ISSN 0029–540X
e-ISSN: 2300-2115

NOWOTWORY. Journal of Oncology 2021, Volume 71, Number 3, 133–183

Nowotwory

Volume 71 | Number 3 | Year 2021

Journal of Oncology

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

VIA MEDICA

3/2021

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

20-0800.011.001

Nowotwory

Journal of Oncology

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VM Media sp. z o.o. VM Group sp.k.
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e-mail: viamedica@viamedica.pl, www.viamedica.pl

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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

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Letter to the Editor

VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 133–138
DOI: 10.5603/NJO.a2021.0019

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

The efficacy of IORT (intraoperative radiotherapy) for early advanced breast cancer depending on the time delay of external beam irradiation (EXRT) post conservative breast surgery (CBS)

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Introduction. The following study focuses on the efficacy of the IORT (14.4 izoGy$_{2.0}$) as part of conservative surgery with adjuvant EXRT (50 Gy in 25 fractions) for low risk 109 early breast cancer patients and 106 intermediate or nonlinear high risk patients with adjuvant chemoradiation or chemotherapy followed by the EXRT.

Material and methods. The accumulation of the rates of local recurrences (LR) and distant metastases (DM) are characterized by nonlinear but two-phase curves.

Results. During the first 5 years, 67% of all LR, and only 43% of all DM occurred, and between the 8th and 10th years the LR curve steeply increases by 25% and the DM by 48%.

Conclusion. This suggest that a 5-year follow-up is too short and should be extended to 10 years. Among the analyzed prognostic factors, the time interval (TI) between IORT and adjuvant EXRT has occurred the major prognostic risk factor. If the TI is extended over 60 days (delayed EXRT), the LR and the DM risk undergoes a3–10 fold increase. Concurrent CH-EXRT significantly lowers local and distant failures, compared with delayed EXRT after completing CHT. Therefore, delayed EXRT completely ruins the expected efficacy of the IORT.

Key words: IORT, early breast cancer, delayed adjuvant EXRT

Introduction

Since the 1960s when Abe and Takahashi [1] presented the basic rationale and methods of intraoperative radiotherapy (IORT), this method has been widely used alone, or combined with external irradiation (EXRT) and/or chemotherapy (CHT) to improve the treatment outcomes of various malignant tumors, including breast cancer. The results of the IORT as a single therapy has been critically evaluated [2, 3]. Reitsamer et al. [4] noted no local recurrences of breast cancer after IORT BOOST combined with EXRT, but the follow-up was too short. Herskind et al. [5–7], presenting the radiobiological aspects of the IORT, has focused on the biological advantages of this method. Recently, Fastner et al. [18] published a comprehensive overview of the role of the IORT as the ESTRO IORT TASK

How to cite:

Celejewska A, Maciejewski B, Wydmański J, Składowski K. ***The efficacy of IORT (intraoperative radiotherapy) for early advanced breast cancer depending on the time delay of external beam irradiation (EXRT) post conservative breast surgery (CBS).*** *NOWOTWORY J Oncol* 2021; 71: 133–138.

Force/ACROP recommendations, suggesting this method as a favorable standard of combined therapy for carefully selected locally advanced breast cancer patients. Despite the many studies, it is not easy to interpret the results of various IORT doses combined with EXRT and/or chemotherapy. The majority of studies concentrate on local recurrence as the major end-point, but incidences of distant metastases are usually ignored. Moreover, adjuvant therapy post conservative surgery (CBS) includes various methods, i.e. concurrent chemoradiation, chemotherapy followed by EXRT or the reverse.

For high risk breast cancer patients, the IORT with CBS might not be effective enough mainly, when adjuvant EXRT is delayed, because among others processes, repopulation of the survived cancer cells accelerates, and therefore decreases or even thwarts the expected efficacy of the IORT. It seems that the longer the delay of postop. EXRT, the higher the risk of local recurrence. Because the prognostic importance of the time interval between CBS (IORT) and EXRT has not been evaluated yet, the present study is mainly focused on this topic.

Material

The retrospective clinical material consists of 215 consecutive breast cancer patients (T1–2N0–N+) treated in a single institution. Clinical and pathological characteristics (tab. I) were used to subdivide all cases into two groups, i.e. (A) – 109 cases with low, and (B) – 106 cases with intermediate or high risk of local and/or distant failure (risk factors: poorly differentiated, positive estrogen/progesterone, HER-2 positive, extracapsular nodal involvement, too narrow surgical margins, regional nodal involvement). There were 162 cases with pT1 (75%), and the remaining cases had pT2. Similarly, a 3:1 ratio concerned the incidence of pN0 versus pN+. In the group A dominated pT1N0 whereas pT2N+ in the group B. A higher rate (45%) of pN+ was in group B, compared to a marginal rate (4%) in group A.

Methods

Treatment characteristics

During CBS, all cases received intraoperative radiotherapy (IORT) performed using the INTRABEAM mobile device emitting low energy X-rays (20–50 kV). Spherical applicators were tailored to the size of the postoperative tumor bed. The planned dose covered 0.5–1 cm of the tissue surrounding the postoperative margin, and usually a single dose of 5 Gy was delivered. Since the RBE for X-rays of 20-50 kV is higher (~1.5–1.6) than that for high energy photons (~1.0), an effective IORT single dose was 7.5 Gy. Postoperative EXRT used 50 Gy in 25 fractions. To estimate the izoeffective biological dose of these two different schedules, a Normalized Biological Effective Dose (NBED) was calculated using a Linear-Quadratic formula with a/b value of 4.0 Gy:

$$NBED_{TOTAL} = RBE \cdot NBED_{IORT} + NBED_{EXT.}$$
$$= 14.4\ izoGy_{2.0} + 50\ izoGy_{2.0} = 64.4\ izoGy_{2.0}$$

assuming that EXRT was delivered in the shortest possible time after completing the CBS.

Table I. Clinical material characteristics

pT, N stage	Group A (n = 109)	Group B (n = 106)	Overall (n = 215)
pT1	95–87%	67–63%	162–75%
pT2	14–13%	39–37%	54–25%
pN0	105–96%	56–55%	161–75%
pN+	4–4%	48–45%	52–24%

Adjuvant therapy

Postoperative radiotherapy (EXRT) of 50 Gy, given in 25 fractions using 3D-IMRT as a sole adjuvant treatment was delivered to patients in group A. In group B, EXRT was combined with CHT as concurrent chemoradiation (with antracyclin, CTX and 5-Fu) in 62 cases (58%), and in the remaining 42%, EXRT was delayed after completing the CHT. Therefore, the time interval (TI) between CBS (IORT) and adjuvant therapy widely differed between group A and B. In group A, the TI was in the range of 10–45 days, whereas in 74% of the B cases, TI was delayed over 90 days, and in 40% of cases it was even longer than 120 days.

Hormonotherapy (tamoxifen) was additionally administered to 75% of patients and continued up to 5 years after completing combined therapy.

End-points

A ten-year follow-up was the only end-point to estimate the incidence of local recurrence free (LRFS) and distant metastases-free (DMFS) survival. The relationships between the accumulated incidence of LR and DM during the follow-up and the sequence of adjuvant treatment, including the TI between CBS (IORT) and the EXRT, were counted using the Spearman correlation, the multivariate Cox' regression analysis and the t-Student test modified by Yates. An estimate of $p < 0.05$ was accepted as a level of significance.

Results

The actuarial 10-year local tumor control (LTC) was 94.4% (97.1% in gr. A and 91.6% in gr. B), and disease-free survival (DFS) of 84.8% (93.5% in gr. A and 74.2% in gr. B).

Incidence and kinetics of local and distant failures

There were 12 local recurrences (LR – 5.6%) and 21 distant metastases (DM – 9.7%) during the 10-year follow-up. Although overall incidence of the LR or DM was not high, the LR rate in group B doubled when compared with group A; the DM incidence in group B was 4-times higher than in group A. Accumulation of the LR and the DM rates during the 10-year follow-up did not regularly and gradually increase, what is unusual attribute of these events. On the contrary, two-phase

Table II. Number, overall and accumulated rates of Local recurrences and distant metastases during three time intervals within 10-year follow-up

Factors	Follow-up in years			Significance (p)
	1–5	6–7	8–10	
local recurrence				
number (No.)	8	1	3	<0.005
overall rate	3.7%	0.5%	1.4%	–
accumulated rate	67%	75%	100%	–
distant metastases				
number (no.)	9	2	10	<0.0001
overall rate	4.1%	0.9%	4.7%	
accumulated rate	43%	52%	100%	

accumulation curves representing both types of failure were noted. The first phase concerns the 5-year follow-up, during which the accumulated rate of the LR gradually increased to 67%, and the DM to 43% (tab. II).

