimmu.2019.00454, indexed in Pubmed: 30967859.
66. Komarova EY, Suezov RV, Nikotina AD, et al. Hsp70-containing extracellular vesicles are capable of activating of adaptive immunity in models of mouse melanoma and colon carcinoma. Sci Rep. 2021; 11(1): 21314, doi: 10.1038/s41598-021-00734-4, indexed in Pubmed: 34716378.
67. Behzadi E, Hosseini HM, Halabian R, et al. Macrophage cell-derived exosomes/staphylococcal enterotoxin B against fibrosarcoma tumor. Microb Pathog. 2017; 111: 132–138, doi: 10.1016/j.micpath.2017.08.027, indexed in Pubmed: 28843722.
68. Eton O, Ross MI, East MJo, et al. Autologous tumor-derived heat-shock protein peptide complex-96 (HSPPC-96) in patients with metastatic melanoma. J Transl Med. 2010; 8: 9, doi: 10.1186/1479-5876-8-9, indexed in Pubmed: 20109236.
69. Bloch O, Crane CA, Fuks Y, et al. Heat-shock protein peptide complex-96 vaccination for recurrent glioblastoma: a phase II, single-arm trial. Neuro Oncol. 2014; 16(2): 274–279, doi: 10.1093/neuonc/not203, indexed in Pubmed: 24335700.
70. Testori A, Richards J, Whitman E, et al. C-100-21 Study Group. Phase III comparison of vitespen, an autologous tumor-derived heat shock protein gp96 peptide complex vaccine, with physician's choice of treatment for stage IV melanoma: the C-100-21 Study Group. J Clin Oncol. 2008; 26(6): 955–962, doi: 10.1200/JCO.2007.11.9941, indexed in Pubmed: 18281670.
71. Wood C, Srivastava P, Bukowski R, et al. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. Lancet. 2008; 372(9633): 145–154, doi: 10.1016/s0140-6736(08)60697-2.
72. Li Z, Qiao Yi, Liu B, et al. Combination of imatinib mesylate with autologous leukocyte-derived heat shock protein and chronic myelogenous leukemia. Clin Cancer Res. 2005; 11(12): 4460–4468, doi: 10.1158/1078-0432.CCR-05-0250, indexed in Pubmed: 15958631.
73. Roman LD, Wilczynski S, Muderspach LI, et al. A phase II study of Hsp-7 (SGN-00101) in women with high-grade cervical intraepithelial neoplasia. Gynecol Oncol. 2007; 106(3): 558–566, doi: 10.1016/j.ygyno.2007.05.038, indexed in Pubmed: 17631950.
74. Victora GD, Socorro-Silva A, Volsi EC, et al. Immune response to vaccination with DNA-Hsp65 in a phase I clinical trial with head and neck cancer patients. Cancer Gene Ther. 2009; 16(7): 598–608, doi: 10.1038/cgt.2009.9, indexed in Pubmed: 19197326.
75. Trimble CL, Peng S, Kos F, et al. A phase I trial of a human papillomavirus DNA vaccine for HPV16+ cervical intraepithelial neoplasia 2/3. Clin Cancer Res. 2009; 15(1): 361–367, doi: 10.1158/1078-0432.CCR-08-1725, indexed in Pubmed: 19118066.
76. Zappasodi R, Pupa SM, Ghedini GC, et al. Improved clinical outcome in indolent B-cell lymphoma patients vaccinated with autologous tumor cells experiencing immunogenic death. Cancer Res. 2010; 70(22): 9062–9072, doi: 10.1158/0008-5472.CAN-10-1825, indexed in Pubmed: 20884630.
77. Krause SW, Gastpar R, Andreesen R, et al. Treatment of colon and lung cancer patients with ex vivo heat shock protein 70-peptide-activated, autologous natural killer cells: a clinical phase i trial. Clin Cancer Res. 2004; 10(11): 3699–3707, doi: 10.1158/1078-0432.CCR-03-0683, indexed in Pubmed: 15173076.
78. Matsui H, Hazama S, Tamada K, et al. Identification of a Promiscuous Epitope Peptide Derived From HSP70. J Immunother. 2019; 42(7): 244–250, doi: 10.1097/CJI.0000000000000274, indexed in Pubmed: 31398179.
79. Shimizu Y, Yoshikawa T, Kojima T, et al. Heat shock protein 105 peptide vaccine could induce antitumor immune reactions in a phase I clinical trial. Cancer Sci. 2019; 110(10): 3049–3060, doi: 10.1111/cas.14165, indexed in Pubmed: 31390678.

80. Shevtsov MA, Pozdnyakov AV, Mikhrina AL, et al. Effective immunotherapy of rat glioblastoma with prolonged intratumoral delivery of exogenous heat shock protein Hsp70. Int J Cancer. 2014; 135(9): 2118–2128, doi: 10.1002/ijc.28858, indexed in Pubmed: 24691976.
81. Chang CL, Tsai YC, He L, et al. Cancer immunotherapy using irradiated tumor cells secreting heat shock protein 70. Cancer Res. 2007; 67(20): 10047–10057, doi: 10.1158/0008-5472.CAN-07-0523, indexed in Pubmed: 17942939.
82. Abkin SV, Pankratova KM, Komarova EYu, et al. Hsp70 chaperone-based gel composition as a novel immunotherapeutic anti-tumor tool. Cell Stress Chaperones. 2013; 18(3): 391–396, doi: 10.1007/s12192-012-0391-x, indexed in Pubmed: 23233202.
83. Shevtsov MA, Kim AV, Samochernych KA, et al. Pilot study of intratumoral injection of recombinant heat shock protein 70 in the treatment of malignant brain tumors in children. Onco Targets Ther. 2014; 7: 1071–1081, doi: 10.2147/OTT.S62764, indexed in Pubmed: 24971017.
84. Tischer S, Basila M, Maecker-Kolhoff B, et al. Heat shock protein 70/peptide complexes: potent mediators for the generation of antiviral T cells particularly with regard to low precursor frequencies. J Transl Med. 2011; 9: 175, doi: 10.1186/1479-5876-9-175, indexed in Pubmed: 21992180.
85. Jiang J, Xie D, Zhang W, et al. Fusion of Hsp70 to Mage-a1 enhances the potency of vaccine-specific immune responses. J Transl Med. 2013; 11: 300, doi: 10.1186/1479-5876-11-300, indexed in Pubmed: 24314011.
86. Schildkopf P, Frey B, Ott OJ, et al. Radiation combined with hyperthermia induces HSP70-dependent maturation of dendritic cells and release of pro-inflammatory cytokines by dendritic cells and macrophages. Radiother Oncol. 2011; 101(1): 109–115, doi: 10.1016/j.radonc.2011.05.056, indexed in Pubmed: 21704416.
87. Ito A, Matsuoka F, Honda H, et al. Antitumor effects of combined therapy of recombinant heat shock protein 70 and hyperthermia using magnetic nanoparticles in an experimental subcutaneous murine melanoma. Cancer Immunol Immunother. 2004; 53(1): 26–32, doi: 10.1007/s00262-003-0416-5, indexed in Pubmed: 14551746.

VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 184–189
DOI: 10.5603/NJO.a2022.0012

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Possibilities of applying a combination of targeted molecular therapies and immunotherapy in NSCLC patients

Magdalena Wójcik-Superczyńska, Tomasz Jankowski, Paweł Krawczyk

Department of Pneumology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland

Non-small cell lung cancer (NSCLC) advanced or metastatic with driver mutations (*EGFR*, *ALK*, *ROS1*) is treated with tyrosine kinase inhibitors (TKIs), respectively anti-EGFR, anti-ALK or anti-ROS1. Immunotherapy with checkpoint inhibitors (anti-PD-1 or anti-PD-L1) alone or in combination with TKIs was considered as a treatment option in several studies, but results are not promising, furthermore the toxicity profile of such a combination is potentially unacceptable. The initial findings suggest that combination therapy has failed to demonstrate clinically meaningful efficacy and there are no strong signals of its future development.

Key words: immunotherapy, lung cancer, targeted therapy, *EGFR*, *ALK*

Rationale for combination of immunotherapy and targeted therapy

Non-small cell lung cancer (NSCLC) represents 85% of diagnosed lung cancer cases. Approximately 50% of patients are diagnosed at stage IV of the disease, and their five-year survival rate is less than 10% [1].

The introduction of immunotherapy with the application of immune checkpoint inhibitors (ICIs) which target programmed death-1 receptor (PD-1), found in cytotoxic T-lymphocytes, or its ligand, PD-L1 (programmed death-1 receptor ligand 1), found, among other things, in cancer cells, has significantly changed the treatment of advanced lung cancer.

Modern methods of immunotherapy focus on the boosting of antitumor T-cell response and the bolstering of cell immunity with the ultimate destruction of the tumor. The impact of PD-1 and PD-L1 leads to the suppression of antitumor T-cell activity. The idea of using antibodies against immune checkpoint inhibitors is based on the blocking of one of these molecules, which restores cytotoxic T-cell activity [2–5].

The phenomenon of the immune checkpoint blockade (ICB) was the point of departure for the development of antibodies which target cytotoxic T-cell antigen 4 (CTL-4) (ipilimumab and tremelimumab). Similar development was observed as regards monoclonal antibody drugs and anti-PD-L1 antibodies, which respectively block PD-1, found in T-cells (nivolumab, pembrolizumab), and PD-L1, found on both the surface of cancer cells and the immune system cells penetrating cancer tissue (durvalumab, atezolizumab, avelumab) [2].

CheckMate 057 and KEYNOTE-010 studies demonstrated a statistically significant improvement in the overall survival in NSCLC patients treated with nivolumab or pembrolizumab in comparison with patients receiving standard 2nd-line docetaxel-based chemotherapy. Those studies pro-

How to cite:

Wójcik-Superczyńska M, Jankowski T, Krawczyk P. ***Possibilities of applying a combination of targeted molecular therapies and immunotherapy in NSCLC patients.*** *NOWOTWORY J Oncol* 2022; 72: 184–189.

ved, however, that *EGFR*-mutant patients did not experience a greater benefit from using immunotherapy compared with chemotherapy. In CheckMate 057, 82 patients (14% of all) were *EGFR*-positive and 21 (4%) were *ALK*-positive. Subgroup analyses of OS revealed that patients with the *EGFR* mutation, having received or receiving an additional line of TKI, did not benefit from nivolumab compared with docetaxel (hazard ratio [HR] 1.18, 95% confidence interval [CI]: 0.69–2.00). In KEYNOTE-010, 86 patients (8.3%) were had the *EGFR*-mutant and 6 (0.6%) were *ALK*-positive. Patients with the *EGFR* mutation did not have prolonged OS in response to pembrolizumab compared to docetaxel. No data on OS were reported for *ALK*-positive patients. In both trials (HR 0.88, 95% CI: 0.45–1.70) [4, 5].

Unfortunately, many NSCLC patients do not benefit from immunotherapy due to their primary resistance whilst others experience disease recurrence after the initial response (secondary resistance). Adaptive resistance can also be observed when the immune system has identified cancer, but it can adapt to the immune attack and, consequently, resist it. The incidence of resistance to immunotherapy has led to the development of a new concept of combination therapy, which utilizes immunotherapy and chemotherapy, radiotherapy or targeted molecular therapies. First-line chemoimmunotherapy became the standard of care in the treatment of NSCLC. Chemotherapy increases the effectiveness of immunotherapy through the increased level of tumor antigens released, the induction of inflammation within the tumor as well as the provoked expression of various molecules found on the surface of tumor cells (e.g. calreticulin). What also became standard practice was the combination of chemotherapy and immunotherapy in the treatment of locally advanced NSCLC patients. The greatest controversy, however, was aroused by the idea of combining immunotherapy and targeted molecular therapies [6].

Undoubtedly, the dawn of targeted molecular therapies has radically changed the prognosis for NSCLC patients. Targeted molecular therapies inhibit the growth and progression of tumors by means of blocking both abnormal proteins and signaling pathways of cancer cells, which are vital to cell survival. During the last decade, considerable progress has been made in the field of identification of driver mutations, and, consequently, of drugs which can delay tumor progression, thus considerably improving the survival of patients with such mutations [7]. Three generations of epidermal growth factor receptor (EGFR), tyrosine kinase inhibitors (TKIs) as well as three generations of anaplastic lymphoma kinase (ALK) inhibitors have been developed. ROS1, BRAF, NTRK and MET kinase inhibitors have also become part of the standard treatment of NSCLC. However, the percentage of mutation-positive or gene-rearrangement-positive patients remains relatively low. For instance, the presence of *EGFR*-mutant Caucasian NSCLC patients ranges from 10 to 16% [8, 9].

Moreover, due to the emergence of tumor cell clones resistant to targeted molecular drugs, the response to this kind of therapy can be short-lived. Even therapeutic strategies developed for patients with secondary mutations, such as *EGFR* T790M, which use the latest generation of inhibitors, do not produce a durable remission. It results from the fact that for every drug, there is a different mechanism of targeted molecular therapy resistance, such as secondary mutations in genes encoding cell surface receptors, gene fusions or the activation of alternative signaling pathways in tumor cells. In case all options of targeted molecular therapy have been exhausted, patients will require standard-of-care chemotherapy [10].

This is why, from the clinical standpoint, it would be worth analyzing a combination of targeted molecular therapy and immunotherapy, aiming to achieve a durable remission. It is believed that genetic alterations in specific driver genes activate the proliferation of tumor cells. It has also been demonstrated that the activation of some oncogene pathways impacts the way tumors are detected by the immune system, especially by cytotoxic T-cells. On the other hand, however, "driver" mutations usually tend to be isolated genetic alterations. It means that such tumor cells have a low count of neoantigens, encoded by mutant genes, and, as a result, they are not recognized by the immune system. That explains the reduced efficiency of immunotherapy in the treatment of non-smoking NSCLC patients, in whose case only isolated genetic alterations develop, such as *EGFR* mutations or *ALK* rearrangements. In the case of smoking patients, however, numerous genetic alterations concur and numerous neoantigens are to be found. This is why, in clinical trials, a high tumor mutation burden (TMB) is considered a positive predictive factor for immunotherapy [11].

There are views, however, that a combination of TKIs and immunotherapy in treatment-naive patients may be well-founded. The results of preclinical and clinical studies demonstrated the immunomodulatory effect of TKI therapy. The studies demonstrated that gefitinib and erlotinib promoted immune response by means of enhancing the cytotoxicity of NK cells [12].

A study by Sheng et al., on the other hand, demonstrated a significant increase in the number of NK cells as well as in the level of IFN-γ, and a decrease of IL-6 in patients' peripheral blood after 4 months of gefitinib treatment. Moreover, tumor samples collected after gefitinib treatment demonstrated a downregulation of PD-L1 expression on tumor cells following the use of this drug [13].

The level of PD-L1 expression is directly modified by EGFR, ALK and other cell receptors as well as by exposure to TKIs, which have an effect on the expression level, the activity of receptor tyrosine kinases and the following signaling cascades. The studies demonstrated that there was a much increased PD-L1 expression level in NSCLC cell lines positive for the *EGFR* mutation and *EML4-ALK* fusion gene [14–16]. There are conflicting reports regarding the effect of EGFR-TKIs on PD-L1

expression in *EGFR*-mutant NSCLC cell lines. According to certain reports, there is a downregulation of PD-L1 expression on tumor cells as a result of tumor cells being exposed to erlotinib or gefitinib. According to other authors, a completely reverse phenomenon takes place. To date, elevated PD-L1 expression on tumor cells has been the only recognized predictive factor for immunotherapy. The identification of PD-L1 expression in over 50% of tumor cells allows patients to be qualified for first-line pembrolizumab therapy [13, 17].

First-line treatment of NSCLC patients

The number of clinical trials which evaluate the efficacy of combination therapy with the application of targeted molecular therapy and immunotherapy is still limited. Unfortunately, the conducted experiments to date have indicated that the benefits resulting from the use of immunotherapy in the treatment of *EGFR*-mutant or *ALK*-positive NSCLC patients are dubious [18]. In fact, clinical trials which employed immunotherapy did not demonstrate any benefit from the use of anti-PD-1 or anti-PD-L1 antibodies in the treatment of *EGFR*-mutant NSCLC patients [19, 20]. The retrospective analysis demonstrated an objective response to immunotherapy in 3.6% of the *EGFR* mutation-positive or *ALK* rearrangement-positive patients in comparison with 23.3% of the patients without these genetic alterations or individuals of an unknown profile as regards the genes under discussion [21].