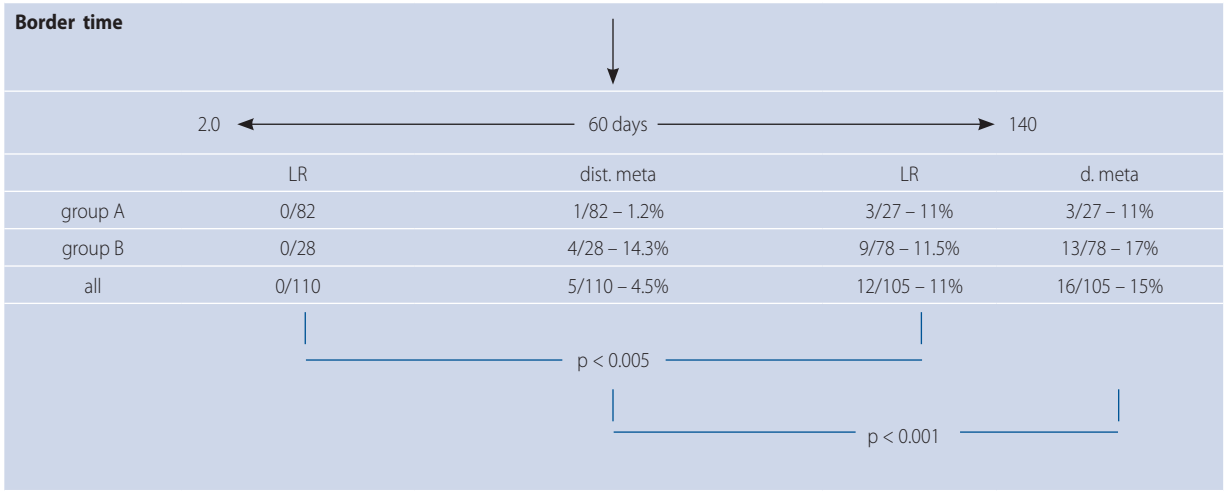
During the next two years (6th and 7th), the LR and DM rates slowed down, showing more or less a "plateau effect", and during the 8th to 10th year the accumulated rate of the LR steeply increased by 25%, and the DM by 48%. It seems that such an irregular accumulation rate of both failures might be explained by the biological and prognostic inhomogeneity of the two groups of patients with low vs. intermediate or high risk, and by the different aggressiveness of combined treatment modalities, lower in group A, and higher in group B.

The impact of the time interval (TI) between CBS (IORT) and adjuvant therapy on treatment outcomes

In 82 cases (75%) in group A, the TI ranged from 10 to 45 days, and in the remaining 27 cases (25%) the postoperative EXRT was delayed to over 60 days (for unknown reasons). On the contrary, in 28 cases (26%) in group B, the TI was shorter than 60 days (all received concurrent chemoradiation). Therefore, the TI of 60 days was arbitrarily chosen as the "TI cut-off limit". Table III shows that the duration of the TI had significant ($p < 0.005$) impact on the incidence of the LR, which in group A and B did not occur if the TI was shorter than 40 days (fig.1). However, the kinetics of the DM differed. For the TI up to 60 days it was low (1.2%) in group A, but in group B it was much higher, up to 14%. When the TI gradually extended above 80 days, the incidence of the LR and the DM significantly ($p < 0.001$) increased, being much higher in group B than A.

Extension of the TI in group B depended on whether EXRT was delivered concurrently with CHT or was delayed after completing CHT. The retrospective character of the analysis does not explain the reason for the two different ways of treatment decision. The delayed EXRT after completing CHT resulted in a 5-fold higher incidence of the LR ($p < 0.005$) and more than doubled incidence of the DM ($p < 0.001$). Figure 1 suggests that postoperative adjuvant therapy should begin as soon as possible but not later than 40–50 days after completing CBS (IORT). Furthermore, for patients in group B (intermediate or high risk) optimally effective is concurrent CHT-EXRT, which lower the risk of both the LR and the DM (tab. IV).

Table III. Incidence of local recurrences (LR) and distant metastases (d. meta) in the group A and B depending on time interval (TI) between CBS (IORT) and adjuvant EXRT. For TI 60 days was accepted as border time



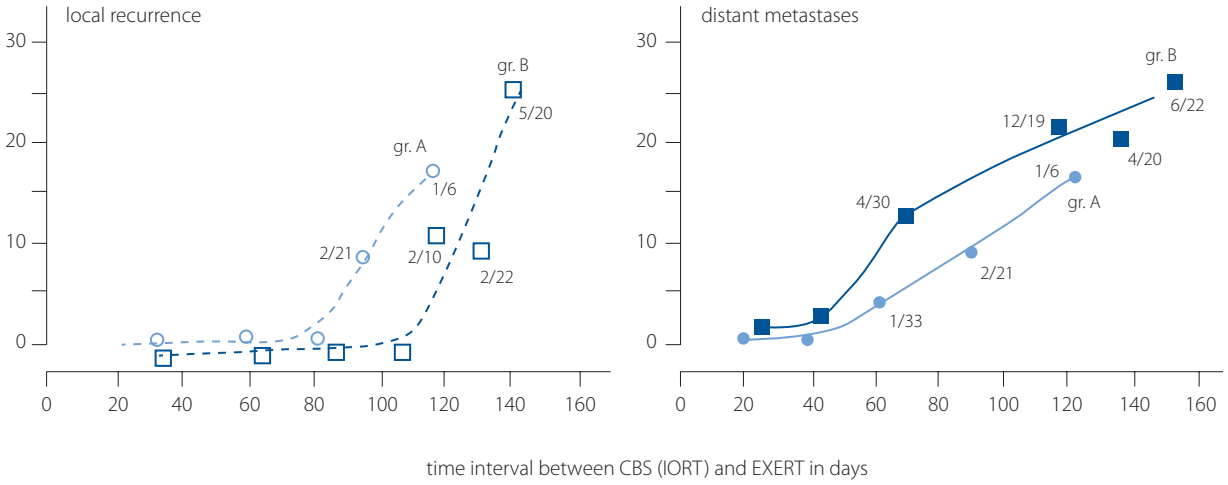


Figure 1. Incidence of local recurrence (LR) and distant metastases (DM) in the group A and B depending on time interval (TI) between CBS (IORT) and EXRT

Table IV. 10-year failure rates depending on the sequence of postoperative combined therapy in the group B

Sequence of postoperative therapy	Failures during 10-year follow-up	
	LR	dist. meta
concurrent cht-exrt	2/62 – 3%	6/62 – 10%
cht followed by exrt	7/44 – 16%	12/4 – 27%
significance (p)	<0.005	<0.001

Multivariate analysis (tab. V) shows that pN is the strongest risk factor of the DM together with the number of involved regional nodes. If their number increases, i.e. from 1 to 5 positive nodes, the DM-HR (hazard ratio) becomes about 2.5-times higher (3.65/1.36 – see the bottom of tab. V). The highest LR risk factor strongly correlated with the EXRT delayed after completing CHT (HR = 14.28). If the TI between CBS (IORT) was 80 days (20 days longer than the TI cut-off limit of 60 days), HR increases to 1.02^{20} = 1.485, which means an increase of the LR and the DM by about 48%, compared with that related to the TI of 60 days or less. On the contrary, concurrent chemo-radiation resulted in significant ($p < 0.001$) decrease of the LR risk by about 94% and the DM risk by 66%. The OTT of the EXRT was more or less the same (about 35 days) in all cases, therefore its prognostic power can be neglected, but the time interval between CBS (IORT) and the start of the postop. EXRT seems to be the major determinant of the LR and DM risk, mainly in group B, if the EXRT was considerably delayed after completing the CHT.

Discussion

Since Veronesi [8] and Bartelink [9, 10] convincingly documented that early advance breast cancer patients need adjuvant radiotherapy after CBS, it was recognized that EXRT alone is not effective enough (7–15% LR), especially for intermediate or high risk patients (11–15%). It became obvious that conventional adjuvant EXRT needs a boost dose. Intraoperative radiotherapy using a single dose became an interesting solution. Although the use of IORT and adjuvant EXRT in the early

Table V. Results of multivariate Cox' regression analysis of the LR and DM risk factors

Factors	LR		DM	
	HR	(p)	HR	(p)
pT	1.95	0.021	2.28	0.014
pN	2.6	0.001	4.75	0.0004
number of involved regional nodes (x)	1.18^{x}	0.32	1.36^{x}	0.0001
time interval (TI) between IORT and EXRT	4.83	0.013	1.29	0.62
delayed time of EXRT after IORT above 60 days (n – days > 60)	1.02^{n}	0.0008	1.02^{n}	0.0007
concurrent CHT-EXRT	0.07•	0.0014	0.34•	0.035
EXRT delayed after completing CHT	14.28	0.001	2.94	0.035

[^{x} – if x = 1 then HR = 1.18, but for x = 5, $HR_{LR} = (1.18)^5 - 1 = 1.29$ and $HR_{DM} = (1.36)^5 = 3.65$

^{n} – if TI increases by 20 days above 60 d limit then $HR = (1.02)^{20} = 1.485$ means an increase of LR/DM by 48.5% of that for TI £ 60 days

• – risk of LR decreases by 93% (1 – HR = 1 – 0.07 = 0.93) and DM by 66% (1 – HR = 1 – 0.34 = 0.66) compared with those for sequential EXRT after CH]

stages of breast cancer with no or low risk factors raised some doubts, Van Dongen et al. [16] and Clark et al. [17] strongly recommended IORT as a boost method preceding CBS. A recent comprehensive overview of the role of IORT in breast conserving therapy [18] provides the largest evidence of the high efficacy of the IORT with a single dose of 10–20 Gy, using electron beams. However, in the majority of the presented studies, the follow-up was shorter than 10 years (3–8 years). The IORT single dose of 14.4 izoGy$_{2.0}$ used in the present study is within the range of electron IORT doses of 10–20 Gy, due to the higher RBE of 20–50 kV X-rays, compared with that of electrons (RBE = 1.0). It is surprising that the recent ESTRO IORT TASK [18] aspires to recommend IORT but it raises some doubts and uncertainties. Local control and overall survival have been the only end-points and are related on average to only a 5-year actuarial follow-up, and the DM incidence has not been considered. The present study shows that beside the LR, the DM risk should not be ignored. Moreover, both failures accumulate nonlinearly during the follow-up (tab. II), and the 5-year follow-up is definitively too short, because about 30% of the LR and 55% of the DM can easily be missed, since they may occur later mainly between the 7th to 10th year of the follow-up.

A recent ESTRO IORT TASK overview is focused on stage I–II breast cancer patients but no/low and intermediate/high risk patients are pulled together, whereas our study suggests that these two groups should be analyzed separately.

Bellon et al. [19] pointed out that sequence of CHT and EXRT for intermediate/high risk patients plays a very important role, but in the ESTRO TASK overview, the time interval (TI) between IORT and adjuvant EXRT was not accounted, for similarly to Vaidya et al. [20, 21] in the TARGIT-A trial. On the contrary, multivariate analyses in the present study indicates the TI as the major determinant of the LR and DM risk. Considerable delay of the EXRT after completing postoperative CHT leads to the highest risk of the LR (HR = 14.28), even in the low risk group, where lengthening the TI over 60 days resulted in an increase of the LR from 0% to 11%, and the DM from 1.2% to 11% (tab. III). A similar trend was also noted in group B. It may suggest that the TI lengthened over 60 days can completely ruin the efficacy of the IORT considered as a boost dose, and therefore, the necessity of its application might be questioned.

Conclusions

The present study suggests that the IORT as a part of conservative combined therapy for early stage breast cancer patients can be an effective boost, but only when the time interval (TI) between the IORT and EXRT is as short as possible. For intermediate/high risk patients, concurrent chemoradiation is highly advantageous to the CHT followed by the EXRT because this sequence lengthens the TI between the IORT and EXRT, and therefore it wastes therapeutic efficacy of the IORT as a boost dose. Finally, it seems that a 10-year follow-up should be considered as standard because in the shorter period (i.e. 5 years) about 40% of LR and even more DM can easily be missed.

Conflict of interest: none declared

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Received: 8 Dec 2020
Accepted: 15 Dec 2020

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VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 139–145
DOI: 10.5603/NJO.2021.0028

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

Long-term results of randomized studies on the use of a gentamicin-collagen sponge in rectal cancer – depending on the length of time between the completion of radiotherapy and the surgery

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Introduction. Two randomized studies on the use of a gentamicin-collagen sponge (GRM01/1997 and GRM02/2007) in rectal cancer surgery showed a statistically significant decrease in the rate of distant metastases in the experimental group and a similar rate of local recurrences. The objective of the presented study was a retrospective evaluation of the effect of the GRM use on the observed rate of generalized recurrences, disease-free survival (DFS), overall survival (OS) and cancer-specific survival (CSS) – depending on the length of the interval between radiotherapy and surgery.

Materials and methods. The study comprised 239 patients, included previously into randomized studies, in whom the 5 x 5 Gy radiotherapy was used. In 204 people, the surgery was made within 7 days of the completion of radiotherapy (group A). The remaining group of 35 patients were operated on after 4–8 weeks (group B). The follow-up period was 5 years. The statistical analysis was made with the Kaplan-Meier test. The value of $\alpha = 0.05$ was degfined as the threshold of statistical significance.

Results. In both groups, there were no statistical differences between the patients operated on with the use of GRM and those operated on without the use of GRM. The analysis took into consideration the most significant parameters, which could affect the oncological results, (ypTNM, lympho-vascular invasion (LVI), blood vessel invasion (BVI). In group A, the use of GRM was connected with a lower rate of metachronic distant metastases ($p = 0.002$; RR 0.41; 95% CI [0.24–0.72]), the prolongation of DFS ($p = 0.008$; HR 2.16; 95% CI [1.20–3.83]) and of CSS ($p = 0.010$; HR 2.37; 95% CI [1.20–4. 67]). No such relationships were observed in group B.

Conclusions. The use of GRM decreases the risk of distant metastases and has an influence on the prolongation of recurrence free survival, but only when surgery is carried out within 7 days of the completion of irradiation.

Key words: rectal cancer, radiotherapy, gentamicin-collagen sponge

Introduction

The results of two randomized clinical studies (GRM01/1997 and GRM02/2007) showed that intraoperative use of a gentamicin-collagen sponge in rectal cancer patients, undergoing preoperative radiotherapy, followed by radical tumour resection, decreases the risk of distant metastases [1, 2].

How to cite:

Dmitruk A, Olesiński T, Hevelke P, Zyskowski Ł, Rutkowski A. ***Long-term results of randomized studies on the use of a gentamicin-collagen sponge in rectal cancer – depending on the length of time between the completion of radiotherapy and the surgery.*** *NOWOTWORY J Oncol* 2021; 71: 139–145.

The objective of the first study (Nowacki et al.) [1] was to determine the effect of GRM on the risk of post-operative complications and oncological results. The surprising results of the 3-year long-term follow-up, showed a significantly lower rate of distant metastases in the group of patients operated on with the use of GRM inspired another study with the objective to confirm the previous results (Rutkowski et al.) [2]. This time, the main objective of the project was to confirm the anti-cancer properties of GRM with regards to a reduction of generalized relapse. The study confirmed earlier observations: in the patient group with GRM, distant metastases occurred twice as rarely than in the control group (8.6% *vs.* 23.5%; HR 2.4; 95% CI: 1.1–5.5; p = 0.005).

Still, the mechanism of action of the studied medicinal product, which led to a decrease in the rate of generalized recurrence, is unknown. One of the considered hypotheses is the correlation between the antibiotic (GRM), which has a local effect on the irradiated area and the previously used ionizing irradiation, with respect to the activation of immunological mechanisms. Radiotherapy, by means of affecting the micro-environment of the tumour, creates the potential to reverse immunosuppressive conditions present in cancer [3]. An important role here is played by a fractional dose of radiotherapy [4]. The objective of the presented study was to evaluate how the interval between the last fractional dose of radiotherapy and the surgery, affects oncological outcomes.

Materials and methods

The analysis concerned the data of the patients who participated in two randomized studies, completed and published. The criteria of participation were described before [1, 2]. Both studies concerned patients with rectal primary adenocarcinoma. The randomization was made with a 1:1 proportion, and the study group were those patients who, after resection of the tumour with mesorectum, had a GRM implanted into the pelvis. The same agent was used in both studies. The clinical stage of the cancer was evaluated on the basis of the computed tomography (CT) of the abdominal cavity and pelvis with the contrast medium administered intravascularly. In the period when the clinical material was collected (1997–1999 and 2008–2011), magnetic resonance imaging (MRI) of the pelvis was not a diagnostic standard in the research centre. Qualification for the treatment was made on the basis of the multidisciplinary team's decision. Radiotherapy with high fractional doses (5 x 5 Gy) was applied in the case of resectable tumours with cT3–4 N0–2 M0 stage.

The treatment standard was a radical resection within 7 days of the completion of radiotherapy. The interval was prolonged only when there were medical contraindications for the surgery at the designed moment (e.g. an active infection, exacerbation of non-cancer related comorbidities). The surgeries were performed by one team of experienced surgeons. The operative technique was total mesorectum excision (TME). All the perioperative and post-operative complications, occurring within 30 days of surgery, were carefully reported. The pathomorphological assessment comprised:

- histological type of the tumour,
- TNM stage,
- radicality of the resection (R feature).