There are still numerous ongoing clinical trials which investigate the efficacy of the combined immunotherapy and EGFR or ALK inhibitors in the treatment of NSCLC patients. The results of the clinical studies which have been published draw attention to the fact that there was a high percentage of adverse events as well as a frequent lack of clinical benefit from the combined therapy.

The phase I–II KEYNOTE-021 study focused on the evaluation of the efficacy of erlotinib or gefitinib in combination with pembrolizumab as first-line therapy in the treatment of *EGFR*-mutant NSCLC patients. In the group of participants enrolled to receive gefitinib, due to the significant toxicity resulting in liver damage (adverse events of the 3rd and 4th grade), the treatment was discontinued in 4 out of 7 patients. In the group of participants enrolled to receive erlotinib, however, the safety profile of the drug combination was acceptable. The patients did not require having their doses reduced and the adverse events were similar to those found in patients who received each drug as monotherapy. These findings corroborated the good safety profile of these combined drugs. The most frequent adverse events related to treatment with pembrolizumab and erlotinib were a rash (50% of the participants), dermatitis acneiform, diarrhea, hypothyroidism, and pruritus (33.3% each). The combination of pembrolizumab and erlotinib, however, did not increase the response rate in comparison with the previous trials which employed EGFR-TKI monotherapy [22].

The unfavorable safety profile of the application of a combination therapy based on EGFR-TKIs and ICIs was also the reason for the termination of a large randomized study (CAURAL) which was terminated early because of the high toxicity of the osimertinib plus durvalumab combination demonstrated in a parallel phase Ib trial (TATTON) [23]. That study CAURAL aimed to combine a third-generation EGFR-TKI, osimertinib, with a PD-L1 inhibitor, durvalumab, in treatment-naive *EGFR*-mutant patients. Aspartate transaminase concentrations of the 3rd and 4th degree were observed in blood plasma in 65% of the patients, which led to the termination of the study. The results in terms of the treatment overall response rate were not different from the previously known results of phase III studies employing osimertinib as monotherapy in treatment-naive *EGFR*-mutant NSCLC patients [24].

In another clinical study, atezolizumab (NCT02013219) was applied in combination with erlotinib in the treatment of *EGFR*-mutant NSCLC patients. 75% of the patients responded to the treatment and the safety profile proved satisfactory [25]. In a phase I trial (NCT02088112), the efficacy of durvalumab in combination with gefitinib was investigated. The participants of the study were EGFR-TKI-naive *EGFR*-mutant NSCLC patients. The first half of the patients received both durvalumab and gefitinib (group 1), while the other half were treated only with gefitinib for 28 days before they started the combination therapy (group 2). The employed combination therapy did not increase the response rate in comparison with gefitinib monotherapy. The objective response rate accounted for 77.8% and 80% of the patients in group 1 and group 2 respectively. The combination therapy induced serious adverse events in 55% of the patients [26].

In a phase I trial (GEFTREM), the efficacy of tremelimumab immunotherapy in combination with gefitinib was investigated in stage IV *EGFR*-mutant NSCLC patients. Stable disease was obtained in 67% of the evaluated patients, and the safety profile was in accord with the previously observed adverse events for each specific drug [27].

In the CheckMate 370 trial, a combination of nivolumab and crizotinib was applied to treat *ALK* translocation-positive NSCLC patients. 38% of them experienced serious adverse events (most frequently hepatotoxicity), which led to the discontinuation of the combination therapy, and which may have contributed to the death of two participants [28].

There are not any available results of clinical trials which evaluated the efficacy of the combined immunotherapy and targeted therapies aimed at areas other than *EGFR* or *ALK* in NSCLC patients. *ROS1* and *NTRK* rearrangements or BRAF and *MET* mutations occur very seldom in NSCLC patients while inhibitors of those proteins have been developed only recently. That is why there is not any data regarding the efficacy and safety of the combined therapy in the treatment of such patients.

Immunotherapy in resistance to targeted therapy

An unusually attractive concept is the idea of applying a combined therapy in the treatment of patients who progressed during the course of a targeted molecular therapy. As therapeutic possibilities to employ new-generation EGFR-TKIs are exhausted, new attempts have been made to overcome EGFR-TKI resistance by means of combining targeted molecular therapy with immunotherapy.

Phase Ib TATTON trial (NCT02143466), in which various treatment combinations were employed, has, to date, been the most advanced clinical study investigating the possibility of combining targeted molecular therapy with immunotherapy in order to overcome EGFR-TKI resistance. In that trial, *EGFR* TKI-pretreated EGFR-mutant advanced NSCLC patients were qualified for a combination therapy with osimertinib and one of the three following drugs: selumetinib (MEK1 and MEK2 inhibitor), savolitinib (MET inhibitor) or durvalumab (anti-PD-L1 antibody). The most frequent adverse events of any grade, which occurred in no less than 20% of all the participants were: diarrhea (75% of the cases), a rash (58% of the cases) and nausea (47% of the cases), developed by patients receiving osimertinib in combination with selumetinib; nausea (67% of the cases), a rash (56% of the cases) and vomiting (50% of the cases), developed by patients receiving osimertinib in combination with savolitinib; a rash (48% of the cases) and vomiting (43% of the cases) and diarrhea (39% of the cases) developed by patients receiving osimertinib in combination with durvalumab. Furthermore, 38% of the patients treated with osimertinib in combination with durvalumab developed interstitial lung disease, which was the reason for the discontinuation of the treatment and the termination of the study. The objective response rate accounted for 42% in the group of patients treated with osimertinib in combination with selumetinib, 44% in the group of patients treated with osimertinib in combination with savolitinib, and 43% in the group of patients treated with osimertinib in combination with durvalumab.

Even though the findings of the TATTON study demonstrated a high frequency of adverse events, which resulted from the combination of targeted molecular therapies and immunotherapy, other studies demonstrated a much better safety profile of this type of treatment. A good example is the CheckMate 012 study, where 21 *EGFR*-mutant NSCLC patients (20 erlotinib-pretreated and 1 EGFR-TKI-naive) received nivolumab in combination with erlotinib in order to overcome resistance to the latter drug. The objective response rate accounted for 19%. The findings demonstrated a 24-week progression-free survival rate of 51%, and a 1-year overall survival rate of 73%. Serious adverse events (diarrhea, nephritis, an increase in liver function enzymes) occurred in 21% of the patients. The findings suggest that a combination of erlotinib and nivolumab has an acceptable safety profile and can ensure certain clinical benefits for *EGFR*-mutant NSCLC patients who developed resistance to previous EGFR-TKI treatment [29].

Conclusions

Currently, there is a number completed and ongoing clinical trials aiming to evaluate the combination of new-generation EGFR and ALK inhibitors and immunotherapy in selected popu-

Table I. Completed and active clinical trials of immune checkpoints inhibitors in combination with EGFR/ALK TKIs in advanced or metastatic NSCLC

Clinical trial	Phase	ICI	TKI	Setting
KEYNOTE-021	I	pembrolizumab	erlotinib/gefitinib	first line EGFR + advNSCLC
CAURAL	III	durvalumab	osimertinib	first line EGFR + advNSCLC
NCT02013219	Ib	atezolizumab	erlotinib	first line EGFR + advNSCLC
NCT02088112	I	durvalumab	gefitinib	first line EGFR + advNSCLC
GEFTREM	I	tremelimumab	gefitinib	first line EGFR + advNSCLC
CheckMate 370	I	nivolumab	crizotinib	first line ALK + advNSCLC
TATTON	I	durvalumab	osimertinib	TKI-pretreated
CheckMate 012	I	nivolumab	erlotinib	20 erlotinib-pretreated patients, 1 TKI-naive
NCT01998126	I	nivolumab/ipilimumab	erlotinib or crizotinib	first line EGFR + or ALK + advNSCLC
NCT02393625	I	nivolumab	ceritinib	first or second line ALK + advNSCLC
LUX LUNG IO	II	pembrolizumab	afatinib	pretreated EGFR + advNSCLC
NCT02511184	I	pembrolizumab	crizotinib	first line ALK + advNSCLC
Javelin Lung 101	Ib/II	avelumab	crizotinib/lorlatinib	first or second line ALK + advNSCLC
NCT02898116	I	durvalumab	ensartinib	first line EGFR + advNSCLC

lations of TKI-naive or EGFR- or ALK-pretreated NSCLC patients who progressed following the applied treatment (tab. I). The initial findings suggest that combination therapy has failed to demonstrate clinically meaningful efficacy and there are no strong signals of its future development; furthermore the safety profile is not always acceptable. The lack of long-term observation does not allow one to draw any definitive conclusions [30].

The ongoing attempts to combine targeted molecular therapies with immunotherapy may evolve into new therapeutic strategies in the treatment of NSCLC patients. However, the application of combined targeted molecular therapy with immunotherapy in treatment-naive patients is probably unfounded. Undoubtedly, the evaluation of the efficacy and safety of combined EGFR and ALK treatment in conjunction with immunotherapy still requires further research [32]. Perhaps the direction of further research should be changed to tumor immunophenotype profiling, and the research itself should focus on methods of modulating the immune response leading to modification of the tumor microenvironment. It appears that targeted molecular therapy can change the tumor immunophenotype from "cold" (no immune infiltration of tumor) to "hot" (significantly more immunogenic and infiltrated by the immune system). Currently, following the failure of *EGFR* TKI treatment of EGFR-mutant NSCLC patients, ongoing clinical trials combine immunotherapy (nivolumab) with chemotherapy and immunomodulating therapy (plinabulin-microtubule polymerization inhibitor) [22]. This creates new possibilities for the conduct of further research and sets a new course in the treatment of NSCLC.

A detailed profile of interactions between cells of the immune system and cancer cells that contain various genetic abnormalities, identification of reliable predictors in the application of immunotherapy, and expertise in the mechanisms of acquired tumor resistance to immunotherapy and targeted molecular therapies are undoubtedly research directions that will contribute to the progress in treatment of patients with NSCLC. The increasing progress of science in terms of mechanisms of targeted molecular therapy and immunotherapy will facilitate the development of new drugs and new effective strategies in the treatment of NSCLC patients.

Conflict of interest: none declared

Tomasz Jankowski
Medical University of Lublin
Department of Pneumology, Oncology and Allergology
Aleje Racławickie 1
20-059 Lublin, Poland
e-mail: tjankowski.onkolog@wp.pl

Received: 7 Jul 2021
Accepted: 10 Feb 2022

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1): 7–30, doi: 10.3322/caac.21442, indexed in Pubmed: 29313949.
2. Wojas-Krawczyk K, Krawczyk P. Anti-PD-1 and anti-PD-L1 antibodies in combination with other methods of treatment – is it the future of therapy for advanced NSCL? Immunotherapy. 2019; 1: 6–15.
3. Karachaliou N, Gonzalez-Cao M, Sosa A, et al. The combination of checkpoint immunotherapy and targeted therapy in cancer. Ann Transl Med. 2017; 5(19): 388, doi: 10.21037/atm.2017.06.47, indexed in Pubmed: 29114546.
4. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373(17): 1627–1639, doi: 10.1056/NEJMoa1507643, indexed in Pubmed: 26412456.
5. Herbst R, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016; 387(10027): 1540–1550, doi: 10.1016/s0140-6736(15)01281-7.
6. Sharma P, Hu-Lieskovan S, Wargo JA, et al. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017; 168(4): 707–723, doi: 10.1016/j.cell.2017.01.017, indexed in Pubmed: 28187290.
7. Ferrara MG, Di Noia V, D'Argento E, et al. Oncogene-Addicted Non-Small-Cell Lung Cancer: Treatment Opportunities and Future Perspectives. Cancers (Basel). 2020; 12(5), doi: 10.3390/cancers12051196, indexed in Pubmed: 32397295.
8. Cheng Y, Mok TS, Zhou X, et al. The epidermal growth factor receptor intron1 (CA) n microsatellite polymorphism is a potential predictor of treatment outcome in patients with advanced lung cancer treated with Gefitinib. Eur J Pharmacol. 2007; 570(1-3): 175–181, doi: 10.1016/j.ejphar.2007.05.015, indexed in Pubmed: 17597605.
9. Marchetti A, Martella C, Felicioni L, et al. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. J Clin Oncol. 2005; 23(4): 857–865, doi: 10.1200/JCO.2005.08.043, indexed in Pubmed: 15681531.
10. Remon J, Caramella C, Jovelet C, et al. Osimertinib benefit in EGFR-mutant NSCLC patients with T790M-mutation detected by circulating tumour DNA. Ann Oncol. 2017; 28(4): 784–790, doi: 10.1093/annonc/mdx017, indexed in Pubmed: 28104619.
11. Zhu C, Zhuang W, Chen L, et al. Frontiers of ctDNA, targeted therapies, and immunotherapy in non-small-cell lung cancer. Transl Lung Cancer Res. 2020; 9(1): 111–138, doi: 10.21037/tlcr.2020.01.09, indexed in Pubmed: 32206559.
12. Kim H, Kim SH, Kim MJ, et al. EGFR inhibitors enhanced the susceptibility to NK cell-mediated lysis of lung cancer cells. J Immunother. 2011; 34(4): 372–381, doi: 10.1097/CJI.0b013e31821b724a, indexed in Pubmed: 21499124.
13. Sheng J, Fang W, Liu X, et al. Impact of gefitinib in early stage treatment on circulating cytokines and lymphocytes for patients with advanced non-small cell lung cancer. Onco Targets Ther. 2017; 10: 1101–1110, doi: 10.2147/OTT.S112158, indexed in Pubmed: 28260924.
14. Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002; 99(19): 12293–12297, doi: 10.1073/pnas.192461099, indexed in Pubmed: 12218188.
15. Ota K, Azuma K, Kawahara A, et al. Induction of PD-L1 Expression by the EML4-ALK Oncoprotein and Downstream Signaling Pathways in Non-Small Cell Lung Cancer. Clin Cancer Res. 2015; 21(17): 4014–4021, doi: 10.1158/1078-0432.CCR-15-0016, indexed in Pubmed: 26019170.
16. Azuma K, Ota K, Kawahara A, et al. Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. Ann Oncol. 2014; 25(10): 1935–1940, doi: 10.1093/annonc/mdu242, indexed in Pubmed: 25009014.
17. Chen N, Fang W, Zhan J, et al. Upregulation of PD-L1 by EGFR Activation Mediates the Immune Escape in EGFR-Driven NSCLC: Implication for Optional Immune Targeted Therapy for NSCLC Patients with EGFR Mutation. J Thorac Oncol. 2015; 10(6): 910–923, doi: 10.1097/JTO.0000000000000500, indexed in Pubmed: 25658629.
18. Karachaliou N, Gonzalez-Cao M, Sosa A, et al. The combination of checkpoint immunotherapy and targeted therapy in cancer. Ann Transl Med. 2017; 5(19): 388, doi: 10.21037/atm.2017.06.47, indexed in Pubmed: 29114546.
19. Lee CK, Man J, Lord S, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol. 2017; 12(2): 403–407, doi: 10.1016/j.jtho.2016.10.007, indexed in Pubmed: 27765535.
20. Rittmeyer A, Barlesi F, Waterkamp D, et al. OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised

controlled trial. Lancet. 2017; 389(10066): 255–265, doi: 10.1016/S0140--6736(16)32517-X, indexed in Pubmed: 27979383.
21. Gainor JF, Shaw AT, Sequist LV, et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. Clin Cancer Res. 2016; 22(18): 4585–4593, doi: 10.1158/1078-0432.CCR-15-3101, indexed in Pubmed: 27225694.
22. Yang JCH, Gadgeel SM, Sequist LV, et al. Pembrolizumab in Combination With Erlotinib or Gefitinib as First-Line Therapy for Advanced NSCLC With Sensitizing EGFR Mutation. J Thorac Oncol. 2019; 14(3): 553–559, doi: 10.1016/j.jtho.2018.11.028, indexed in Pubmed: 30529597.
23. Karachaliou N, Gonzalez-Cao M, Sosa A, et al. The combination of checkpoint immunotherapy and targeted therapy in cancer. Ann Transl Med. 2017; 5(19): 388, doi: 10.21037/atm.2017.06.47, indexed in Pubmed: 29114546.
24. Yang JCH, Shepherd FA, Kim DW, et al. Osimertinib Plus Durvalumab versus Osimertinib Monotherapy in EGFR T790M-Positive NSCLC following Previous EGFR TKI Therapy: CAURAL Brief Report. J Thorac Oncol. 2019; 14(5): 933–939, doi: 10.1016/j.jtho.2019.02.001, indexed in Pubmed: 30763730.
25. Ma B, Rudin CM, Cervantes A, et al. 441O Preliminary safety and clinical activity of erlotinib plus atezolizumab from a Phase Ib study in advanced NSCLC. Ann Oncol. 2016; 27(suppl_9), doi: 10.1093/annonc/mdw594.005.
26. Gibbons DL, Chow LQ, Kim DW, et al. 57O Efficacy, safety and tolerability of MEDI4736 (durvalumab [D]), a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib (G): A phase I expansion in TKI-naïve patients (pts) with EGFR mutant NSCLC. J Thorac Oncol. 2016; 11(4): S79, doi: 10.1016/s1556-0864(16)30171-x.
27. Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016; 17(3): 299–308, doi: 10.1016/S1470-2045(15)00544-6, indexed in Pubmed: 26858122.
28. Spigel DR, Reynolds C, Waterhouse D, et al. Phase 1/2 Study of the Safety and Tolerability of Nivolumab Plus Crizotinib for the First-Line Treatment of Anaplastic Lymphoma Kinase Translocation - Positive Advanced Non-Small Cell Lung Cancer (CheckMate 370). J Thorac Oncol. 2018; 13(5): 682–688, doi: 10.1016/j.jtho.2018.02.022, indexed in Pubmed: 29518553.
29. Gettinger S, Chow LQ, Borghaei H, et al. Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC. Int J Radiat Oncol Biol Phys. 2014; 90: S34–5.
30. Moya-Horno I, Viteri S, Karachaliou N, et al. Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC). Ther Adv Med Oncol. 2018; 10: 1758834017745012, doi: 10.1177/1758834017745012, indexed in Pubmed: 29383034.
31. Bruno D, Dowlati A. Immunotherapy in EGFR mutant non-small cell lung cancer: when, who and how? Transl Lung Cancer Res. 2019; 8(5): 710–714, doi: 10.21037/tlcr.2019.06.02, indexed in Pubmed: 31737508.
32. ESMO Oncology News. Combination immunotherapies for immune hot, altered and cold tumor. Understanding underlining mechanisms is crucial to boost a weak antitumour immunity. Date: 29 May 2019. Topics: Cancer Immunology and Immunotherapy.

VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 190–194
DOI: 10.5603/NJO.a2022.0023

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Cancer and rheumatic diseases. Methodological and clinical pitfalls in searching links between these diseases

Krzysztof Jeziorski[1, 2]

[1]*Department of Gerontology, Public Health and Didactics, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland*
[2]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Results of studies on coexistence of rheumatic and oncological diseases are somewhat conflicting in the literature. This is probably due to various methodological problems of the conducted research such as: small groups of patients, possible Berkson's bias, lack of information about the most important factors affecting the risk of developing cancer including lifestyle, body mass index, use of tobacco and alcohol, family history of cancer and autoimmune diseases, misclassification of diseases in administrative registries, differences including geographical, racial factors, and a relatively short observation period. The risk of cancer development or recurrence in patients treated for rheumatic disease is very low, estimated as 2–5 cases per 1000 patients treated annually, and even lower in patients with cured cancer and 5 years after completion of oncological treatment. In the absence of clear recommendations for cancer screening of patients with rheumatic diseases, there is a need to develop guidelines for screening.

Key words: cancer, rheumatologic diseases, screening, coexisting diseases and malignancies, multi-disease phenomenon

Introduction

The literature data on the relationship between rheumatic diseases and malignancies dates back to the second decade of the 20th century, when Stertz described a case in 1916 of a patient with inflammatory muscle disease and coexisting gastric cancer [1]. Cancer and rheumatic diseases have similar etiological factors, which generally boil down to the lack of or impaired immune surveillance of the body. The main cause of cancer development in patients with rheumatic diseases is a chronic activation of the immune system and inflammatory process, which may be explained to some extent by common etiopathological factors in both groups of diseases: genetic, environmental, immune surveillance disorders, which is referred to as multi-disease phenomenon.

Methodological pitfalls

The results of studies on coexistence of rheumatic and oncological diseases are somewhat conflicting in the literature [2, 3]. This is probably due to various methodological problems of the conducted research. Most analyses of the association between rheumatic diseases and cancer are based on small groups of patients, which, from a statistical point of view, make it difficult to see possible associations. Moreover, in analyses of hospital registries of oncological patients or patients with rheumatic di-

How to cite:
Jeziorski K. ***Cancer and rheumatic diseases. Methodological and clinical pitfalls in searching links between these diseases.*** *NOWOTWORY J Oncol* 2022; 72: 190–194.

seases, Berkson's bias may appear when paradoxically, there are more patients with rheumatic and cancer diseases than with rheumatic diseases alone. This happens when control groups are not included. What is more, the literature reports generally do not provide information about the most important factors affecting the risk of developing cancer including lifestyle, body mass index, use of tobacco and alcohol, family history of cancer and autoimmune diseases. In addition, based on available data from administrative registries, there is a possibility of misclassification of diseases with respect to both rheumatic and cancer diseases, which in turn may lead to misinterpretation of data on cancer risk. Also, associations between rheumatic diseases and cancer vary by type of disease, population and geographic zones, racial and ethnic factors. For example, a study performed in one geographical area is not corroborated by a study performed in another part of the world. Meta-analyses concerning cancer development in the course of biological therapy of rheumatic diseases, and likewise, are burdened with methodological errors such as a relatively short observation period compared to known and long-used cytostatic drugs, basing the assessment of treatment effectiveness on time to disease progression instead of overall survival time. Another problem is survival bias resulting from the fact that rapidly progressive malignancies may be underrepresented because patients may die prematurely or die from other (noncancerous) causes before cancer diagnosis [4].

Many studies use short follow-up periods making long-term cancer risk analysis difficult. Studies on the association of drugs used in rheumatology in the induction of secondary cancers are often based on data from transplantation. However, the use of observations from transplantation has its limitations, as multiple drugs are used in immunosuppressive therapy after transplantation and it is difficult to determine which (if any) drug is responsible for tumor development or recurrence. Moreover, it is difficult to translate data from immunosuppression used in transplantology to immunosuppression used in rheumatology, because in the first case there is no autoimmune disease, and in rheumatic diseases autoimmune processes are usually present. Some authors raise the problem that data obtained from randomized clinical studies and meta-analyses do not always meet the needs of patients and clinicians due to potential biases favoring positive results of these studies and a paucity of head-to-head comparisons between biologically active agents [5].

Coexistence of rheumatic diseases and cancer

Taking into account all the above mentioned methodological limitations, many publications point to the coexistence of rheumatic diseases and cancer, which can take the form of paraneoplastic syndromes, cancers induced by rheumatic disease therapy and conversely rheumatic disease induced by anticancer therapy [6–8]. Some rheumatic diseases may increase the incidence of cancer and a problem of particular importance is the induction of cancer under the influence of antirheumatic therapy. The extent of this problem is impossible to assess due to the lack of complete knowledge about the etiopathogenesis of both groups of the diseases and the inability to distinguish secondary from primary metachronous tumors.

Basically, the risk of cancer development or recurrence in patients treated for rheumatic disease is very low, estimated as 2–5 cases per 1000 patients treated annually, and even lower in patients with cured cancer and 5 years after completion of oncological treatment [9].

A study by Chang et al. evaluating cancer incidence in patients with different rheumatic diseases showed that different rheumatic diseases are associated with the risk of specific cancers [3]. According to Penn, the risk of cancer recurrence after rheumatic disease therapy can be defined as:

- low (0–10%) and concerning cancers of: testicle, cervix, thyroid and lymphoma,
- medium (11–25%) and concerning cancers of the endometrium, colon, prostate, breast, Wilms tumor,
- high (above 25%) and it involves bladder cancer, kidney, skin, malignant melanoma, sarcomas and multiple myeloma [10].

The mutual association between cancer and rheumatic diseases is best known in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), inflammatory myopathies, scleroderma and vasculitis. The highest association was described in lymphomas, but the association of rheumatic diseases with solid tumours has been inconsistent. In the epidemiological study based on the National Health and Nutrition Examination Survey (NHANES), breast and prostate cancer were the most common malignancies observed in patients with rheumatoid arthritis [11]. Meta-analysis of Simon et al. showed increased risk in RA patients for lymphomas, and to a lower degree for lung cancer but not for other malignancies [12]. These results are consistent with reports from other publications [13–14]. RA conveys some risk for cancer development but also influences cancer survival in patients with concomitant RA, especially in elderly patients with breast and prostate cancer [15]. In a retrospective cohort study, higher mortality was also found in RA patients with lung cancer [16]. Giat et al. showed that biologic therapy in RA does not significantly increase the risk of malignancy in RA patients, but this is influenced by different ethnic and environmental factors [17]. RA and dermatomyositis and polymyositis is associated with higher mortality in patients with lung and breast cancer, whereas systemic sclerosis is associated with decreased mortality in patients with lung cancer [17]. Environmental and geographic factors were shown to play a role in development of dermatomyositis and polymyositis in different types of cancer. For example, nasopharyngeal cancer is common among Chinese and Korean patients with dermatomyositis and polymyositis while seldom in Jordan's population.

The incidence of SS is associated with a risk of malignancy, especially of the lymphatic system. Patients with that disease have a 10-fold to 44-fold greater risk of developing malignant lymphoma than the healthy population; among this group of malignancies the most common are mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma and marginal zone lymphoma, which account for 90% of the lymphomas developed in SS [18]. SS is also associated with an increased risk of multiple myeloma and lung cancer. The latter is 5 times more common in SS. A nationwide retrospective case-control study in Taiwan showed that patients with SLE and SS have a significantly increased risk of nonmelanoma skin cancer [19]. Decades of research on the association of SLE with cancer provide interesting data. While SLE is associated with a 4-fold increased risk of non-Hodgkin lymphoma, some studies report a decreased risk of female hormone- dependent cancers: breast, ovarian and endometrial [20–22]. Several studies also reported increased risk of cervical, vulva/vaginal, head and neck, thyroid, bladder and kidney, liver and nonmelanoma skin cancer in patients with SLE [20, 21, 23–27]. The risk of malignancy in scleroderma has been described in three meta-analyses [28–31]. Onishi et al. examined 6641 people with scleroderma from Australia, northern Europe, Taiwan and the United States and showed an increased risk of lung, liver and hematologic cancers overall, as well as an increased risk of bladder cancer in women and nonmelanomatous skin cancer in men [29]. Similar results were observed in meta-analysis by Zhang et al. [30]. The authors observed increased cancer risk for lung cancer, hematopoietic cancer and non-Hodgkin lymphoma. The largest meta-analysis to date was conducted by Bonifazi et al. [31]. This meta-analysis was based on 16 observational studies and included publications presented by two earlier mentioned research groups. Investigators have demonstrated the risk of lung cancer and hematologic malignancies in patients diagnosed with scleroderma.

The idiopathic inflammatory myopathies (IIMs) are multisystemic diseases that include different systemic autoimmune rheumatic diseases such as: polymyositis (PM), adult dermatomyositis (DM), necrotizing myopathy (NM), myositis associated with another autoimmune diseases, cancer-associated myositis, juvenile myositis (JDM) and inclusion body myositis (IBM) [31]. The association between IIMs and cancer development is described in many large population studies [33–37] and is strong for patients with DM and less for PM, uncertain for NM or IBM, and not present with JDM. Clinical risk factors for cancer development include: age over 50 years, male gender, dysphagia, cutaneous necrosis, ulceration and vasculitis, sudden onset of myositis, refractory myositis, abnormalities in laboratory tests, especially concerning markers of inflammatory process [38–44].

Special attention is paid to targeted oncology therapies as they are associated with rheumatic immune-related adverse events (irAEs), estimated to be 5–10% in cancer patients treated with immune-checkpoint inhibitors (ICis) [45]. The most frequent rheumatic irAEs are: arthritis (1–7%), sicca (1.2–24.2%), myositis (0.4–6%) and polymyalgia rheumatica (0.2–2.1%). Less commonly observe syndromes are: de novo onset of sarcoidosis, vasculitis, lupus, antiphospholipid syndrome, sclerodermа-like syndromes, bone abnormalities [45].

Screening for malignant diseases

Some authors point out that patients treated for rheumatic diseases should be monitored for the development of possible malignancies. The issue of screening for malignant diseases in patients with diagnosed rheumatic disease is at least debatable. In general, the number of cancer types for which screening is justified is small. In addition, the highest incidence of cancer and rheumatic diseases is observed in the elderly, but current recommendations and guidelines do not provide screening tests for people over 65 years of age. Nevertheless, there are reports in the literature recommending certain examinations to be performed in patients after antirheumatic treatment in search of possible neoplastic disease. This is difficult because it is unclear what such monitoring should look like, especially since most of the described cancers do not involve screening for these diseases in potentially healthy, non-cancerous individuals. Moreover, the most frequently diagnosed neoplastic diseases arising in the course of antirheumatic therapy (for example lymphoid malignancies, bladder cancer) are not screened in the healthy population. Also, it is not known which examinations at what time after the completion or duration of antirheumatic therapy should be done and whether all or only a selected group of patients should be screened for the presence of neoplastic diseases. What is more, screening procedures may vary in different countries. Therefore, instead of carrying out screening tests, which do not exist for certain diseases, one should pay attention to such symptoms as, for example: weight loss, sub-febrile states, enlarged lymph nodes (lymphoid tumors), hematuria (bladder cancer). It seems that in the absence of standards for treatment, guidelines and recommendations for screening patients with rheumatic diseases for neoplastic diseases should be developed. Such standards arguably should look similar to, for example, genetic syndromes leading to colorectal cancer, where specific screening tests are performed in the appropriate time sequence. A proposal for such an algorithm procedure was presented by Moghadam-Kia and coauthors for IIMs. This scheme recommends three types of patient screening for cancer depending on the degree of risk. For patients at high risk, intermediate risk, and low risk, comprehensive screening, enhanced screening, and basic screening are recommended, respectively [32]. For high risk patients, screening should be performed annually for three consecutive years after IIMs diagnosis and for enhanced and basic screening, testing should be performed only once at baseline. The basic screening includes routine blood tests,

chest radiograph, age-appropriate screening (colonoscopy, mammography, cervical cytology, PSA). The enhanced screening includes basic screening and consideration of one or more of the following evaluations: computed CT scanning of the chest, abdomen and pelvis, gynecologic/pelvic ultrasound examination in women and testicular ultrasound examination and tumor markers in men. The comprehensive screening includes basic or enhanced screening with consideration of PET-CT scanning of the chest, abdomen, and pelvis [32].

It is generally believed that an intensive diagnostic work-up for neoplastic diseases in rheumatic patients should not be performed unless symptoms clearly indicate the development of neoplastic disease. Markers – especially AFP, PSA, CA-125, CA-19-9 and CA-3 – have low sensitivity and specificity for cancer screening in patients with rheumatic diseases. Moreover, the recommended determination of tumor markers is not justified as they serve to monitor the treatment of cancer and not its diagnosis. It is not uncommon to find elevated tumor markers in patients treated for rheumatic diseases without coexisting neoplastic diseases [46]. Tumor-associated antigens (TAA) may be elevated in rheumatoid arthritis (RA), rheumatic musculoskeletal diseases (RMDs), systemic sclerosis (Ssc), and systemic lupus erythematosus (SLE) [44, 46–52].The misleading concept of using markers in cancer screening is particularly evident in IIMs, where despite initial reports of the role of markers, current studies do not support their role in cancer detection [39, 52].

Conclusions

In the search for associations between cancers and rheumatic diseases, there is a need to construct methodologically valid studies based on a large patient populations. In the absence of clear recommendations for cancer screening of patients with rheumatic diseases, there is a need to develop guidelines for screening.

Conflict of interest: none declared

Krzysztof Jeziorski
National Institute of Geriatrics, Rheumatology and Rehabilitation
Department of Gerontology, Public Health and Didactics
ul. Spartańska 1
02-637 Warszawa
e-mail: krzysztof.jeziorski@spartanska.pl

Received: 14 Feb 2022
Accepted: 18 Mar 2022

References

1. Stertz O. Polymyositis. Berl Klin Wochenschr. 1916; 53: 489.
2. Bernatsky S, Ramsey-Goldman R, Clarke A. Malignancy and autoimmunity. Curr Opin Rheumatol. 2006; 18(2): 129–134, doi: 10.1097/01.bor.0000209423.39033.94, indexed in Pubmed: 16462517.
3. Chang SH, Park JK, Lee YJ, et al. Comparison of cancer incidence among patients with rheumatic disease: a retrospective cohort study. Arthritis Res Ther. 2014; 16(4): 428, doi: 10.1186/s13075-014-0428-x, indexed in Pubmed: 25163486.
4. Karmacharya P, Shahukhal R, Ogdie A. Risk of Malignancy in Spondyloarthritis: A Systematic Review. Rheum Dis Clin North Am. 2020; 46(3): 463–511, doi: 10.1016/j.rdc.2020.04.001, indexed in Pubmed: 32631600.
5. Ioannidis JPA, Karassa FB, Druyts E, et al. Biologic agents in rheumatology: unmet issues after 200 trials and $200 billion sales. Nat Rev Rheumatol. 2013; 9(11): 665–673, doi: 10.1038/nrrheum.2013.134, indexed in Pubmed: 23999553.
6. Kwiatkowska B, Przygodzka M, Filipowicz-Sosnowska A. Rheumatic symptoms in malignant disease. NOWOTWORY J Oncol. 2006; 56: 693–699.
7. Cioffi G, Viapiana O, Tarantini L, et al. The troubling liaison between cancer and metabolic syndrome in chronic inflammatory rheumatic diseases. Arthritis Res Ther. 2021; 23(1): 89, doi: 10.1186/s13075-021-02465-3, indexed in Pubmed: 33741041.
8. Ytterberg SR, Bhatt DL, Mikuls TR, et al. ORAL Surveillance Investigators. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022; 386(4): 316–326, doi: 10.1056/NEJMoa2109927, indexed in Pubmed: 35081280.
9. Davis JM. Overview of the Associations Between Cancer and Rheumatic Disease. Rheum Dis Clin North Am. 2020; 46(3): 417–427, doi: 10.1016/j.rdc.2020.05.002, indexed in Pubmed: 32631597.
10. Penn I. The effect of immunosuppression on pre-existing cancers. Transplantation. 1993; 55(4): 742–747, doi: 10.1097/00007890-199304000-00011, indexed in Pubmed: 8475546.
11. Bhandari B, Basyal B, Sarao MS, et al. Prevalence of Cancer in Rheumatoid Arthritis: Epidemiological Study Based on the National Health and Nutrition Examination Survey (NHANES). Cureus. 2020; 12(4): e7870, doi: 10.7759/cureus.7870, indexed in Pubmed: 32489725.
12. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015; 17(1): 212, doi: 10.1186/s13075-015-0728-9, indexed in Pubmed: 26271620.
13. Klein A, Polliack A, Gafter-Gvili A. Rheumatoid arthritis and lymphoma: Incidence, pathogenesis, biology, and outcome. Hematol Oncol. 2018; 36(5): 733–739, doi: 10.1002/hon.2525, indexed in Pubmed: 29862535.
14. Khurana R, Wolf R, Berney S, et al. Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans. J Rheumatol. 2008; 35(9): 1704–1708, indexed in Pubmed: 18634160.
15. Nayak P, Luo R, Elting L, et al. Impact of Rheumatoid Arthritis on the Mortality of Elderly Patients Who Develop Cancer: A Population-Based Study. Arthritis Care Res (Hoboken). 2017; 69(1): 75–83, doi: 10.1002/acr.22997, indexed in Pubmed: 27483088.
16. Park JK, Yang JiAe, Ahn EY, et al. Survival rates of cancer patients with and without rheumatic disease: a retrospective cohort analysis. BMC Cancer. 2016; 16: 381, doi: 10.1186/s12885-016-2444-5, indexed in Pubmed: 27412038.
17. Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev. 2017; 16(10): 1049–1057, doi: 10.1016/j.autrev.2017.07.022, indexed in Pubmed: 28778707.
18. Igoe A, Merjanah S, Scofield RH. Sjögren Syndrome and Cancer. Rheum Dis Clin North Am. 2020; 46(3): 513–532, doi: 10.1016/j.rdc.2020.05.004, indexed in Pubmed: 32631601.
19. Tseng HW, Huang WC, Lu LY. The influence of immunosuppressants on the non-melanoma skin cancer among patients with systemic lupus erythematosus and primary Sjögren's syndrome: a nationwide retrospective case-control study in Taiwan. Clin Exp Rheumatol. 2019; 37(6): 946–952, indexed in Pubmed: 31074727.
20. Ladouceur A, Tessier-Cloutier B, Clarke AE, et al. Cancer and Systemic Lupus Erythematosus. Rheum Dis Clin North Am. 2020; 46(3): 533–550, doi: 10.1016/j.rdc.2020.05.005, indexed in Pubmed: 32631602.
21. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun. 2013; 42: 130–135, doi: 10.1016/j.jaut.2012.12.009, indexed in Pubmed: 23410586.
22. Bernatsky S, Ramsey-Goldman R, Foulkes WD, et al. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: a meta-analysis. Br J Cancer. 2011; 104(9): 1478–1481, doi: 10.1038/bjc.2011.115, indexed in Pubmed: 21487409.
23. Zard E, Arnaud L, Mathian A, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature. Autoimmun Rev. 2014; 13(7): 730–735, doi: 10.1016/j.autrev.2014.03.001, indexed in Pubmed: 24657969.
24. Chang SL, Hsu HT, Weng SF, et al. Impact of head and neck malignancies on risk factors and survival in systemic lupus erythematosus. Acta Otolaryngol. 2013; 133(10): 1088–1095, doi: 10.3109/00016489.2013.800228, indexed in Pubmed: 24032572.

25. Song L, Wang Yi, Zhang J, et al. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther. 2018; 20(1): 270, doi: 10.1186/s13075-018-1760-3, indexed in Pubmed: 30522515.
26. Ni J, Qiu LJ, Hu LF, et al. Lung, liver, prostate, bladder malignancies risk in systemic lupus erythematosus: evidence from a meta-analysis. Lupus. 2014; 23(3): 284–292, doi: 10.1177/0961203313520060, indexed in Pubmed: 24429300.
27. Cao L, Tong H, Xu G, et al. Systemic lupus erythematous and malignancy risk: a meta-analysis. PLoS One. 2015; 10(4): e0122964, doi: 10.1371/journal.pone.0122964, indexed in Pubmed: 25885411.
28. Weeding E, Casciola-Rosen L, Shah AA. Cancer and Scleroderma. Rheum Dis Clin North Am. 2020; 46(3): 551–564, doi: 10.1016/j.rdc.2020.03.002, indexed in Pubmed: 32631603.
29. Onishi A, Sugiyama D, Kumagai S, et al. Cancer incidence in systemic sclerosis: meta-analysis of population-based cohort studies. Arthritis Rheum. 2013; 65(7): 1913–1921, doi: 10.1002/art.37969, indexed in Pubmed: 23576072.
30. Zhang JQ, Wan YN, Peng WJ, et al. The risk of cancer development in systemic sclerosis: a meta-analysis. Cancer Epidemiol. 2013; 37(5): 523–527, doi: 10.1016/j.canep.2013.04.014, indexed in Pubmed: 23725641.
31. Bonifazi M, Tramacere I, Pomponio G, et al. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. Rheumatology (Oxford). 2013; 52(1): 143–154, doi: 10.1093/rheumatology/kes303, indexed in Pubmed: 23175568.
32. Moghadam-Kia S, Oddis CV, Ascherman DP, et al. Risk Factors and Cancer Screening in Myositis. Rheum Dis Clin North Am. 2020; 46(3): 565–576, doi: 10.1016/j.rdc.2020.05.006, indexed in Pubmed: 32631604.
33. Yang Z, Lin F, Qin B, et al. Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. J Rheumatol. 2015; 42(2): 282–291, doi: 10.3899/jrheum.140566, indexed in Pubmed: 25448790.
34. Stockton D, Doherty VR, Brewster DH. Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study. Br J Cancer. 2001; 85(1): 41–45, doi: 10.1054/bjoc.2001.1699, indexed in Pubmed: 11437400.
35. Buchbinder R, Forbes A, Hall S, et al. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann Intern Med. 2001; 134(12): 1087–1095, doi: 10.7326/0003-4819-134-12-200106190-00008, indexed in Pubmed: 11412048.
36. Chow WH, Gridley G, Mellemkjaer L, et al. Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. Cancer Causes Control. 1995; 6(1): 9–13, doi: 10.1007/BF00051675, indexed in Pubmed: 7718740.
37. Sigurgeirsson B, Lindelöf B, Edhag O, et al. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. N Engl J Med. 1992; 326(6): 363–367, doi: 10.1056/NEJM199202063260602, indexed in Pubmed: 1729618.
38. Wang J, Guo G, Chen G, et al. Meta-analysis of the association of dermatomyositis and polymyositis with cancer. Br J Dermatol. 2013; 169(4): 838–847, doi: 10.1111/bjd.12564, indexed in Pubmed: 23909921.
39. András C, Ponyi A, Constantin T, et al. Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. J Rheumatol. 2008; 35(3): 438–444, indexed in Pubmed: 18203322.
40. Ponyi A, Constantin T, Garami M, et al. Cancer-associated myositis: clinical features and prognostic signs. Ann N Y Acad Sci. 2005; 1051: 64–71, doi: 10.1196/annals.1361.047, indexed in Pubmed: 16126945.
41. Prohic A, Kasumagic-Halilovic E, Simic D, et al. Clinical and biological factors predictive of malignancy in dermatomyositis. J Eur Acad Dermatol Venereol. 2009; 23(5): 591–592, doi: 10.1111/j.1468-3083.2008.02971.x, indexed in Pubmed: 18752541.
42. Sparsa A, Liozon E, Herrmann F, et al. Routine vs extensive malignancy search for adult dermatomyositis and polymyositis: a study of 40 patients. Arch Dermatol. 2002; 138(7): 885–890, doi: 10.1001/archderm.138.7.885, indexed in Pubmed: 12071815.
43. Leow YH, Goh CL. Malignancy in adult dermatomyositis. Int J Dermatol. 1997; 36(12): 904–907, doi: 10.1046/j.1365-4362.1997.00190.x, indexed in Pubmed: 9466195.
44. Basset-Seguin N, Roujeau JC, Gherardi R, et al. Prognostic factors and predictive signs of malignancy in adult dermatomyositis. A study of 32 cases. Arch Dermatol. 1990; 126(5): 633–637, indexed in Pubmed: 2334184.
45. Thanarajasingam U, Abdel-Wahab N. Immune Checkpoint Inhibition--Does It Cause Rheumatic Diseases? Mechanisms of Cancer-Associated Loss of Tolerance and Pathogenesis of Autoimmunity. Rheum Dis Clin North Am. 2020; 46(3): 587–603, doi: 10.1016/j.rdc.2020.04.003, indexed in Pubmed: 32631606.
46. Szekanecz Z, Gomez I, Soós B, et al. Hungarian OncoRheumatology Network (HORN) initiative. Eight pillars of oncorheumatology: Crossroads between malignancies and musculoskeletal diseases. Autoimmun Rev. 2020; 19(11): 102658, doi: 10.1016/j.autrev.2020.102658, indexed in Pubmed: 32942035.
47. Szekanecz Z, Haines GK, Harlow LA, et al. Increased synovial expression of the adhesion molecules CD66a, CD66b, and CD31 in rheumatoid and osteoarthritis. Clin Immunol Immunopathol. 1995; 76(2): 180–186, doi: 10.1006/clin.1995.1113, indexed in Pubmed: 7614736.
48. Szekanecz E, Sándor Z, Antal-Szalmás P, et al. Increased production of the soluble tumor-associated antigens CA19-9, CA125, and CA15-3 in rheumatoid arthritis: potential adhesion molecules in synovial inflammation? Ann N Y Acad Sci. 2007; 1108: 359–371, doi: 10.1196/annals.1422.037, indexed in Pubmed: 17893999.
49. Szekanecz E, Szucs G, Szekanecz Z, et al. Tumor-associated antigens in systemic sclerosis and systemic lupus erythematosus: associations with organ manifestations, immunolaboratory markers and disease activity indices. J Autoimmun. 2008; 31(4): 372–376, doi: 10.1016/j.jaut.2008.08.008, indexed in Pubmed: 18926664.
50. Kimura K, Ezoe K, Yokozeki H, et al. Elevated serum CA125 in progressive systemic sclerosis with pleural effusion. J Dermatol. 1995; 22(1): 28–31, doi: 10.1111/j.1346-8138.1995.tb03336.x, indexed in Pubmed: 7897020.
51. Safadi R, Ligumsky M, Goldin E, et al. Increased serum CA 19-9 antibodies in Sjögren's syndrome. Postgrad Med J. 1998; 74(875): 543–544, doi: 10.1136/pgmj.74.875.543, indexed in Pubmed: 10211329.
52. Wong RCW, Brown S, Clarke BE, et al. Transient elevation of the tumor markers CA 15-3 and CASA as markers of interstitial lung disease rather than underlying malignancy in dermatomyositis sine myositis. J Clin Rheumatol. 2002; 8(4): 204–207, doi: 10.1097/00124743-200208000-00005, indexed in Pubmed: 17041361.

VIA MEDICA

COVID-19

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 195–199
DOI: 10.5603/NJO.2022.0027

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

One year into COVID-19 – the infodemiology of cancer screening

Robert Olszewski[1, 2], Justyna Obiała[1], Karolina Obiała[1], Małgorzata Mańczak[1], Jakub Owoc[1], Klaudia Ćwiklińska[1], Krzysztof Jeziorski[1, 3]

[1]*Department of Gerontology, Public Health and Didactics, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland*
[2]*Department of Ultrasound, Institute of Fundamental Technological Research, Polish Academy of Sciences, Warsaw, Poland*
[3]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction. To investigate the public interest in cancer screening before, during and after one year of the COVID-19 pandemic, in relation to the number of cases and deaths caused by the coronavirus.

Material and methods. Google Trends (GT) was used to obtain data on online interest in screening for the most common cancer types during COVID-19 pandemic.

Results. It was found that although online interest in screening collapsed during the early stages of the pandemic, it managed to gradually return to its pre-pandemic levels six months later despite a growing number of COVID-19 related deaths. Nevertheless, some data and reports suggest that this unprecedented crisis may result in increased mortality and incidence rates.

Conclusions. The study raises the importance of continuous and active actions aimed at raising cancer awareness which appears to be crucially important during a public health crisis such as the COVID-19 pandemic.

Key words: cancer screening, cancer information seeking, COVID-19, infodemiology, public health

Introduction

Cancer is considered one of the leading causes of death globally, and the rate of cancer-related deaths is expected to increase significantly in the future. However, none of the calculations or estimates took into account the extraordinary situation that the world has been dealing with since the beginning of 2020 – the coronavirus pandemic that deprioritized, delayed or even ceased a lot of cancer care on a global scale [1]. It spurred the World Health Organization (WHO) to issue a statement saying that although COVID-19 poses multiple threats, the epidemic of cancer is one that cannot be ignored and ensuring continuity of care is one of the key challenges [2].

The latest research and data indicate the alarming impact of the COVID-19 pandemic on healthcare systems, contributing to reduced cancer detection and treatment, which may increase cancer morbidity and mortality for years to come [3]. As early detection through screening may substantially increase the likelihood of cancer survival, reduce morbidity rates and improve patients' quality of life, the stakes are significant [4]. This refers not only to the human aspect but also the capabi-

How to cite:
Olszewski R, Obiała J, Obiała K, Mańczak M, Owoc J, Ćwiklińska K, Jeziorski K. ***One year into COVID-19 – the infodemiology of cancer screening.*** *NOWOTWORY J Oncol* 2022; 72: 195–199.

lities of healthcare systems to absorb the additional burden. The unexpected circumstances may make some previously curable tumors more difficult to treat, increase their number and eventually lead to more deaths [5]. Snyder et al. already found that globally public interest in cancer screening tests decreased by as much as 76% during the first wave of the pandemic [6].

The common characteristic of this and numerous other studies is that they all investigated public health issues by using Google Trends (GT). This widespread tool presents data on keywords typed into the Google search engine and is used for identifying popular health topics as well as other purposes such as evaluating interventions for policymakers, monitoring population concerns or even predicting waves of influenza [7, 8].

The previous reports on online cancer screening covered only the early stages of the coronavirus pandemic [6]. This paper scrutinizes public interest in cancer screening during the pandemic at the global level, to cover the entire year, checks for any associations with the number of coronavirus deaths and the latest available data on cancer.

Methods

We used GT to obtain data on online interest in cancer screening during the COVID-19 pandemic.

Google Trends is an analytic tool, widely used in health research, that "analyzes Google Search searches and provides data on temporal patterns in relative search volumes (RSV) for user-specified terms". RSV presents selected timeframes (weeks, months etc.) in which a period of time with the highest interest equals to 100 while others are shown as percentages relative to the 100 [9].