Additionally, the second study also assessed:

- the stage of the primary tumour (ypT),
- the condition of the regional lymph nodes (ypN),
- tumour differentiation (G feature),
- cancer invasion of lymphatic and/or blood vessels,
- radicality of the mesorectum resection,
- the length of the resection margin.

The data from the pathomorphological protocol, which were not routinely specified in the first study (Nowacki et al. [1]), were completed retrospectively. Patients with the third TNM stage of the disease also underwent adjuvant treatment (chemotherapy : 5 FU + LV, and, in the second study also OX + 5 FU + LV). The long-term observation consisted of an evaluation of the clinical condition with the CEA determination:

- every 3 months – for the first 2 years after the surgery,
- then – every 6 months – up to 5 years after the surgery.

Imaging diagnostics of the abdominal cavity were performed routinely, once per year, or more frequently in the case when a relapse was suspected. A colonoscopy was a standard assessment in the third and fifth year postoperatively. The criterion for diagnosing local recurrence was the presence of a tumor in the pelvis or within the anastomosis. Distant metastases were defined as the presence of tumors in any other location. If there was any doubt concerning the character of the observed lesions, then a biopsy and microscope verification were recommended.

The selection criteria for this study are presented in figure 1. Patients undergoing preoperative radio-chemotherapy were excluded from the study as in the study period, this method of treatment was applied solely in patients with a primarily non-resectable tumour. Depending on the length of the interval between the completion of the irradiation and the surgery, two groups of patients were distinguished:

- A: a short interval between the end of radiotherapy and surgery (the surgery was performed within 0–7 days from the completion of radiotherapy) – 204 patients,
- B: a long interval between the end of radiotherapy and surgery (the surgery was performed within 4–8 weeks from the completion of radiotherapy) – 35 patients.

In both groups, instead of the randomization result, the clinical data concerning the actual use of GRM (or not) were taken into consideration. The comparative characteristics of both groups are presented in table I. The grade of the disease, determined on the basis of the histopathological assessment of the resected post-operative material in patients in group B was lower than in group A (p = 0.005). In 22 (63%) operated

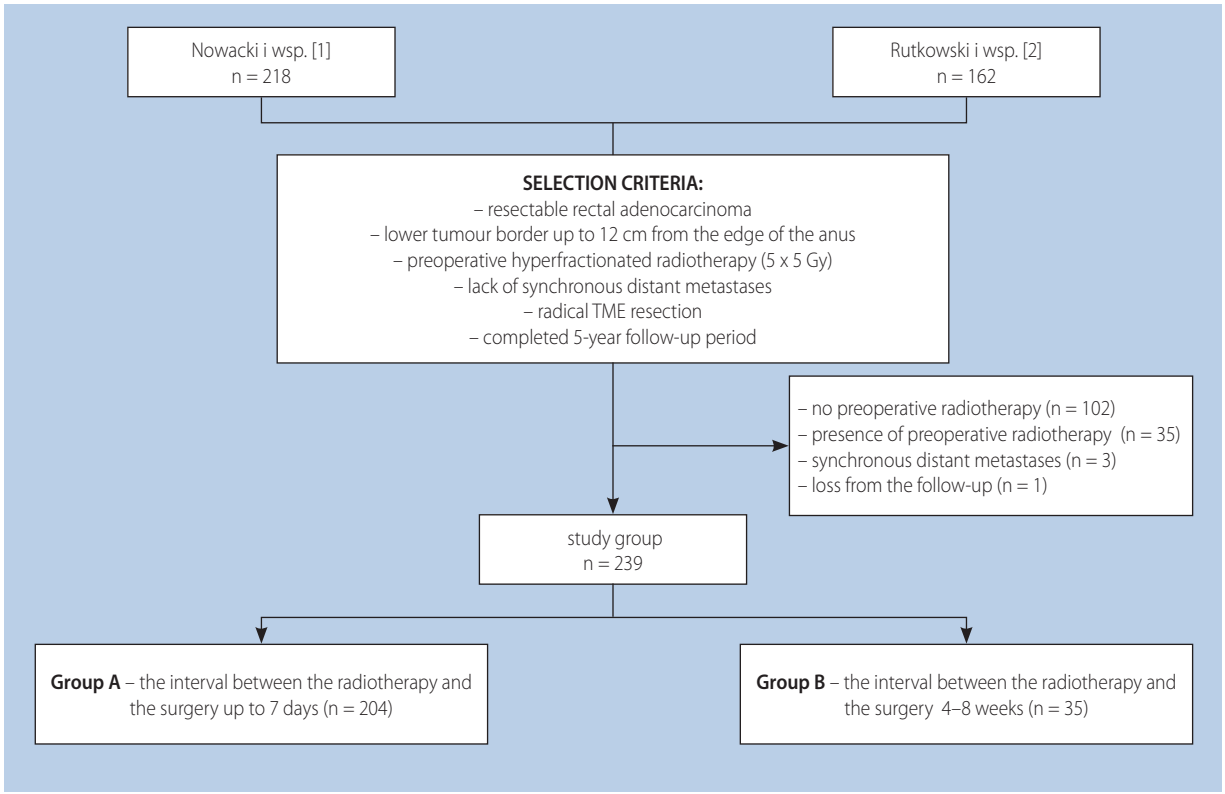


Figure 1. Patient selection

Table I. Comparative characteristics of the patients within the groups selected on the basis of the length of the interval between the completion of hyperfractionated radiotherapy and the surgery

Patients' characteristics		Group A n (%)	Group B n (%)	p
sex:	• men • women	134 (66) 70 (34)	24 (69) 11 (31)	0.739
age:	• median [range]	63 [25–84]	62 [38–81]	0.941
the distance between the tumour and the anus (cm)	• median [range]	5 [0–12]	5 [1–10]	0.878
surgery type:	• LAR • AR • ASAR • Hrtm.	87 (43) 39 (19) 60 (29) 18 (9)	23 (66) 5 (14) 5 (14) 2 (6)	0.094
the use of GRM:	• yes • no	102 (50) 102 (50)	19 (54) 16 (46)	0.716
post-operative complications:	• yes • no	62 (30) 142 (70)	11 (31) 24 (69)	0.902
radicality of the resection:	• R0 • R1	200 (98) 4 (2)	35 (100) 0 (–)	1.000
ypTNM:	• stage 0 (CR) • stage I • stage II • stage III	1 (0,5) 43 (21) 66 (32) 94 (46)	3 (9) 12 (34) 10 (29) 10 (29)	0.005
surgical margin:	• ≥2 mm • <2 mm • not specified	125 (93) 9 (7) 70 (–)	27 (96) 1 (4) 7 (–)	0.196
lymphatic vessels invasion:	• yes • no • not specified	53 (35) 97 (66) 54 (–)	6 (22) 21 (78) 8 (–)	0.267
blood vessels invasion:	• yes • no • not specified	51 (35) 92 (64) 61 (–)	7 (26) 20 (74) 8 (–)	0.328

GRM – gentamicin-collagen sponge; LAR – low anterior resection; AR – anterior resection; ASAR – abdominosacral amputation of the rectum; Hrtm. – Hartmann procedure

patients, after a long break, the grade was determined to be I or II. In 3 patients (9%), a complete pathomorphological remission was observed, which may be related to cancer remission observed after radiotherapy.

The statistical analysis was made on the basis of actual use, or not, of GRM (per-protocol analysis) made in two subgroups of patients selected on the basis of the interval between radiotherapy and surgery. The differences between the categorised variables were assessed with the use of χ^2 test or Fisher's exact test. Continuous variables were compared with the Mann-Whitney U-test. Overall survival (OS), disease free survival (DFS) and cancer specific survival (CCS) were assessed with the Kaplan-Meier method and compared with the long-rank test. The level of statistical significance was established in all the tests on the level of $\alpha = 0.05$.

Results

GRM was applied in 102 (50%) patients in group A and in 19 (54%) in group B. In both groups, there were no statistically significant differences between the operated patients with the use of GRM and the operated patients without the use of GRM. The comparison took into consideration the most important parameters which might affect the oncological results, such as:

- ypTNM cancer stage (group A: p = 0.207; group B: p = 0.401),
- lympho-vascular invasion (LVI) (group A: p = 0.865; group B: p = 0.182),
- blood vessel invasion (BVI) (group A: p = 0.221; group B: p = 0.408) (tab. II).

Metachronic distant metastases were observed in 48 (23.5%) patients in group A and in 3 (8.6%) in group B (p = 0.07;

Table II. Patients' characteristics, taking into consideration the use of gentamicin-collagen sponge (GRM)

Patients' characteristics	Group A		p	Group B		p
	GRM (+) n (%)	GRM (–) n (%)		GRM (+) n (%)	GRM (–) n (%)	
sex:						
• men	69 (68)	65 (64)	0.658	12 (63)	12 (75)	0.493
• women	33 (32)	37 (36)		7 (37)	4 (25)	
age:						
• median	63	62	0.638	60	70	0.159
[range]	[30–84]	[25–83]		[38–81]	[52–75]	
the distance between the tumour and the anus (cm)						
• median	6	5	0.159	5	6	0.382
[range]	[0,5–12]	[0–12]		[1–10]	[1–8]	
surgery type:						
• LAR	42 (41)	45 (44)	0.648	12 (63)	11 (68)	1.000
• AR	23 (23)	16 (16)		3 (16)	2 (13)	
• ASAR	29 (28)	31 (30)		3 (16)	2 (13)	
• Hrtm.	8 (8)	10 (10)		1 (5)	1 (6)	
post-operative complications:						
• yes	27 (26)	35 (34)	0.287	5 (26)	6 (37)	0.716
• no	75 (74)	67 (66)		14 (74)	10 (63)	
radicality of the resection:						
• R0	99 (97)	101 (99)	0.621	19 (100)	16 (100)	1.000
• R1	3 (3)	1 (1)		0 (0)	0 (0)	
ypTNM:						
• stage 0 (CR)	0 (0)	1 (1)	0.207	3 (16)	0 (0)	0.401
• stage I	25 (25)	18 (18)		6 (32)	6 (37)	
• stage II	36 (35)	30 (29)		4 (20)	6 (37)	
• stage III	41 (40)	53 (52)		6 (32)	4 (26)	
surgical margin:						
• ≥2 mm	61 (92)	64 (94)	0.742	14 (93)	13 (100)	1.000
• <2 mm	5 (8)	4 (6)		1 (7)	0 (0)	
• not specified	36 (–)	34 (–)		4 (–)	3 (–)	
lymphatic vessels invasion:						
• yes	25 (24)	28 (36)	0.865	5 (33)	1 (8)	0.182
• no	48 (66)	49 (64)		10 (77)	11 (92)	
• not specified	29 (–)	25 (–)		4 (–)	4 (–)	
blood vessels invasion:						
• yes	21 (30)	30 (41)	0.221	5 (33)	2 (16)	0.408
• no	49 (70)	43 (59)		10 (77)	10 (84)	
• not specified	32 (–)	29 (–)		4 (–)	4 (–)	

GRM – gentamicin-collagen sponge; LAR – low anterior resection; AR – anterior resection; ASAR – abdominosacral amputation of the rectum; Hrtm. – Hartmann procedure

RR 2.75; 95% CI: 0.90–8.33). The use of GRM in operated patients within a short interval after the end of radiotherapy (group A) was connected with a lower rate of metachronic distant metastases (13.7% *vs.* 33.3%; p = 0.002; RR 0.,41; 95% CI: 0.24–0.72). No similar relationship was observed in the case of surgery performed after a longer interval (p = 1.000; RR 1.68; 95% CI: 0.17–16.91).

Irrespective of the length of the interval between the end of radiotherapy and surgery, the application of GRM did not affect the rate of 5-year overall survival (group A: p = 0.484; HR 1.20; 95% CI: 0.72–1,99; group B: p = 0.956; HR 1.04; 95% CI: 0.23–4.66) (fig. 2).

The use of GRM improved the 5-year disease free survival rate, but only in cases when the surgery was performed within 7 days of the completion of radiotherapy (p = 0.008 HR 2.16; 95% CI [1.20–3.83] *vs.* p = 0.892 HR 1.11; 95% CI [0.25–4.96]) (fig. 3).

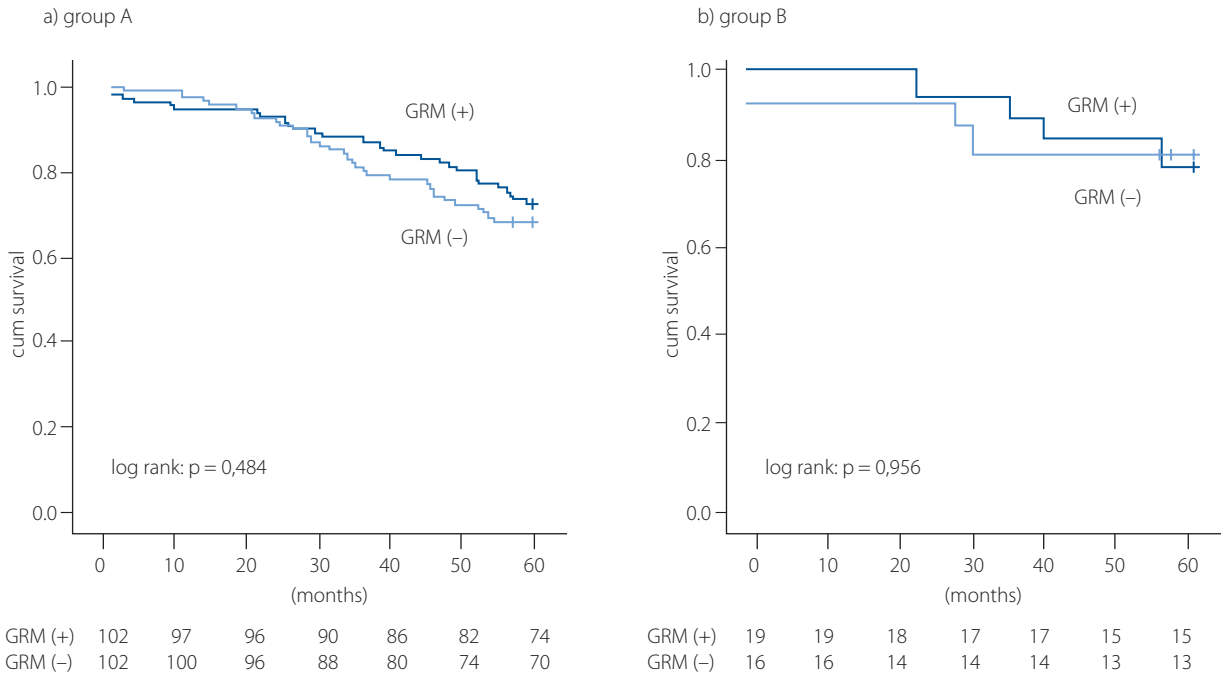
The analysis of 5-year cancer specific survival shows an improvement in results in the case of surgery performed after a short interval (group A) and the intraoperative use of GRM (p = 0.010; HR 2.37; 95% CI: 1.20–4.67 *vs.* p = 0.820; HR 0.80; 95% CI: 0.11–5.66) (fig. 4).

Discussion

Long-term results of the randomized study carried out by the Dutch Colorectal Cancer Group, showed that a short-lasting radiotherapy with high fractionated doses connected with immediate TME radical resection, decrease the risk of local recurrence of rectal cancer. This, however, does not translate into a prolongation of overall survival [5]. Some studies suggested that the prolongation of the interval between the radiotherapy and surgery by >4 weeks in patients suffering from resectable rectal cancer in stage cT3N+, increases the rate of complete pathological remissions and overall survival [6].

The Stockholm III study has proven that a delay of surgery by 6–8 weeks after a short-lasting brachytherapy, increases the rate of clinical remissions, but does not affect the prolongation of overall survival [7]. Two randomized studies which were carried out concerning the effect of the intraoperative use of GRM on the results of the treatment of patients with rectal cancer, showed a significant decrease in the risk of distant metastases, but the mechanism of anti-cancer action of the agent remained unknown [1, 2].