We performed worldwide searches in Google Trends on 7 May 2021 covering the period from 5 January 2020 to 2 May 2021. The following search terms were used: "mammogram" for breast cancer, "colonoscopy" for colorectal cancer, "Pap smear" for cervical cancer and "PSA test" for prostate cancer. We also performed the same search covering a 5-year period (from 8 May 2016 to 2 May 2021) to check for any cyclical changes over time. Each of the final search terms was selected based on its relative popularity measured with GT. For example, we compared terms "mammography", "mammogram", "breast cancer screening", "breast examination" or "breast test" to eventually choose "mammogram".

Three 10-week time periods were selected in order to compare online interest: one year before the COVID-19 outbreak (3 March 2019–5 May 2019), the COVID-19 outbreak (1 March 2020–3 May 2020), one year after the COVID-19 outbreak (28 February 2021–2 May 2021). RSV values were compared using the Wilcoxon test. Data are presented as median and interquartile range (IQR). The "health" query category was used to obtain the most relevant data.

The queries referred to screening tests for the most common global types of cancer were selected according to the WHO Cancer Fact Sheets [10]. Lung cancer was excluded from the analysis to reduce the bias of increased interest in chest computed tomography (CT) used in medical procedures for COVID-19 [11].

Data on weekly COVID-19 deaths came from the Our World in Data and compared with GT results which allowed us to compare online interest in cancer screening against the course of the pandemic over time [12].

Results

The interest of Internet users in cancer screening over the 4 years before the pandemic outbreak was fairly constant (fig. 1). Colonoscopy had the greatest number of searches (4-year mean RSV of 74), followed by mammogram (35), pap smear (30) and PSA test (9). A sharp drop of interest in cancer screening started around 15 March 2020. Approximately six months later RSV values managed to slowly return to their original pre-pandemic levels. There were cyclical declines of RSV values for each of the search terms in the second half of December. The interest in mammography grew cyclically each October.

The decline in cancer screening interest in March 2020 coincides with the COVID-19 outbreak (fig. 2). In the following months, RSV values began to increase despite a growing num-

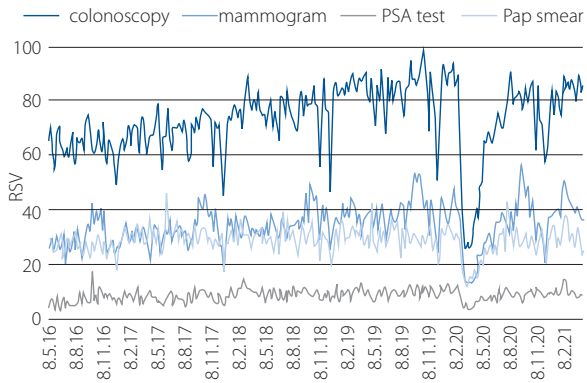

Figure 1. The interest of Internet users in cancer screening over 4 years before the pandemic outbreak (2016–2020)

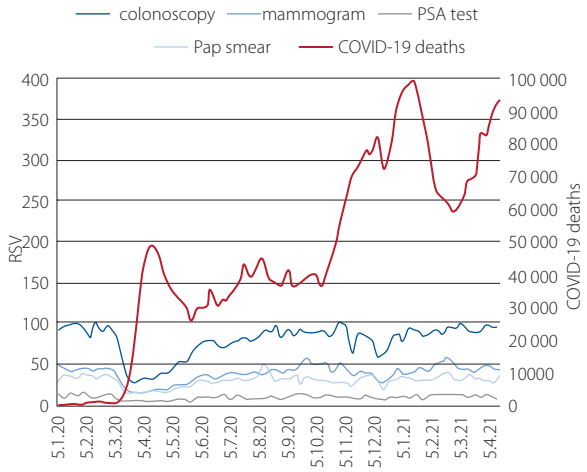

Figure 2. The interest of Internet users in cancer screening after the pandemic outbreak (March 2020–April 2021)

Table I. Comparison of RSV during three 10-week periods: one year before the COVID-19 outbreak (3 March 2019-5 May 2019), the COVID-19 outbreak (1 March 2020-3 May 2020) and one year after the COVID-19 outbreak (28 February 2021–2 May 2021)

Search term	One year before the COVID-19 outbreak median (IQR)		The COVID-19 outbreak median (IQR)		One year after the COVID-19 outbreak median (IQR)		p[a]	p[b]
colonoscopy	87	(84–88)	33	(28–48)	85	(85–87)	0.0077	0.5751
mammogram	38	(36–42)	15	(14–24)	41	(39–44)	0.0051	0.0191
PSA test	10	(9–11)	6	(4–6)	10	(9–10)	0.0051	0.4838
Pap smear	31	(29–33)	16	(14–18)	29	(27–30)	0.0051	0.6784

[a] – comparison between the COVID-19 outbreak and one year after the COVID-19 outbreak periods; [b] – comparison between one year before the COVID-19 outbreak and one year after the COVID-19 outbreak periods

ber of cases and deaths. Moreover, the second wave of the pandemic that started in November 2020 did not coincide with a similar decline in cancer screening interest recorded during the first wave.

Table I presents median values of RSV for three 10-week periods: March–April 2019, March–April 2020 and March–April 2021. The data show that the RSV values in the initial period of the pandemic (March–April 2020) were significantly lower than in the corresponding period one year later. On the other hand, a comparison of RSVs one year after the COVID-19 outbreak with the year before the outbreak, indicates that they are comparable (the differences are not statistically significant for colonoscopy, PSA test, Pap smear), and mammography searches were even more frequent in the March–April 2021 than in March–April 2019. The largest drops independently for each of the search terms were:

- 76% for mammography,
- 75% for PSA test,
- 72% for colonoscopy,
- 66% for Pap smear.

Discussion

The need for investigation into how COVID-19 impacts long-term cancer-related mortality has already been emphasized, nevertheless some negative effects of the pandemic are already observable [1].

The largest drop of online interest in cancer screening was around mid-March to mid-April 2020, which corresponds with the onset of the coronavirus pandemic officially declared on 11 March 2020 by the WHO. This may well be an important observation as it has been recognized that people who seek health information online are more likely to get a timely screening [13]. However, it has also been found that patients with initial symptoms, diagnosed cancer, or limited access to medical care turn to the Internet for information, especially social media, cancer institute's websites, or support groups [14, 15].

Thus, it seems that the world had experienced a novel situation of both phenomena – limited access to care caused by lockdowns and a drop in interest at the same time. The natural cause of this seems to be the unprecedented redirecting of everybody's attention to coronavirus – the most popular topic in 2020 globally according to Google's Year in Search 2020 [16].

Another finding is that one year into the pandemic people were looking for information on cancer screening more often, although the number of deaths from COVID-19 is much higher. It is not clear to what extent this may be triggered by prevention needs or first symptoms. However, this short-lasting phenomenon – regardless of its root causes, be it lack of interest, lockdowns or both – appears to already have real and serious consequences regarding delayed diagnoses [2].

Although the long-term consequences of limited access to healthcare and screening due to all sorts of lockdowns are yet to be seen, the alarmingly high number of excess deaths not directly associated with the COVID-19 in some countries is already concerning [17].

The data from Poland, collected on a monthly basis, show that the monthly number of new suspected cases of cancer dropped significantly during the first lockdown in March 2020 (by 38.4% in March 2020 year to year) to increase to all-time highs a year later (by 82.9% in March 2021 year to year) [18]. The study of Koczkodaj et al. showed a decrease in the number of issued oncology diagnosis and treatment cards in breast, cervix and colorectal cancers during the pandemic [19]. Data confirm that sudden and significant drops in cancer diagnoses that started in March 2020 were observed also in the United States [20], Denmark [21], or even Sweden [22] where a full lockdown was not enforced.

Although the long-term consequences of limited access to healthcare and screening due to all sorts of lockdowns are yet to be seen, the alarmingly high number of excess deaths not directly associated with COVID-19 in some countries is concerning. In 2018, the number of new cancer cases worldwide was predicted to reach 19.3 million by 2020. Naturally, this estimate did not include the impact of the COVID-19 pandemic. It is likely though that it will have a potential impact on mortality and delay diagnosis [23]. The WHO already reported that 1 in 3 European Union countries had partially or completely disrupted cancer services [2]. Some researchers suggested that preventive cancer screening should not be limited – even during pandemics [24].

One year after the pandemic unfolded, the Google Trends data suggest that the number of searches was gradually returning to its pre-pandemic level. Although we saw significant declines in searches in December, long-term data presented in the publication of Ellery et al. suggest that interest seen in health-related searches is cyclical [25]. Data suggest that the pandemic did not change search behaviors in this regard. There were occasional increases of online interest in specific types of cancer screening procedures during the pandemic with the most notable referring to mammography searches that regularly spiked in October. This is most likely linked to the Breast Cancer Awareness Month and a clear indication that proper prevention campaigns may have considerable impact [26].

The pandemic did not affect the order of the most popular cancer screening searches with colonoscopy still topping the list.

Conclusions

The unprecedented drop in March–April 2020 was the largest one in the entire history of searching for cancer screening online. As this decline coincided with the peak of "covid test" searches, it is likely that the online interest and health-related concerns of people shifted largely to pandemic related threats. It took approximately six months for online interest to return to its original values, however this gap is likely to result in increased rates of mortality and incidence.

The study raises the importance of continuous and active actions aimed at raising cancer awareness, something that is critically important during a public health crisis such as the COVID-19 pandemic. Strengthening cancer awareness and targeting health strategies at cancer screening is crucial as patients with cancer history are over four times more likely to develop critical illness while being hospitalized with COVID-19 [27].

The Google Trends cannot be used as a substitute for traditional data about cancer screening. Nevertheless, as GT has already proven effective in predicting flu waves, one cannot exclude that GT fluctuations in cancer screening would be eventually followed by real data. There are some concerning indications that such processes may already be taking place. There is a need to closely monitor how the situation evolves and possibly brace cancer care for additional burdens.

Availability of data and material

The data that support the findings of this study are openly available at www.trends.google.com and www.ourworldindata.org/covid-death.

Conflict of interest: none declared

Robert Olszewski
National Institute of Geriatrics
Rheumatology and Rehabilitation
Department of Gerontology, Public Health and Didactics
ul. Spartańska 1
02-637 Warszawa, Poland
e-mail: robert.olszewski@spartanska.pl

Received: 17 Feb 2022
Accepted: 18 Mar 2022

References

1. Safeguarding cancer care in a post-COVID-19 world. Lancet Oncol. 2020; 21(5): 603, doi: 10.1016/s1470-2045(20)30243-6.
2. World Health Organization Statement – Catastrophic impact of COVID-19 on cancer care; 2021. https://www.euro.who.int/en/media-centre/sections/statements/2021/statement-catastrophic-impact-of-covid-19-on-cancer-care (04.2021).
3. Patt D, Gordan L, Diaz M, et al. Impact of COVID-19 on Cancer Care: How the Pandemic Is Delaying Cancer Diagnosis and Treatment for American Seniors. JCO Clin Cancer Inform. 2020; 4: 1059–1071, doi: 10.1200/CCI.20.00134, indexed in Pubmed: 33253013.
4. Whitaker K. Earlier diagnosis: the importance of cancer symptoms. Lancet Oncol. 2020; 21(1): 6–8, doi: 10.1016/s1470-2045(19)30658-8.
5. COVID-19 and cancer: 1 year on. Lancet Oncol. 2021; 22(4): 411, doi: 10.1016/s1470-2045(21)00148-0.
6. Snyder A, Jang S, Nazari IS, et al. Google search volume trends for cancer screening terms during the COVID-19 pandemic. J Med Screen. 2021; 28(2): 210–212, doi: 10.1177/0969141321999426, indexed in Pubmed: 33663240.
7. Springer S, Menzel LM, Zieger M. Google Trends provides a tool to monitor population concerns and information needs during COVID-19 pandemic. Brain Behav Immun. 2020; 87: 109–110, doi: 10.1016/j.bbi.2020.04.073, indexed in Pubmed: 32360607.
8. Dugas AF, Jalalpour M, Gel Y, et al. Influenza forecasting with Google Flu Trends. PLoS One. 2013; 8(2): e56176, doi: 10.1371/journal.pone.0056176, indexed in Pubmed: 23457520.
9. Nuti SV, Wayda B, Ranasinghe I, et al. The use of google trends in health care research: a systematic review. PLoS One. 2014; 9(10): e109583, doi: 10.1371/journal.pone.0109583, indexed in Pubmed: 25337815.
10. World Health Organization. Cancer; 2021. https://www.who.int/news-room/fact-sheets/detail/cancer (6.04.2021).
11. Bao C, Liu X, Zhang H, et al. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. J Am Coll Radiol. 2020; 17(6): 701–709, doi: 10.1016/j.jacr.2020.03.006, indexed in Pubmed: 32283052.
12. Roser M, Ritchie H, Ortiz-Ospina E, et al. Coronavirus Pandemic (COVID-19) - Statistics and Research; 2020. https://ourworldindata.org/coronavirus (9.11.2020).
13. Shneyderman Y, Rutten LJ, Arheart KL, et al. Health Information Seeking and Cancer Screening Adherence Rates. J Cancer Educ. 2016; 31(1): 75–83, doi: 10.1007/s13187-015-0791-6, indexed in Pubmed: 25619195.
14. Soroya SH, Farooq A, Mahmood K, et al. From information seeking to information avoidance: Understanding the health information behavior during a global health crisis. Inf Process Manag. 2021; 58(2): 102440, doi: 10.1016/j.ipm.2020.102440, indexed in Pubmed: 33281273.
15. Yan AP, Howden K, Mahar AL, et al. Gender differences in adherence to COVID-19 preventative measures and preferred sources of COVID-19 information among adolescents and young adults with cancer. Cancer Epidemiol. 2022; 77: 102098, doi: 10.1016/j.canep.2022.102098, indexed in Pubmed: 35104772.
16. Google Trends. 2020: Year in Search; 2020. https://trends.google.com/trends/yis/2020/GLOBAL/ (14.05.2021).
17. Richards M, Anderson M, Carter P, et al. The impact of the COVID-19 pandemic on cancer care. Nat Cancer. 2020; 1(6): 565–567, doi: 10.1038/s43018-020-0074-y, indexed in Pubmed: 35121972.
18. National Health Fund. Online database with monthly data; 2020. https://shiny.nfz.gov.pl/dilo_dash/ (5.05.2020).
19. Koczkodaj P, Sulkowska U, Kamiński M, et al. SARS-CoV-2 as a new possible long-lasting determining factor impacting cancer death numbers. Based on the example of breast, colorectal and cervical cancer in Poland. Nowotwory J Oncol. 2021; 71(1): 42–46, doi: 10.5603/njo.2021.0007.
20. Kaufman HW, Chen Z, Niles J, et al. Changes in the Number of US Patients With Newly Identified Cancer Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic. JAMA Netw Open. 2020; 3(8): e2017267, doi: 10.1001/jamanetworkopen.2020.17267, indexed in Pubmed: 32749465.
21. Skovlund CW, Friis S, Dehlendorff C, et al. Hidden morbidities: drop in cancer diagnoses during the COVID-19 pandemic in Denmark. Acta Oncol. 2021; 60(1): 20–23, doi: 10.1016/j.lanepe.2021.100188.
22. Regionala cancercentrum i samverkan. Uppskjuten cancervård, Jämforelse av antalet nyregistrerade cancerfall under covid-19-pandemin 2020 och motsvarande period 2019. https://cancercentrum.

se/globalassets/covid-19/rapport_uppskjuten_cancervard_covid19--varen2020_vers1.0.pdf (19.07.2021).
23. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
24. Issaka RB, Somsouk M. Colorectal Cancer Screening and Prevention in the COVID-19 Era. JAMA Health Forum. 2020; 1(5), doi: 10.1001/jamahealthforum.2020.0588, indexed in Pubmed: 34532717.
25. Ellery P, Vaughn W, Ellery J, et al. Understanding internet health search patterns: An early exploration into the usefulness of Google Trends. J Commun Health. 2013; 1(4): 441–456, doi: 10.1179/cih.2008.1.4.441.
26. Patel MS, Halpern JA, Desai AS, et al. Success of Prostate and Testicular Cancer Awareness Campaigns Compared to Breast Cancer Awareness Month According to Internet Search Volumes: A Google Trends Analysis. Urology. 2020; 139: 64–70, doi: 10.1016/j.urology.2019.11.062, indexed in Pubmed: 32001306.
27. Liang W, Liang H, Ou L, et al. China Medical Treatment Expert Group for COVID-19. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. 2020; 180(8): 1081–1089, doi: 10.1001/jamainternmed.2020.2033, indexed in Pubmed: 32396163.

VIA MEDICA

Pictures in oncology

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 200
DOI: 10.5603/NJO.a2022.0021

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Rectal cancer as a rare cause of Fournier's gangrene

Michał Kisielewski[1], Anna Mydłowska[2], Michał Nowakowski[3]

[1]*Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[2]*Department of Surgery, University of Alabama, Birmingham, United States*
[3]*II Department of General Surgery, Collegium Medicum, Jagiellonian University, Krakow, Poland*

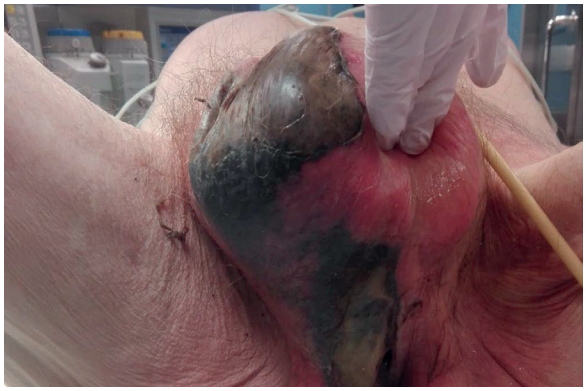

Figure 1. Fournier's gangrene prior to surgery

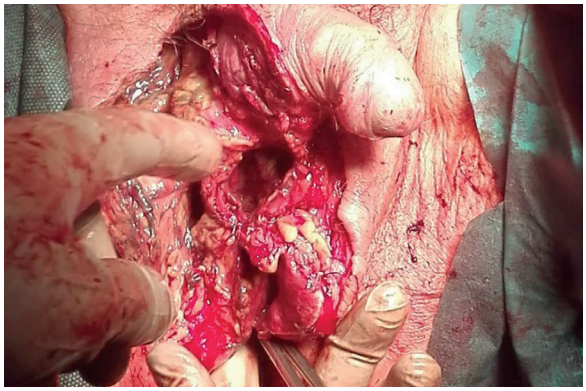

Figure 2. View after surgical debridement

Fournier's gangrene (FG) is a rapidly progressive infection due to invasion of aerobic and anaerobic bacteria. Patient presents with septic shock [1]. Fournier's gangrene in a rectal cancer setting is very rare [2]. We report a patient with severe FG as a first presentation of locally advanced rectal cancer. An 86-year-old man was brought to the emergency room due to discolouration of the scrotal region and a decrease in mental status. At admission the patient there was necrotic swelling with black discolouration of the scrotum and perianal region (fig. 1) with subcutaneous emphysema. *Per rectum* examination revealed multiple anterior fistulas with a bleeding mass noted right above the margin of the anus. The patient was qualified for emergency surgery. Surgery revealed a pelvic mass without signs of metastatic disease to the peritoneum. A diverting sigmoid colostomy was created. Urological intervention consisted of bilateral orchiectomy with extensive debridement of the scrotum and perianal region (fig. 2). A suprapubic cystostomy was also created. Patient was discharged home with a colostomy bag in a good general state after a total hospital stay of 27 days. The histopathological report revealed infiltrative adenocarcinoma G2 with angioinvasion. Scrotal and testicular specimen revealed necrosis of the scrotum and oedema and fibro-pustular infiltration of the testes.

References

1. Klement RJ, Schäfer G, Sweeney RA. A fatal case of Fournier's gangrene during neoadjuvant radiotherapy for rectal cancer. Strahlenther Onkol. 2019; 195(5): 441–446, doi: 10.1007/s00066-018-1401-4, indexed in Pubmed: 30470845.
2. Błaszkowski T, Celban G, Domagała M, et al. Surgical treatment of rectal cancer in Poland – a report from a prospective, multi-centre observational study PSSO_01 conducted under the auspices of the Polish Society of Surgical Oncology. Nowotwory. Journal of Oncology. 2018; 68(3): 118–126, doi: 10.5603/njo.2018.0019.

How to cite:
Kisielewski M, Mydłowska A, Nowakowski M. ***Rectal cancer as a rare cause of Fournier's gangrene.*** *NOWOTWORY J Oncol* 2022; 72: 200.

VIA MEDICA

Pictures in oncology

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 201
DOI: 10.5603/NJO.a2022.0020

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Peritoneal recurrence of RCC and gastric cancer treated with cytoreductive surgery and HIPEC

Tomasz Jastrzębski[1, 2], Marian Brodecki[2], Michał Spychalski[2], Tomasz Sylwestrzak[1], Adam Dziki[2, 3]

[1]*Surgical Oncology Department, Medical University of Gdansk, Gdansk, Poland*
[2]*Surgical Oncology Department, District Health Centre Hospital, Brzeziny, Poland*
[3]*General and Colorectal Surgery Department, Medical University in Lodz, Lodz, Poland*

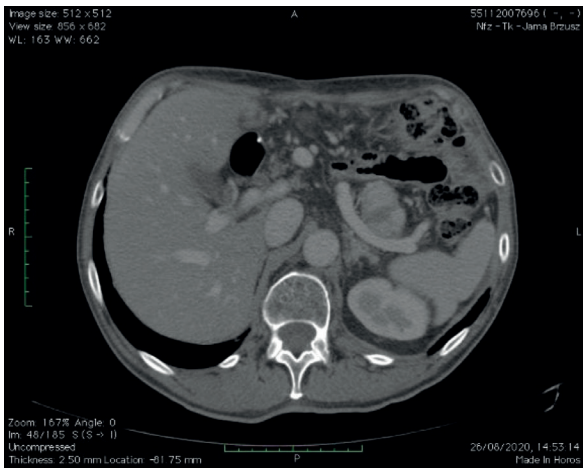

Figure 1. A CT scan of a gastric stump tumor

A 65-year-old male patient was admitted to the surgical oncology clinic after an examination in August 2020 revealed 10 mm ulceration in the gastric stump (fig. 1); earlier, on 1st Feb 2019, a subtotal gastric resection was performed due to a gastric adenocarcinoma. A histopathological examination revealed cancer cells in 4 out of 10 of the removed lymph nodes, the margins – R0. The patient did not qualified for adjuvant therapy after the surgery, but was qualified for another surgical procedure and HIPEC in a clinical center accredited by the surgical associations after considering the non-radical character of the previous gastric surgery [1]. During the surgery on 16th Sep 2020 on the gastric stump, the intestinal loop, pancreas tail, part of the pancreas body, the spleen and tumor were removed. Cisplatin was administered. PCI was 2 points and the procedure was macroscopically radical – CC-0. The histopathological examination revealed high grade adenocarcinoma in the gastric stump with the obstruction of the lymphatic vessels. Renal clear cell carcinoma presence was confirmed in the spleen and pancreas area. Furthermore, there were renal cancer cells in the splenic vessels and pancreas tail vessels. The radiological examination from March 2021 did not show any signs of cancer recurrence. It may be the first record describing treatment of recurrent renal cancer with HIPEC. This example suggests that in some cases of metastatic RCC in the abdominal cavity, it is worth considering, further research on the subject due to the known fact of HIPEC being an effective solution in different cases of neoplasms [2] and lack of trials in that specific matter.

References

1. Jastrzębski T, Richter P, Zegarski W, et al. Guidelines from the Polish Surgical Society and Polish Society of Oncological Surgery Concerning Quality Assurance for Centres Performing Cytoreductive Procedures and HIPEC Procedures in the Treatment of Primary and Secondary Peritoneal Tumours. Nowotwory J Oncol. 2020; 70(3): 85–91, doi: 10.5603/njo.2020.0019.
2. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003; 21(20): 3737–3743, doi: 10.1200/JCO.2003.04.187, indexed in Pubmed: 14551293.

How to cite:

Jastrzębski T, Brodecki M, Spychalski M, Sylwestrzak T, Dziki A. *Peritoneal recurrence of RCC and gastric cancer treated with cytoreductive surgery and HIPEC.* *NOWOTWORY J Oncol* 2022; 72: 201.

VIA MEDICA

Oncogeriatrics

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 202–206
DOI: 10.5603/NJO.2022.0029

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Postoperative functional results of older patients after pancreas and liver surgery

Jakub Kenig, Jerzy Krzeszowiak, Kuba Kupniewski

Department of General, Gastrointestinal, Oncologic Surgery and Transplantology, I Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland

In clinical observational studies, overall survival and cancer-specific survival are usually considered the gold standard endpoints. Equally or even more important for older patients are patient-reported outcomes, defined as a set of patient-centered measures that evaluate physical, mental, and social health.

This is particularly important due to the complexity of surgical treatment and the higher risk of postoperative morbidity and mortality. The studies showed that after these operations, the quality of life (QoL) decreases and that is improving with time. After 6 months there was no difference in QoL between younger and older patients. Nevertheless, the results refer mostly to the group of patients who survived the follow-up period and had no recurrence. Therefore, age itself should not be a contraindication for pancreatic or liver surgery. QoL of patients not qualified for surgery decreased constantly.

Key words: older patients, frailty, functional results, quality of life

Chronological age alone is a poor predictor of cancer treatment outcomes and toxicities [1]. Therefore, chronological age alone should not be a contraindication for radical oncological treatment in older patients. As was mentioned in our previous publications, the population of the elderly is very heterogeneous in terms of co-morbidity, physical reserve, psycho-cognitive function, and social support [2]. Current routine pre-operative assessments cannot adequately identify older patients at risk. The frailty (surrogate of the biological age) evaluation should be the basis for the discussion on treatment planning. At present, it is one of the most reliable factors predicting outcomes in the geriatric population [3]. Therefore, the comprehensive geriatric assessment (CGA) was introduced to help to determine the primary status of the older patient, to diagnose frailty syndrome and to identify how to optimize the patient's condition before the start of treatment [4]. Subsequently, more and more organisations, including the International Society of Geriatric Oncology, the National Comprehensive Network, the European Organisation for the Research and Treatment of Cancer, the American College of Surgeons' National Surgical Quality Improvement Program, and the American Geriatric Society have called for the routine use of the Geriatric Assessment. Before treatment begins, the following questions should be discussed:

- Is the currently planned treatment strategy correct? Are there alternative treatment options?
- What is the result of the comprehensive geriatric assessment?
- Can frailty syndrome be diagnosed in the patient?
- What is the risk of complications?

How to cite:

Kenig J, Krzeszowiak J, Kupniewski K. ***Postoperative functional results of older patients after pancreas and liver surgery.*** *NOWOTWORY J Oncol* 2022; 72: 202–206.

- What would be the patient's lifespan be without treatment?
- What are the goals, preferences and expectations of the patient?
- What effect might the treatment have on these goals, particularly in terms of quality of life?
- Is it possible to improve the patient's state prior to the surgical procedure? [4].

Fit and prefrail patients, according to the comprehensive geriatric assessment, should be qualified for the same treatment as younger patients. Frail patients should be discussed in the oncogeriatric meeting [5]. The goal of the modifications is to reduce surgical stress. In older patients (aged 75 years or older), pathological outcomes and postoperative complications are predictors of survival, whereas pathological outcomes and chemotherapy are predictors of survival in younger population (aged 74 years or less). Thus, prevention of postoperative morbidity may contribute to an improved prognosis for older patients with cancer [6, 7]. However, we still need better designed studies on a larger group of patients using frailty evaluations – not only chronological age and comorbidity. Existing studies on this topic are limited, too small, lack important details with unsatisfactory statistical power. In clinical observational studies, overall survival or cancer-specific survival are usually considered the gold standard endpoint because it is simple and reliable to measure. Equally or even more important for older patients are patient-reported outcomes, defined as a set of patient-centered measures that evaluate physical, mental, and social health [8]. This is particularly important in the case of older patients with pancreas or liver cancer due to the complexity of surgical treatment and the higher risk of postoperative morbidity and mortality.

Quality of life after pancreatectomy

Although there are many studies on postoperative morbidity and mortality in older patients, there are only few on how this population's quality of life is affected by pancreas resection. The most important are presented below.

The aim of the study conducted by Gestenhaber et al. was to observe long-term outcomes in a group of ≥70 patients who underwent a pancreatoduodenectomy (PD) (96%) or total pancreatectomy (TP) (4%). Patients with metastatic disease or incomplete data were excluded. 168 patients met the inclusion criteria. Patients were interviewed with EORTC QLQ C-30 questionnaire 3, 6, and 12 months after surgery. 96% of patients underwent PD, while the remaining 4% TP. In 76% of patients, cancer was depicted as invasive and the most common histology was ductal adenocarcinoma (49%). There were no intraoperative deaths. The 30- and 60-day postoperative mortality was 5.9% and 6.5%, while the most common cause of death was sepsis leading to multi-organ failure. The overall postoperative complication rate accounted for 39% and the most frequent were septic complications. The median follow-up lasted 32 months. QoL evaluation was performed in 70 individuals who were free of disease in the first year after surgery. Results of the QoL assessment were compared with the results of 20 matched (sex, age, comorbidities) patients who underwent a laparoscopic cholecystectomy (LC). After 3 months PD group more frequently than LC group reported:

- fatigue (75% *vs.* 13%),
- loss of efficiency (70% *vs.* 20%),
- weight loss (51% *vs.* 0%),
- pain (35% *vs.* 10%)
- nausea and vomiting (68% *vs.* 10%),
- diarrhea (29% *vs.* 5%)

– all these differences were statistically significant. Comparing results 6 months postoperatively in the following domains:

- physical (73% *vs.* 78%),
- psychological (69% *vs.* 67%),
- global health (79% *vs.* 84%),
- global quality of life (73% *vs.* 79)

– the differences were not statistically significant. In patients after PD results in functional, symptoms and global QoL domains indicated constant improvement in subsequent time intervals. Comparing PD subgroups results in all domains were being slightly higher in patients with benign or premalignant pathology than in the group with malignant pathology (physical 75% *vs.* 72%; psychological 70% *vs.* 69%; global health 83% *vs.* 78%; global quality of life 77% *vs.* 72%), but none of the differences were statistically significant. The study revealed that the quality of life in patients after a pancreatoduodenectomy is improving with time from the period of surgery. The limitation of the study is that the results only refer to patients who survived at least a year after the operation and who in this time did not have a recurrence of the disease [9].

The research of Kim et al. analyzed QoL in 154 patients ≥65, operated due to periampullary neoplasms with regard to the stage of nutrition. Patients undergoing palliative resection, with metastases or recurrence, treated with neoadjuvant therapy, with a history of other abdominal operations, after cerebrovascular accident or with ASA score >III were excluded from the study. The primary outcome was postoperative morbidity related to nutritional status and the secondary outcomes were: Clavien-Dindo classification, rate of postoperative pancreatic fistula, cognitive score and quality of life. According to a preoperatively performed Mini Nutritional Assessment, patients were divided into three groups: well-nourished (13%), at risk of malnutrition (59.7%), and malnourished (27.3%); this resulted in statistically significant differences in body mass index (mean values respectively: 25.6 kg/m^2, 23.4 kg/m^2 and 21.1 kg/m^2). Types of operations included in the study were: pancreatoduodenectomy with pylorus resection (12.3%) and pylorus-preserving pancreatoduodenectomy (87.7%) performed due to malignant (79.2%) or benign (22.8%) neoplastic disease of the periampullary area. Patients were also dichotomized based on age, into 65–74 (n = 117) and 75–85 (n = 37) years old groups.

Overall morbidity was 41.6%. It was more frequent in patients with a poorer stage of nutrition, with statistically significant difference between well-nourished and malnourished groups. There were no significant differences in morbidity between the younger and older group. A cognitive evaluation was performed with the use of 4-point scale of cognitive function, based on the EORTC QLQ-C30 questionnaire. Cognitive function was evaluated preoperatively, the results were higher in patients with better nutrition, but not significantly. There were also no significant differences in cognitive score between age groups. Quality of life was assessed using global health status from EORTC QLQ-C30. Questionnaires were completed before the operation and 3, 6, and 12 months after surgery. Preoperatively, QoL was higher in patients with better nutrition and in the older group, but the differences were not significant. After 12 months, across all nutrition groups, an increase of QoL was observed, compared to preoperative results. The intergroup differences in QoL 12 months after surgery were not significant, but in the evaluation after 6 months it was significantly higher in the well-nourished and at-risk of malnutrition group than in the malnourished group [10].

Parray et al. investigated perioperative, long-term, and quality of life results of elderly patients undergoing pancreatoduodenectomy. 94 patients ≥70 years old operated on due to a malignant or non-malignant pathology between January 2007 and December 2019 were included. Distal pancreatic resections, median pancreatectomies, enucleations or palliative procedures were excluded. The average age was 73 years (70–85) with male prevalence (71%). The majority of the patients underwent surgery due to the adenocarcinoma of periampullary region (63%), the second most common was pancreatic ductal adenocarcinoma (22%). Based on the histopathological results, 46 patients had tumors described as T1 or T2 stage, while 39 had T3 or T4. The 30- and 90-day postoperative mortality was 3.1% and 5.3% respectively. Median follow-up lasted 25 months (0–108 months) and it was completed in 95% (n = 89) of patients. 53% (n = 47) were alive at the end of the median follow-up. The QLQ-PAN26 questionnaire was used to evaluate patients' long-term quality of life at the end of the follow-up period.