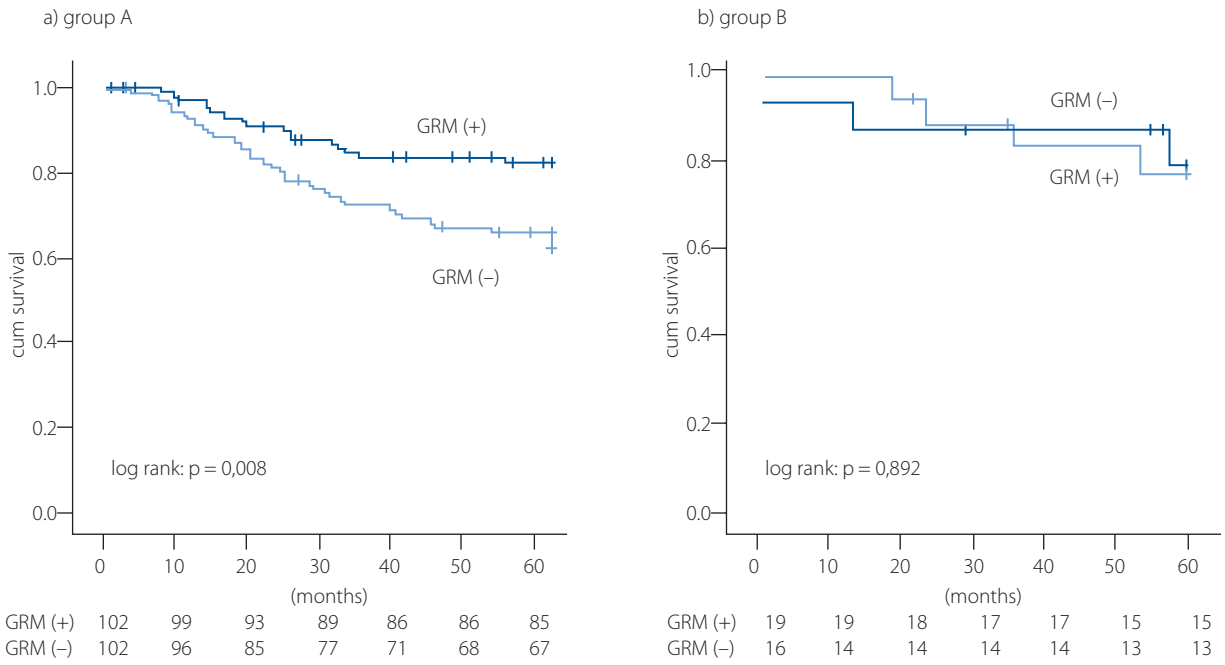
The objective of the current retrospective studies, based on the materials from the two randomized studies, was to explain whether the length of the interval between the completion of hyper-fractionated short-term preoperative radiotherapy had any effect on the obtained oncological results. Each time, the prolongation of the interval was only the result of the medical contraindications for the surgery performed immediately after the completion of radiotherapy. Therefore, the difference in the numbers of the two compared groups was so high (group A: 204 patients *vs.* group B: 35 patients). In those patients with a delayed surgery, the disease stage as evaluated preoperatively (ypTNM) was lower (p = 0.005) – this is shown in table I. The explanation for this may be the pathomorphological remission



GRM (+): patient group with the use of the gentamicin-collagen sponge

GRM (–): patient group without the use of the gentamicin-collagen sponge

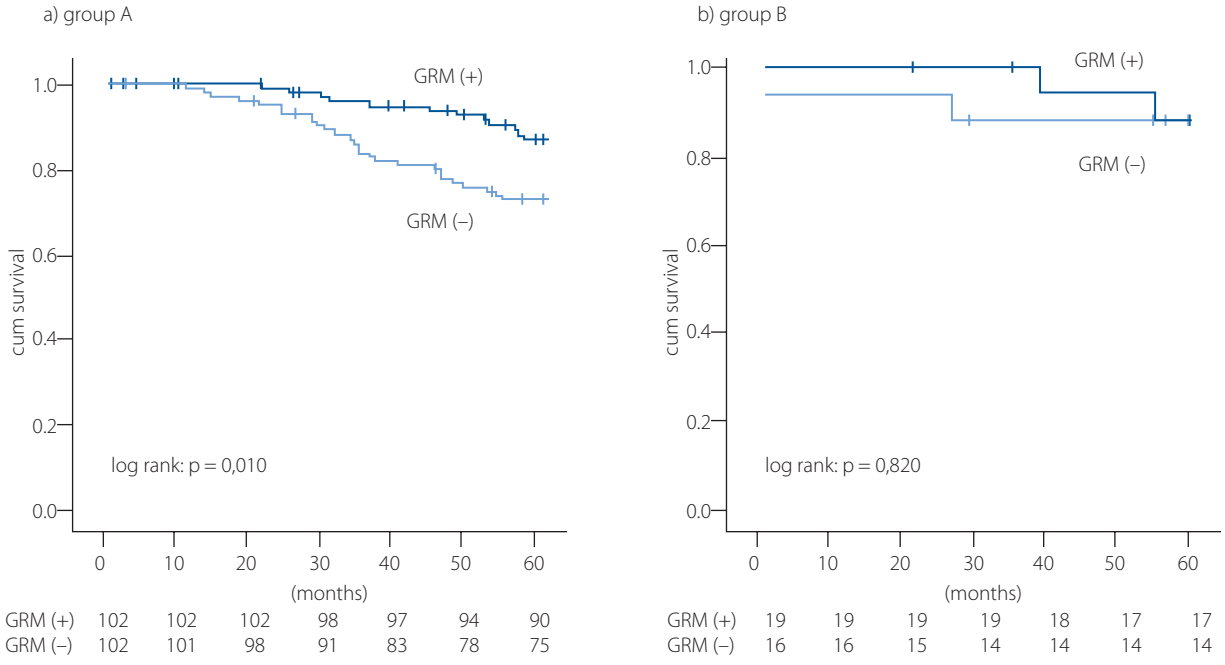
Figure 2. 5-year overall survival



GRM (+): patient group with the use of the gentamicin-collagen sponge

GRM (–): patient group without the use of the gentamicin-collagen sponge

Figure 3. 5-year disease free survival period



GRM (+): patient group with the use of the gentamicin-collagen sponge

GRM (–): patient group without the use of the gentamicin-collagen sponge

Figure 4. 5-year cancer specific survival period

of the cancer [8]. The use of GRM in patients operated on after a short break (group A) was connected with a lower rate of metachronic distant metastases (3.7% *vs.* 33.3%; p = 0.002). No similar relationship was observed in group B (p = 1.000). The improvement of the rate of 5-year disease free survival was seen solely in the case of the application of GRM in the patients operated on immediately after radiotherapy (group A; p = 0.008). This, however, did not affect the 5-year overall

survival. However, the analysis of cancer specific survival may suggest a beneficial anti-cancer effect of GRM, provided it is used during surgery performed immediately (≤7 days) after the completion of irradiation.

In spite of these encouraging results, the mechanism of anti-cancer activity of GRM remains unknown. Moreover, the fact that the observed anti-cancer effect of the application of this agent is stronger in the case of surgery performed immediately after the end of irradiation, cannot be explained either. A postulated hypothesis may be the modulation of the developing inflammatory reaction in the irradiated area by means of locally acting antibiotics. There are data which support the activation of the immunological response after the use of short-term radiotherapy [9–11]. The damaged cells from the tissues undergoing irradiation and immunologically-inflammatory resident cells release factors which attract the cells from the blood and (or) lymphatic circulation [12, 13]. The effect of the immunological response to the applied radiotherapy may concern not only the irradiated tissues, but also distant ones, which is known as the abscopal effect [3, 14, 15]. The key factor here may be the fact that during the short break between the end of radiotherapy and surgery, a bactericidal, and also indirectly, anti-inflammatory agent is implanted into the area of the developing post-irradiation inflammatory reaction. As a result, this may affect the final shape of the immunological response, and thus, the obtained oncological results.

In spite of the fact that the material comes from randomized prospective studies, the results of the presented study must be interpreted with the utmost caution. This is the outcome, first of all, of the fact that the study was retrospective. The length of the interval was not the outcome of random selection, and the delay in surgery might have concerned patients in whose cases the prognosis of survival was poorer on account of their comorbidities. In a large proportion of patients (20–23%), significant data was missing: the length of the resection margin, the invasion of blood and/or lymphatic vessels and the radicality of mesorectal resection were not analysed. Moreover, the disproportion in the numbers of the studied patient group, has significantly decreased the power of the sample. A small number of patients with a long interval between the end of radiotherapy and surgery does not allow for a definite conclusion whether the use of GRM affects the long-term oncological results.

To sum up, the study results may suggest that the intraoperative use of GRM is beneficial as it decreases the risk of distant metastases and the prolongation of disease free survival, first of all in situations when surgery is performed within a short period of time (≤7 days) after the completion of irradiation. This, however, requires confirmation by a randomized and multi-centre clinical trial.

Conflict of interest: none declared

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Received: 10 Dec 2020
Accepted: 19 Dec 2020

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VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 146–152
DOI: 10.5603/NJO.2021.0029

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

Radiotherapy treatment planning for breast cancer patients after a subcutaneous mastectomy with the use of a prosthesis or expander

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Introduction. Medical physicists planning radiation treatment are increasingly confronted with situations that require special attention. Undoubtedly, one such situation is the postoperative irradiation of a patient with breast cancer in which there is a prosthesis or an expander. In recent years, expanders have appeared in this location, which, due to the density of the device's valve makes it difficult to prepare an acceptable treatment plan. The study aims to present treatment planning in these situation in various Polish cancer centres and to compare overall patient preparation for the treatment.

Material and methods. A questionnaire was prepared and sent to more than 20 radiotherapy departments, which included basic questions regarding the preparation of an irradiation plan for patients treated for breast cancer after a subcutaneous mastectomy with immediate reconstruction with a prosthesis or expander. The survey encompassed eight radiotherapy departments.