The questionnaire included answers: "not at all", "a little", "quite a bit" and "very much". For symptoms-based questions answers: "quite a bit" or "very much" were reported most commonly for weakness (94%) and backache (78%). 100% of patients reported "very much" in health care support, while 97% of patients chose the answer "not at all" for frequency of stools. 61% of patients answered "not at all" about weight loss. The most common answer for: abdominal pain (57%), food restriction (74%), and activity restriction (97%) was "a little". The postoperative complication appeared in 76.6% of patients ≥70 years old and in 63% of patients <70, but the differences were not statistically significant. The differences in mortality between the study group and the control group were also not statistically significant. The conclusion of the authors was that age alone should not be a contraindication for PD [11].

In turn, Torphy et al. compared the QoL results in the open and laparoscopic approach groups of patients undergoing pancreatic resection. Patients after pancreatoduodenectomy or distal pancreatectomy in either the open or laparoscopic approach were included. There were no age restrictions for the inclusion. The only exclusion criteria for undergoing a laparoscopic procedure was receiving neoadjuvant therapy or vessel involvement. 159 patients were included in the study, 60.4% in the open approach group and 39.6% in laparoscopic. 71.7% of all procedures were PD and DP accounted 28.3%. Patients were also dichotomized depending on age. There were 80 patients ≤65 and 79 >65 years old. 52 patients >65 underwent laparotomy, while remaining 27 laparoscopy. The overall complication rate was 66.7%. All participants were asked to complete the FACT-Hep questionnaire preoperatively and 2 weeks, 1 month, 3 months, and 6 months after surgery. Response rates were the highest preoperatively (96.6%) and decreased to 69.2% at the last evaluation. The internal consistency of the questionnaire assessed with standardized Cronbach alpha at subsequent time intervals were respectively: 0.80, 0.76, 0.81, 0.81, and 0.86. Quality of life in comparison with age groups was emphasized with the estimated beta coefficient, with a 95% confidence interval. Evaluated in physical, emotional, social, functional, hepatobiliary domains, and FACT-Hep Total, there were no significant differences in either postoperative period, or in the long-term recovery between ≤65 and >65 patients. The conclusion for the whole group of included patients is that there is no significant difference in QoL after pancreatic surgery when compared to the open and laparoscopic surgical approach [12].

Watanabe et al. was to observe long-term outcomes of patients after a total pancreatectomy. The study group comprised 44 consecutive patients between 1990–2013. At the time of the study there were 25 survivors who were assessed cross-sectionally. Their body weight and blood chemical parameters were evaluated. They also completed an institutional questionnaire about sociodemographic data, ambulatory care, exocrine and endocrine function. To collect QoL results, 25 survivors completed the SF-36v2 questionnaire – a tool consisting of 36 questions on eight different domains:

- physical functioning (PF),
- role physical (RP),
- body pain (BP),
- general health perceptions (GH),
- vitality (VT),
- social functioning (SF),
- role emotional (RE),
- mental health (MH).

The separate domain results were calculated into three summarized component scores (SCS): physical component score (PCS), mental component score (MCS), and the role-social

component score (RCS). The SF-36v2 standard values were determined based on general Japanese population results. To assess the influence of age, patients were divided into <70 (n = 21) and ≥70 (n = 23) groups. Median age was 71 (46–88), with a prevalence of males (29 *vs.* 15). The indications for total pancreatectomy were pancreatic ductal adenocarcinoma (PDAC) (45%), intraductal papillary mucous neoplasm (IPMN) or mixed PDAC and IPMN etiology (10%). Overall morbidity rate was 32%, while postoperative mortality was 5%. There were no significant differences in histological diagnoses, length of stay or surgical procedure between the younger and older group, but the postoperative complications were more frequent in the older group (48% *vs.* 14%; p = 0.02). Median follow-up lasted 21 months (2–222). Apart from 2 patients (5%) who died postoperatively, another 17 died during the follow-up period. The majority of deaths were caused by underlying pancreatic disease. The 3- and 5-year survival rate was 64% and 48% respectively. From 25 survivors, 5 patients had a recurrence during the follow-up. Their PF, RP, RE, and SCS scores were significantly lower than in the non-recurrence group (n = 16, without octogenarians). For accurate evaluation, patients who experienced recurrence were excluded from the comparison with national population. In two domains (PF and GH) and one SCS (PCS), the QoL results were significantly lower than the reference values. Patients who complained about diarrhea (n = 5) had significantly lower results in VT and MCS than those without such symptoms (n = 16). Due to the large group of young people in the national population, patients aged 60–69 and 70–79 were compared with their age-matched with individuals of a similar age. As a result, no significant differences between study and general population individuals were found in any QoL domain or SCS. Results among 60–69, 70–79, and the octogenarians groups did not reveal any significant differences in QoL. Comparing <70 (n = 9) and ≥70 (n = 11) patients, the outcomes were almost indistinguishable with the exception of the mental component score, which was significantly lower in the younger group. In conclusion, QoL after total pancreatectomy is satisfactory even in the elderly and age itself should not be a contraindication for surgery. However, the complication rate is more often higher in the older group and the study was conducted on a very small population [13].

A comparison between the studies is difficult because of their heterogeneity. The endpoints were evaluated using different questionnaires: EORTC QLQ-C30 [9, 11], EORTC QLQ-PAN26 [12], FACT-Hep [10] and SF-36v2 [13]. Among the studies there were different criteria for inclusion to the QoL evaluation. Two of the studies collected PRO only once, at the end of the follow-up [12, 13]. Multiple postoperative assessments were conducted in three studies: 3-months, 6-months, and 12-months postoperatively [9, 11] and 2-weeks, 1-month, 3-months, and 6-months postoperatively [10].

Concluding, the QoL in older patients decreases after surgery and then is improving with time. Six months post pancreatic surgery, there was no difference in QoL between younger and older patients. Therefore, age itself should not be a contraindication for pancreatic surgery. Nevertheless, the results refer mostly to the group of patients who survived the follow-up period and had no recurrence. This systematic review revealed a lack of high-quality data in this area and incontestably it undoubtedly indicated the demand for further research in this area.

Quality of life after liver resection

There are many studies analyzing postoperative outcomes in older patients after liver resection, however, there are only few on how this population's quality of life is affected by liver resection. Most of the studies are retrospective in design. Only a few are prospective, and none of them are randomized control trials [14–17]. Moreover, the tools used to evaluate the QoL is Is different in each of the studies, which makes metaanalysis impossible. A systemic review on instruments measuring quality of life found that there is no gold standard in the field; these different measures make comparisons between studies difficult if not impossible [18].

Chen et al. compared patients ≥70 years of age with hepatocellular carcinoma who underwent liver resections with those who did not using European Cooperative Oncology Group (ECOG). Comparing pre- and postoperative performance status scores, ECOG in the conservative group only worsened. All patients received at least 6 months of follow up. In the surgery group, postoperatively 7 patients received a score of 0, 7 a score of 1, and 2 a score of 2. No patient in the resection group received a score of 3–5 [19].

Nomi et al. compared patients ≥75 undergoing laparoscopic liver resection (LLR) and open liver resection (OLR). In order to minimize selection bias, propensity score-based analysis was performed, after which 155 patients were in the LLR group and 155 in the OLR group. After propensity score matching, 3 patients in the LLR group and 13 in the OLR group were transferred to rehabilitation facilities, 12 in the LLR group and 14 in the OLR group had their comorbidities exacerbated, and 2 patients in the LLR group and 7 in the OLR group developed dementia [20].

Mise et al. used the Short Form-36 questionnaire to assess QoL in 108 patients who underwent liver resection between January 2004 and January 2008. Patients were assessed before surgery, 3 months after surgery, and 6 months after surgery. Physical Component Summaries (PCS) and Mental Component Summaries (MCS) were determined and compared between patients at or above 70 and patients below 70. PCS decreased at 3 months, then increased at 6 months for both groups. Patients <70 experienced a more drastic drop in PCS at 3 months than patients ≥70. MCS increased at 3 months and 6 months for patients <70, while it decreased at 3 months and increased at 6 months for patients ≥70 [21]. Quality of life appears to either remain stable or improve in the long term in older patients undergoing liver resection. There is still a deficit in high quality studies exploring this issue.

Conclusions

To conclude, pancreas and liver surgery influence quality of life in the short term. However, after 3–6 months quality of life level is rising and is comparable with the preoperative time. We have to remember that it was evaluated only in patients that had a radical operation and survived the follow-up time. Moreover, chronological age was the inclusion criteria in all of the studies and not biological age. This is also important, in the context that all patients not qualified for surgery had a QoL that was constantly decreasing.

Conflict of interest: none declared

Jakub Kenig
Jagiellonian University Medical College
Department of General, Oncologic, Gastrointestinal Surgery and Transplantology
I Chair of General Surgery
ul. Jakubowskiego 2
30-688 Kraków, Poland
e-mail: jkenig@cm-uj.krakow.pl

Received: 19 Apr 2022
Accepted: 27 Apr 2022

References

1. Rostoft S, Audisio RA. Recent advances in cancer surgery in older patients. Research. 2017; 6(F1000 Faculty Rev): 1242.
2. Kenig J. Oncogeriatrics (part 1.). Frailty in older adults with cancer. Nowotwory. Journal of Oncology. 2019; 69(2): 55–57, doi: 10.5603/njo.2019.0010.
3. Kenig J, Szabat K, Mituś J, et al. Short- and long-term predictive power of the preoperative Geriatric Assessment components in older cancer patients undergoing high-risk abdominal surgery. Eur J Surg Oncol. 2022 [Epub ahead of print], doi: 10.1016/j.ejso.2022.01.004, indexed in Pubmed: 35027232.
4. Kenig J, Szabat K. Oncogeriatrics (part 7.). Geriatric assessment for older patients with cancer. Nowotwory. Journal of Oncology. 2020; 70(4): 153–157, doi: 10.5603/njo.2020.0031.
5. Grodzicki T, Kenig J. Problemy okołooperacyjne u osób w wieku podeszłym. PZWL Wydawnictwo Lekarskie 2018.
6. Kenig J. Hepatocellular cancer and colorectal liver metastasis treatment in the older population. Nowotwory. Journal of Oncology. 2022; 72(1): 52–57, doi: 10.5603/njo.2022.0006.
7. Kenig J, Richter P. Pancreatoduodenectomy due to cancer in the older population. Nowotwory. Journal of Oncology. 2021; 71(5): 321–327, doi: 10.5603/njo.2021.0061.
8. Knight J, Ayyash K, Colling K, et al. A cohort study investigating the relationship between patient reported outcome measures and pre-operative frailty in patients with operable, non-palliative colorectal cancer. BMC Geriatr. 2020; 20(1): 311, doi: 10.1186/s12877-020-01715-4, indexed in Pubmed: 32854632.
9. Gerstenhaber F, Grossman J, Lubezky N, et al. Pancreaticoduodenectomy in elderly adults: is it justified in terms of mortality, long-term morbidity, and quality of life? J Am Geriatr Soc. 2013; 61(8): 1351–1357, doi: 10.1111/jgs.12360, indexed in Pubmed: 23865843.
10. Kim E, Lee DH, Jang JY. Effects of Preoperative Malnutrition on Postoperative Surgical Outcomes and Quality of Life of Elderly Patients with Periampullary Neoplasms: A Single-Center Prospective Cohort Study. Gut Liver. 2019; 13(6): 690–697, doi: 10.5009/gnl18469, indexed in Pubmed: 30970428.
11. Parray A, Bhandare MS, Pandrowala S, et al. Peri-operative, long-term, and quality of life outcomes after pancreaticoduodenectomy in the elderly: greater justification for periampullary cancer compared to pancreatic head cancer. HPB (Oxford). 2021; 23(5): 777–784, doi: 10.1016/j.hpb.2020.09.016, indexed in Pubmed: 33041206.
12. Torphy RJ, Chapman BC, Friedman C, et al. Quality of Life Following Major Laparoscopic or Open Pancreatic Resection. Ann Surg Oncol. 2019; 26(9): 2985–2993, doi: 10.1245/s10434-019-07449-x, indexed in Pubmed: 31228131.
13. Watanabe Y, Ohtsuka T, Matsunaga T, et al. Long-term outcomes after total pancreatectomy: special reference to survivors' living conditions and quality of life. World J Surg. 2015; 39(5): 1231–1239, doi: 10.1007/s00268-015-2948-1, indexed in Pubmed: 25582768.
14. Bruns H, Krätschmer K, Hinz U, et al. Quality of life after curative liver resection: a single center analysis. World J Gastroenterol. 2010; 16(19): 2388–2395, doi: 10.3748/wjg.v16.i19.2388, indexed in Pubmed: 20480524.
15. Poon RT, Fan ST, Yu WC, et al. A prospective longitudinal study of quality of life after resection of hepatocellular carcinoma. Arch Surg. 2001; 136(6): 693–699, doi: 10.1001/archsurg.136.6.693, indexed in Pubmed: 11387012.
16. Mise Y, Satou S, Ishizawa T, et al. Impact of surgery on quality of life in patients with hepatocellular carcinoma. World J Surg. 2014; 38(4): 958–967, doi: 10.1007/s00268-013-2342-9, indexed in Pubmed: 24305919.
17. Riffat F, Chu F, Morris DL. Liver resection in octogenarians. HPB (Oxford). 2006; 8(3): 206–210, doi: 10.1080/13651820500497173, indexed in Pubmed: 18333278.
18. Pequeno NP, Cabral NL, Marchioni DM, et al. Quality of life assessment instruments for adults: a systematic review of population-based studies. Health Qual Life Outcomes. 2020; 18(1): 208, doi: 10.1186/s12955-020-01347-7, indexed in Pubmed: 32605649.
19. Chen G, Zhang J, Sun J, et al. Revisiting Partial Hepatectomy of Large Hepatocellular Carcinoma in Older Patients. Sci Rep. 2018; 8(1): 14505, doi: 10.1038/s41598-018-32798-0, indexed in Pubmed: 30266965.
20. Nomi T, Hirokawa F, Kaibori M, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in elderly patients: a multi-centre propensity score-based analysis. Surg Endosc. 2020; 34(2): 658–666, doi: 10.1007/s00464-019-06812-z, indexed in Pubmed: 31093748.
21. Mise Y, Satou S, Ishizawa T, et al. Impact of surgery on quality of life in patients with hepatocellular carcinoma. World J Surg. 2014; 38(4): 958–967, doi: 10.1007/s00268-013-2342-9, indexed in Pubmed: 24305919.

VIA MEDICA

Genetics and oncology

NOWOTWORY Journal of Oncology
2022, volume 72, number 3, 207–210
DOI: 10.5603/NJO.2022.0030

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

The role of genetic counselling in oncology

Agnieszka Stembalska[1], Karolina Pesz[2]

[1]*Department of Genetics, Wroclaw Medical University, Wroclaw, Poland*
[2]*Queen Elizabeth University Hospital, Glasgow, United Kingdom*

All cancers are genetic disorders, but not all genetic disorders are inherited. Most cancers are sporadic, independent events that do not affect other family members. There is a population risk of developing any cancer and it mainly depends on the individual's age and environmental factors. Cancers linked to predisposition syndromes constitute about 5–10% of all cancer cases. Although it is a small group, making the right diagnosis is important, because of the consequences to the individual, his/her relatives and the benefits they can acquire from surveillance, early therapy and/or surgical interventions.

Genetic counselling plays an important role in diagnosing cancer predisposition syndromes. Hereditary cancer risk assessment includes evaluation of personal and family history, as well as other medical and environmental risk factors. Indications for genetic testing, scope of tests, possible results and their consequences for the patient and his/her family should be discussed.

Key words: cancer, predisposition, sporadic cancer, hereditary cancer, genetic counselling

Cancer as a genetic disease

Any malignant tumour might be regarded as a "disease of the genes". Cancer cells harbour a plenitude of gene mutations and/or chromosomal aberrations that lead to the formation of a "cancer genome", substantially different from the "constitutional genome" of an individual. Those genetic alterations constitute the essence of neoplastic development through which the cells acquire the ability to proliferate uncontrollably, evade growth suppressors, immune response and apoptosis, become immortal, induce angiogenesis, infiltrate surrounding tissues and metastasize [1–3].