Results. Not all radiotherapy departments require a manufacturer's certificate, which shows that the manufacturer does not prohibit the use of a prosthesis/expander during treatment with ionizing radiation. The X 6MV photons and the supine position, total and fraction doses: from 40 to 60 Gy and from 2 to 2.67 Gy, respectively, are the most commonly used. The way of defining them also depends on the oncological centre. The most commonly used irradiation technique is VMAT.

Conclusion. The conclusion from the questionnaire – no standardisation of treatment planning – should encourage the community, at least medical physicists, to develop rules of conduct in this case. Irradiation techniques are mainly dynamic ones. The expander or prosthesis does not significantly affect the dose distributions.

Key words: breast cancer, subcutaneous mastectomy, prosthesis, expander, radiotherapy techniques, dose calculation algorithms

Introduction

Irradiation of patients with breast cancer is well-established. It has a positive effect on local control, but also on long-term survival, which has been proven in many clinical studies [1, 2]. The use of radiotherapy in these patients has a long tradition. The arrangement, due to the anatomy of the patients, were

How to cite:

Kędzierawski P, Buliński K, Kuszewski T, Wnuk K, Dąbrowski A, Lis K, Braziewicz J, Ślosarek K. ***Radiotherapy treatment planning for breast cancer patients after a subcutaneous mastectomy with the use of a prosthesis or expander.*** *NOWOTWORY J Oncol* 2021; 71: 146–152.

two opposite fields. At that time, this technique and an energy of 250 KeV were used. In the 1970s, in Poland, cobalt machines started to be used in radiotherapy. In this case, the technique of "tangential" open fields was supplemented with wedge filters. Instead of two fields, there were four – two open and two with wedges. Various types of patient immobilisation systems, such as breast boards, T-holders, or vacuum mattresses, slowly began to enter clinical practice. In the first years of the use of linear accelerators, the techniques of irradiating breast cancer patients did not change much. The technique of opposite fields was still dominant. The situation did not change with the implementation of computed tomography (CT) in planning and the use of a multi-leaf collimator (MLC) [3, 4].

A radical change took place when planning physicists got the opportunity to plan a dynamically changing dose – intensity-modulated radiotherapy (IMRT) [5]. Slowly but surely, the technique of opposite fields was replaced by several beams with a dynamic dose change. In recent years, the dynamic arc technique (volumetric modulated arc therapy – VMAT) has been increasingly used as a technique in the irradiation of breast cancer patients [6]. The calculated dose distributions are influenced not only by beam geometry but also by algorithms used in treatment planning systems. The irradiated volume contains different anatomical structures with different densities: lung tissue, bones (ribs), and soft (glandular and fatty) tissue. While simple algorithms (based on the dose decrease as a function of depth and distance from the beam axis) give a good approximation of the dose distribution in a medium (section) of the same density; at the border of mediums of different density they completely distort the dose distribution. The currently used algorithms take into account most of the physical phenomena related to radiation absorption, therefore the calculated and measured dose distributions are consistent within the measurement uncertainty. Another problem in the irradiation of patients with breast cancer is the mobility of the chest wall and the increasingly frequent appearance of high-density implants in the irradiated volume. The presence of high-density materials can be considered in at least three aspects. There are program algorithms that calculate dose distributions that have upper-density limitations. This means that when planning treatment, it is necessary to change this value to an acceptable value for the algorithm used. This procedure causes the calculations to be inconsistent with reality. The presence of high-density material alters the energy spectrum at the volume boundary, which affects the dose. Finally, artifacts make it much harder to properly contour target volumes. Artifacts can be reduced using appropriate software or manually. Typically one calibration curve is used: HU – density [7]. The latter issue was the reason for surveying in Polish radiotherapy departments regarding the irradiation of breast cancer patients after a subcutaneous mastectomy with the use of a prosthesis or an expander.

Material and methods

Questionnaire results

The questionnaire prepared by the University of Jan Kochanowski in Kielce, Holycross Cancer Center in Kielce and the Polish Society of Medical Physics were sent to more than 20 Polish radiotherapy departments (RD). Seven RDs that routinely use radiotherapy in breast cancer patients after subcutaneous mastectomy with the use of a prosthesis or an expander responded to it, and one RD that performed this procedure several times and had no experience in this field. Therefore, they did not answer the questionnaire directly but sent their comments, which we will quote in full:

1. In planning radiotherapy in such cases, the biggest challenge was obtaining a satisfactory dose in the areas between the implant and the lung/rib (thin layer) and the second the area between the implant and the body surface (essentially skin and subcutaneous tissue/a postoperative scar).
2. The second challenge was the limitation of the treatment planning system, which takes Hounsfield Units (HU) values to 3000, with the implant material having this parameter much higher. We can measure its HU, but the system does not accept it anyway and overwrites this value.
3. Flares caused by the presence of metal clips cause significant disturbances in CT, which can significantly disrupt the dose distribution. The use of density correcting algorithms in CT is of minimal help.

It is a pity that the other RDs, to which the questionnaire was sent, did not answer as to why they do not routinely use this type of irradiation.

The questionnaire (tab. I) contained questions on formal issues (certificates), treatment planning (beam geometry, normalisation, algorithms), and the values of the total and fraction doses used.

Results

The values presented in the table show that not all RDs require a manufacturer's certificate, showing that the manufacturer does not prohibit the use of a prosthesis/expander during treatment with ionizing radiation. This is an important aspect of therapy. The lack of a certificate in the medical records can make the legal assessment of treatment very complicated. It would be prudent to require such a certificate before starting treatment. The density of the prosthesis or expander may be much greater than that of the soft tissue. Six RDs declared that the density value was known from the CT examination. The most commonly used irradiation technique is VMAT. Interestingly, none of the radiotherapy departments declared that they (routinely) used the tangential field technique (fig. 1), perhaps they were qualified for the 3DCRT technique).

The most commonly used energy is the X6MV beam. Only one radiotherapy department also uses X15MV radiation. The

Table I. Questionnaire with answers. Seven sites responded to the questionnaire, the sum of the points in the question is not always equal to seven, as, for example, different dose fractionation schemes can be used in one site

Questionnaire concerning radiotherapy treatment planning for a breast cancer patient irradiated after a subcutaneous mastectomy with immediate reconstruction with a prosthesis or expander

1. Do you use postoperative radiotherapy in patients after a subcutaneous mastectomy with simultaneous reconstruction?

yes – 6	no – 0

2. Do you use postoperative radiotherapy in patients after a subcutaneous mastectomy with simultaneous reconstruction with the use of an expander?

yes – 5	no – 1

3. Do you require the delivery of the prosthesis manufacturer's or expander's certificate for the use of radiotherapy?

yes – 5	no – 2

4. Do you have the exact value of the prosthesis/expander density resulting from the tomographic examination?

yes – 6	no – 1

5. What techniques of radiotherapy do you use in patients irradiated with a prosthesis or an expander?

3D-CRT/tangential fields	2
IMRT	2
VMAT	4
tomotherapy	2
3D-CRT (field in field)	1
hybrid 3D-CRT 20%, VMAT 80%	2

6.What kind of radiation do you use in patients irradiated with a prosthesis or an expander?

photons: X6MV – 5	electrons: 0	mixed photons: X6MV and X15MV – 1

7. What fraction doses do you use in these patients?

1.8 Gy – 1	2 Gy – 4	2.25 Gy – 1	2.5 Gy – 1	2.67 Gy – 1

8. What total doses do you use in these patients?

45 Gy – 1	45 Gy – 1	50 Gy – 3	50.4 Gy – 1	40 Gy – 1	60 Gy – 1

9. How the dose is specified?

point	0
isodose	2: 95%; 98%
volume	2: 100%; 95% PTV
mean	4
minimum	0
other	raport ICRU 83

10. How is the patient positioned?

supine position – 6	srone position – 1

11. Do you use skin bolus in these patients?

yes – 2	no – 5

12. What calculation algorithms do you use in these patients?

CCCS	1
PBC	0
AAA	4
Acuros	2
Monte Carlo	1
other	0

13. At what distances are computed tomography scans?: 1.5; 2 and 3 [mm]

1,5 mm – 1	2,5 mm – 2	3 mm – 5

14. What value of the calculation grid is used in the dose calculation?: 2.5; 3; 5 [mm]

2,5 mm – 5	3 mm – 2

15. Please attach prepared DVH for treated patient

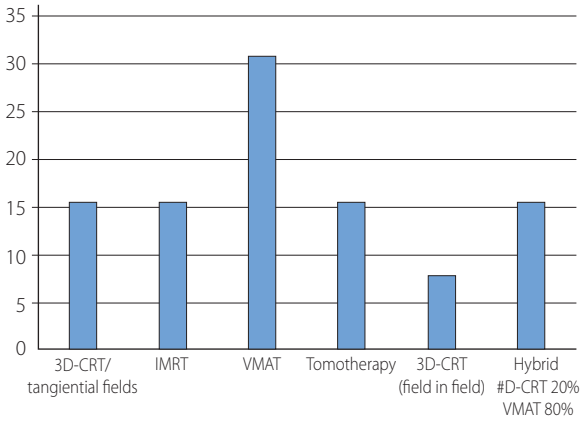

Figure 1. Percentage of irradiation techniques in patients treated for breast cancer after a subcutaneous mastectomy with the use of a prosthesis or expander in seven Polish radiotherapy departments

planned total and fraction doses are in the range from 40 to 60 Gy and from 2 to 2.67 Gy, respectively. The spread is quite significant. If we add to this that these doses are normalised to the mean value (57% of RDs), the remaining ones to the volume (100% or 95%) and dose (98% or 95%), it may turn out that despite the records in the treatment card in different RDs are the same, but in reality, they differ significantly [8].