Sporadic cancers

In most cases, genetic alterations leading to cancer development arise as "somatic events" in the cells of a given organ during an individual's lifetime, and hence cannot be passed on to the next generation (are not inherited). The risk of these acquired changes increases with age and is often connected to environmental, lifestyle or medical factors. The risk of cancer development in another organ depends on another somatic mutation. Those events are independent of each other and the probability is as high as population risk for a given cancer. In these cases we can talk about sporadic cancers. All people have the risk of cancer development, because cancers are relatively common in human populations. Therefore, in the same family there might be more than one case of sporadic cancer. These are independent events. Although in sporadic cancer cases a specific build-up of mutations (changes) in specific genes may be important for treatment or prognosis (personalised treatment) [4–6], these genetic changes cannot influence the risk of cancer in any relatives of an individual who has a sporadic cancer. Each family member has their own risk of cancer development [1–3].

How to cite:
Stembalska A, Pesz K. ***The role of genetic counselling in oncology.*** *NOWOTWORY J Oncol* 2022; 72: 207–210.

Hereditary cancers

Some cancers are the result of so called "germline mutations", that is single gene pathogenic variants from reproductive cells in the parent generation that have been transmitted and are present in every cell of an individual. These variants can be passed on to the next generation, so the presence of genetic changes in an individual with cancer can influence the relatives (children).

In such cases we can talk about hereditary cancers [1, 2, 7, 8]. Since it is not the cancer itself that is inherited, rather the susceptibility to cancer, the condition should be referred to as "cancer predisposition syndrome".

A cancer predisposition syndrome means that there is an increased risk of cancer development from the spectrum of cancers associated with a particular gene. An individual who developed a cancer in one organ still has an increased risk of other cancers. For example: a female carrier of a *BRCA1* mutation has an increased risk of breast, ovarian and pancreatic cancers; with male carriers this also includes prostate cancer [9,10]. Although cancer development risk may be much higher than the population risk and tends to increase with a patient's age, it is not the same for all cancers on the spectrum. The risk of developing a cancer from outside the spectrum is as high as in the remainder of the population (population risk).

Because the gene mutation is present in every cell, genetic testing in any tissue (e.g. blood or saliva) detects gene mutations that cause hereditary cancer.

Although cancer patients with inherited susceptibility constitute only 5–10% of all cancer cases, they cannot be neglected considering the magnitude of risk of malignancy development [11–13]. Diagnosing cancer predisposition syndromes is important, despite their rarity, because of consequences to individual patients and their families and the benefits they can acquire from surveillance, early therapy and/or surgical interventions.

In this article, the diagnostic and clinical aspects of cancer predisposition syndromes in the context of genetic counselling are discussed.

Genetic counselling in oncology

The main challenge in a genetic clinic is distinguishing between those individuals (and/or families) with high or moderate cancer risk from those with low risk to appropriately provide genetic testing and management [5, 11, 12].

The most numerous group of patients referred for genetic counselling would be individuals suffering from cancers that are common in the general population (breast, ovarian, colorectal cancers) but in rare instances falling into the category of mendelian inheritance (single gene disorders). Most hereditary predispositions to cancers follow an autosomal dominant pattern of inheritance, with a 50% probability of passing it on to the next generation [12, 14, 15]. It should be underlined that diagnosing a predisposition syndrome means an increased risk of cancer development in an individual, not a diagnosis of cancer itself. Consequently, in the first instance, genetic testing should be offered to an individual with a history of cancer. Only in cases when it is not possible to test a relative with cancer (the individual died or declines genetic testing), should molecular testing be offered to relatives (initially first-degree relatives, and then others). Negative results of genetic testing in healthy individuals (without a proven genetic mutation in a relative) do not exclude a cancer predisposition syndrome due to genetic heterogeneity of such syndromes (mutations in different genes might be responsible for similar cancer spectra), the limitations of methods employed in genetic testing and the current knowledge of hereditary predispositions [8, 16–18].

Diagnosis of hereditary cancer predisposition syndromes is based on pedigree-clinical criteria, different for particular syndromes (currently approx. 50 syndromes) [8, 14, 16]. It is important that in some cancer predisposition syndromes, apart from malignancies, there are also noted multiple benign tumours (examples include MEN1, MEN2, neurofibromatosis type 1, Cowden syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis). A separate group are additionally genetically determined syndromes/disorders in which there is a risk of cancer development, such as: Fanconi aneamia, *Xeroderma pigmentosum*, Ataxia-teleangiectasia, Nijmegen syndrome, which are inherited in an autosomal recessive manner. Diagnosis of these syndromes/disorders is based on assessment of clinical features and genetic testing.

Pre-test and post-test genetic consultations

An ideal setting for oncogenetic counselling includes pre-test and post-test genetic consultations. The initial visit to a genetic clinic concentrates on collecting the family history and pedigree construction, as well as taking a personal medical history [8, 19].

Medical information should be gathered on family members from at least three generations. It includes details of any malignant and benign tumours and other features such as consanguinity. The evaluation of clinical and pedigree data not only serves the purpose of diagnosing an alleged cancer predisposition syndrome, but also the selection of individuals eligible for genetic testing [8, 12, 16, 17].

Suspicion/recognition of hereditary cancer predisposition

Families with the same or related types of cancer affecting numerous family members, early onset of cancers (usually younger than in sporadic forms of cancer, often younger than the age of 50) and atypical or rare cancers (for example, male breast cancer), multifocal cancers or multiple cancers in one person comprise red flags for cancer predisposition syndromes.

A meticulous analysis of family history serves the purpose of identifying cancer patterns that fulfil criteria for recognition of cancer predisposition syndromes. Especially in situations of

three affected relatives with the same related cancer across a minimum of two generations and at least one patient under 50 years of age [8, 9, 20].

However, due to the high overall frequency of cancers, not all individuals with cancer from a family with a hereditary predisposition will carry a causative mutation. For example: larynx cancer in a lifelong cigarette smoker should not be assumed to be caused by a familial *BRCA1* mutation. Furthermore, in family with a *BRCA1* mutation, there might be relatives without a *BRCA1* mutation who develop breast or ovarian cancer. This phenomenon is called "phenocopy". It means that independent, different environmental or genetic factors are responsible for the same type of cancer.

In some instances the structure of the family itself (a small number of relatives or early deaths, no information on relatives, adoption or assisted reproduction, etc.) limits pedigree assessment. Negative family history might be also the result of false data, incomplete penetrance (not all people with a genetic change will develop cancer) or sex-related penetrance, for example, inheriting through a male line a genetic variant consistent with ovarian cancer. Those factors are: atypically young age of cancer onset, multiple tumours in one individual, rare types of cancers or tumour properties (ex. triple negative breast cancer or microsatellite instability in colorectal cancer) may indicate a genetic background without specifically meeting the diagnostic criteria for a syndrome. For example, early onset female breast cancer (before age 31 years) or adrenocortical carcinoma or choroid plexus tumour irrespective of family history might be indicative of Li-Fraumeni syndrome [21].

Personal history may prove relevant to making the correct diagnosis. The presence of hamartomatous gastrointestinal polyps would require a differential diagnosis between Peutz-Jeghers syndrome, juvenile polyposis syndrome and Cowden syndrome in the least. A history of multinodular goitre and uterine fibroids may prompt a careful dermatological examination of a patient for pathognomonic signs of Cowden syndrome [7, 15].

Genetic tests

Assessment of family and personal histories forms the basis for formulating indications for genetic testing. There are several approaches that depend not only on the clinical findings but also on other factors such as the resources available for testing. Molecular genetic testing may include:

- direct mutation diagnosis,
- single gene sequencing,
- multigene panels.

Direct mutation analysis is required when a pathogenic variant has previously been found in a relative. In cases when it is clinically possible to determine a diagnosis or at least have a high probability of making one, single gene testing might be considered. In instances when the condition might be related to mutations in many different genes, multigene panels have been introduced. There are no uniform recommendations on the number of genes that should be included in such a panel, and there are ongoing discussions on the relevance of particular genes to some cancers [18, 22, 23].

Discussion on genetic testing

The pre-test consultation should include a comprehensible evaluation of the advantages and disadvantages of molecular genetic testing for the patient and the possible outcomes of the testing (positive result, negative result, inconclusive result and accidental findings), as well as the consequences of diagnosing cancer predisposition syndrome for other family members. Acknowledging the magnitude of risk of developing cancer caused by the identified mutation, gives the individual opportunities for managing that risk by making life style changes, undergoing regular screening or having preventive surgical treatment. For many individuals it relieves the anxiety connected to the uncertainty of not knowing the risk. However, there are limitations to genetic testing that necessitate consideration. Receiving a negative result will never alleviate the risk of developing cancer – most of the cases are caused by acquired somatic mutations.

It is also important to remember that there are no indications for genetic testing in a relative of an individual with cancer and a negative genetic test result. However, in some cases a different test might be offered, but this depends on additional circumstances and might be prompted by acquiring more clinical and family history information.

When the clinical criteria of a cancer predisposition syndrome are fulfilled, but no genetic alteration can be found, counselling about the management of cancer risk should be provided to individuals elected on the basis of a pedigree.

Sometimes the results might be inconclusive, not providing an accurate answer to the question of the exact level of risk. Those genetic alterations are known as variants of unknown significance. In some rare instances, performing a genotype-phenotype correlation in family members might elucidate the significance of a change that has been found.

For some individuals, a positive result may cause permanent anxiety of a diagnosis that seems all but inevitable. Each of the above-mentioned issues should be brought to the individual's attention and hence they formulate the underpinnings of informed consent. Signing a consent form should be preceded by disclosing full information on the possibilities and limitations of a given genetic test, the consequences of diagnosing a cancer predisposition syndrome and its management [8, 16, 17, 22, 23].

Consultations after genetic test

The post-test consultation includes the explanation of the result of the genetic testing to the individual and his family and the various possibilities of cancer risk management that are open to the individual. Depending on the gene involved, a positive result (pathogenic or likely pathogenic variant) may convey different levels of risk of cancer development in dif-

ferent organs. For example, particular mutations in *TP53* have been linked to different levels of risk of different types of cancer (https://tp53.isb-cgc.org/). Each significant change (pathogenic or potentially pathogenic) will be related to a specific clinical course of action in the field of prophylaxis and the treatment of the patient. This is reflected in various clinical recommendations [9, 15, 24].

A positive result is also a proof of hereditary cancer predisposition syndrome, hence it is important to relatives at risk of harbouring the mutation. With which relatives to disclose the information should be discussed. If the result of the genetic testing is negative – it must be interpreted in the context of the information gathered during previous consultations. A negative result might not exclude a cancer predisposition syndrome. One of the most difficult issues are inconclusive results. With the introduction of next generation sequencing, variants of unknown significance (VUS) have become a considerable problem, requiring great caution when attempting interpretation. It is important to attempt reanalysis of VUS as their interpretation might change as more evidence becomes available.

It is important to remember that the risk of cancer development is never zero. Each individual, even in a situation of exclusion of a cancer predisposition syndrome, has a population risk of cancer development. Individuals, according to their genetic makeup, have different levels of cancer risk development. Life style changes, screening strategies and, in some cases, prophylactic surgical interventions, according to the level of cancer risk development should be discussed.

Conclusion

Cancer predisposition syndromes are rare in oncological practise. However, their recognition has a significant impact on screening and the management of individuals with a high risk of cancer development. Adequate care for these patients can be provided only in a multidisciplinary setting that includes an oncologist and clinical geneticist.

Conflict of interest: none declared

Agnieszka Stembalska
Wroclaw Medical University
Department of Genetics
ul. K. Marcinkowskiego 1
50-368 Wrocław, Poland
e-mail: agnieszka.stembalska@umw.edu.pl

Received: 7 May 2022
Accepted: 9 May 2022

References

1. Schaaf CP, Zschocke J, Potocki C. Cancer genetics. In: Human Genetics: from molecules to medicine. Lippincott Wiliams&Wilkins, a Wolters Kluwer business 1st ed, Baltimore, Philadelphia 2012: 90–94.
2. Claussnitzer M, Cho JH, Collins R, et al. A brief history of human disease genetics. Nature. 2020; 577(7789): 179–189, doi: 10.1038/s41586-019-1879-7, indexed in Pubmed: 31915397.
3. Pecorino L. Biologia molekularna nowotworów w praktyce klinicznej. Wyd. 4. In: Dzięgiel P, Marszałek A. ed. Wydanie polskie. Edra Urban & Partner, Wrocław 2018.
4. Sąsiadek M, Łaczmańska I, Maciejczyk A, et al. Fundamentals of personalised medicine in genetic testing-based oncology. Nowotwory J Oncol. 2020; 70(4): 144–149, doi: 10.5603/njo.2020.0029.
5. Doraczyńska-Kowalik A, Janus-Szymańska G, Matkowski R, et al. Genetyka i onkologia (część 2.). Podstawy medycyny personalizowanej w leczeniu raka piersi i raka jajnika. Nowotwory J Oncol. 2020; 70(5): 187–202, doi: 10.5603/njo.2020.0040.
6. Kamps R, Brandão RD, Bosch BJ, et al. Next-Generation Sequencing in Oncology: Genetic Diagnosis, Risk Prediction and Cancer Classification. Int J Mol Sci. 2017; 18(2), doi: 10.3390/ijms18020308, indexed in Pubmed: 28146134.
7. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol. 2005; 23(2): 276–292, doi: 10.1200/JCO.2005.10.042, indexed in Pubmed: 15637391.
8. Hampel H, Bennett RL, Buchanan A, et al. Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015; 17(1): 70–87, doi: 10.1038/gim.2014.147, indexed in Pubmed: 25394175.
9. Daly MB, Pal T, Berry MP, et al. CGC, CGC, LCGC, CGC, CGC. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19(1): 77–102, doi: 10.6004/jnccn.2021.0001, indexed in Pubmed: 33406487.
10. Forbes C, Fayter D, de Kock S, et al. A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of -mutated breast cancer. Cancer Manag Res. 2019; 11: 2321–2337, doi: 10.2147/CMAR.S189627, indexed in Pubmed: 30962720.
11. Buchanan AH, Stopfer JE. Genetic counseling in oncology. JAMA. 2011; 306(13): 1442; author reply 1442–3, doi: 10.1001/jama.2011.1402, indexed in Pubmed: 21972303.
12. Genetic counseling: an indispensable step in the genetic testing process. J Oncol Pract. 2008; 4(2): 96–98, doi: 10.1200/JOP.0827002, indexed in Pubmed: 20856787.
13. Van Cott C. Cancer Genetics. Surg Clin North Am. 2020; 100(3): 483–498, doi: 10.1016/j.suc.2020.02.012, indexed in Pubmed: 32402295.
14. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. J Genet Couns. 2012; 21(2): 151–161, doi: 10.1007/s10897-011-9462-x, indexed in Pubmed: 22134580.
15. Hereditary Cancer Syndromes and Risk Assessment. Obstet Gynecol. 2019; 134(6): e143–e149, doi: 10.1097/aog.0000000000003562.
16. National Cancer Insitute, NCI. http://www.cancer.gov (6.05.2022).
17. European Society for Medical Oncology, ESMO. http://www.esmo.org/guidelines (6.05.2022).
18. Stoffel EM, Carethers JM. Current Approaches to Germline Cancer Genetic Testing. Annu Rev Med. 2020; 71: 85–102, doi: 10.1146/annurev-med-052318-101009, indexed in Pubmed: 31756137.
19. Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008; 17(5): 424–433, doi: 10.1007/s10897-008-9169-9, indexed in Pubmed: 18792771.
20. Pujol P, Barberis M, Beer P, et al. Clinical practice guidelines for BRCA1 and BRCA2 genetic testing. Eur J Cancer. 2021; 146: 30–47, doi: 10.1016/j.ejca.2020.12.023, indexed in Pubmed: 33578357.
21. Schneider K, Zelley K, Nichols KE. et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA. et al. ed. GeneReviews® [Internet]. University of Washington, Seattle (WA) 1993-2020.
22. King E, Mahon SM. Genetic Testing: Challenges and Changes in Testing for Hereditary Cancer Syndromes. Clin J Oncol Nurs. 2017; 21(5): 589–598, doi: 10.1188/17.CJON.589-598, indexed in Pubmed: 28945723.
23. Harris G, Hutson S. Hereditary Cancer Genetic Panel Testing: A Review of the Literature. SAGE Open. 2019; 9(1): 215824401983593, doi: 10.1177/2158244019835936.
24. Weiss JM, Gupta S, Burke CA, et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2021. J Natl Compr Canc Netw. 2021; 19(10): 1122–1132, doi: 10.1164/jnccn.2021.0048, indexed in Pubmed: 34666312.