The algorithms used to calculate the doses take into account "almost" all the physical phenomena related to radiation absorption. None of the RDs declared that they used the Pencil Beam algorithm [9]. Therefore, it is very likely that the obtained calculation results are consistent with the actual doses, of course within the limits of measurement uncertainty. However, it should be remembered that the results refer to absorbed energy, i.e. a physical phenomenon. They do not take into account the change in the energy spectrum that may occur on the border of two densities and which affects the biological effects. This is one reason to be very careful when planning when there is an "object" of high density within the delivery volume. Computed tomography is performed with distances between the layers from 1.5 to 5 mm and the computational grid from 2.5 to 5 mm. The questionnaire also asked for a sample DVH. It is difficult to discuss and compare dose values on DVH charts when the planned total doses are different. Therefore, it is worth looking at the anatomical structures that are analysed. All the graphs show: PTV, heart, lungs: right and left and their sum, but only one has an "expander". This outline is introduced not to know what doses are in it, but to exclude it from the PTV volume because it distorts the information about its distribution.

Since the information that we obtained from the questionnaire speaks about differences in dose definition and data acquisition from a CT scanner, it is worth analysing how large the differences in doses may be.

Discussion

The total dose, fractional dose and the method of its normalisation

Figure 2 shows an example of the dose distribution with an expander. Most of the valves used are less than 3000 HU and have no significant effect on the dose distributions.

The most frequently planned fraction dose is 2 Gy, and the total 50 Gy normalised to the mean dose value in PTV (fig. 3). The differences between dose distributions when normalised to a mean value or 95% dose in 95% PTV volume are negligible, both in PTV/CTV and critical structures.

Fraction and total doses may have a much greater impact on the results of treatment. Let us assume $\alpha / \beta = 4$ Gy, let us assume the administration of a fractionated dose of 50 Gy at 2 Gy and 2.5 Gy. The biologically equivalent doses (DizoGy2)

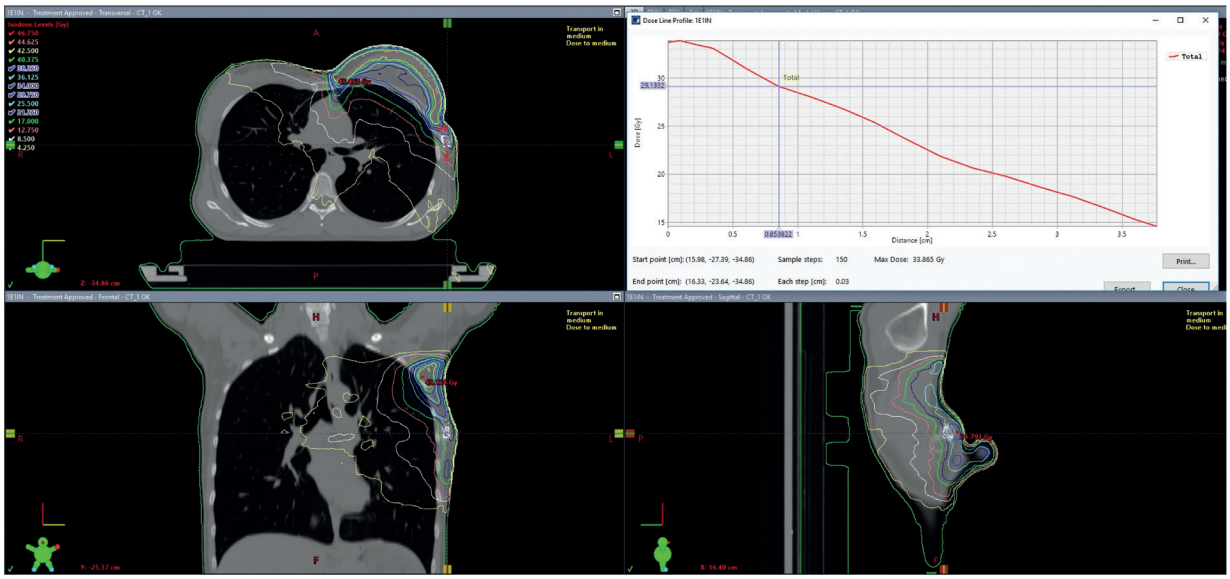

Figure 2. An example of dose distribution with an expander

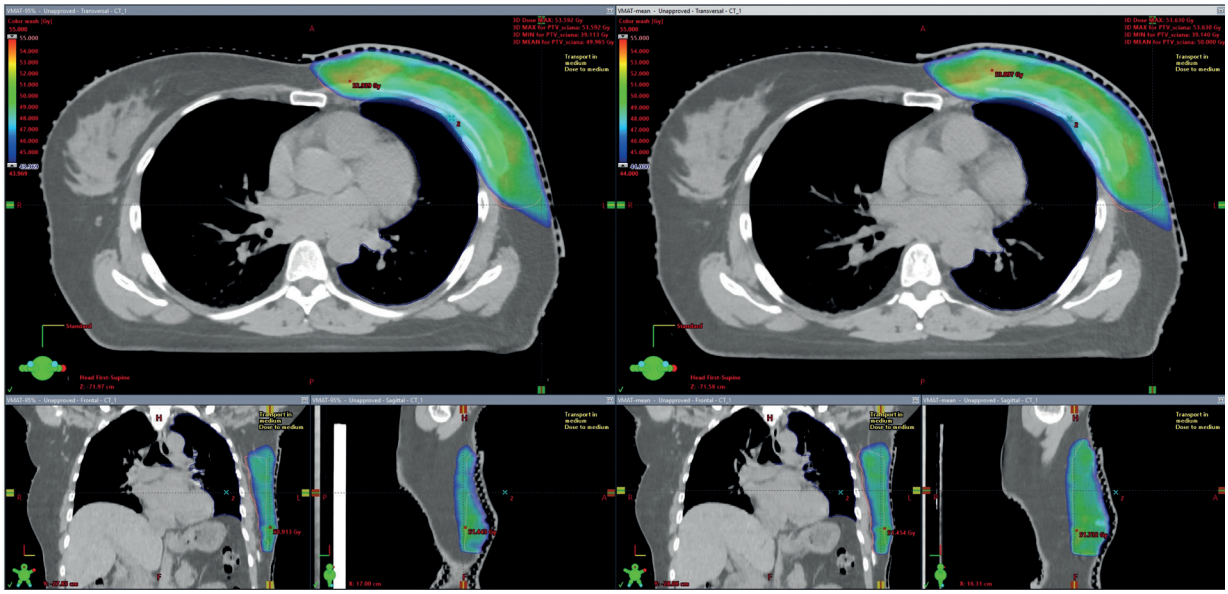

Figure 3. An example of 50 Gy total dose distribution in PTV. Normalisation to 95% of the dose in 95% PTV (A) and the mean value in PTV (B), 2.5 mm dose grid, Acuros v 15.6 algorithm (VMS). In this case, the values of the maximum, minimum, and average doses differ by no more than 0.2 Gy

will be 50 Gy and 54.2 Gy. These differences may be important in the assessment of treatment effects [10].

Effect of the calculation grid on the results of the dose distribution

Dose distributions were calculated for the calculation grid: 1 mm and 5 mm, the results indicate that there is a difference in the dose distributions, especially in PTV (fig. 4). Significant differences occur in the area of dose escalation (the PTV area under the skin) and on the border: chest wall – lungs which could be important in the analysis of the correlation between the dose and the likelihood of local cure.

There are differences between the calculations performed by different algorithms. However, they are difficult to estimate based on this questionnaire. Since these are algorithms that take into consideration most of the physical phenomena, including the boundary effects related to the difference in density, it can be assumed that the calculated dose distributions are consistent with the measurement results. The questionnaire did not include the question of whether the dose distribution was verified in the case of dynamic techniques before starting treatment. As this is a formal requirement, we recognise that all centres comply with the applicable regulations.

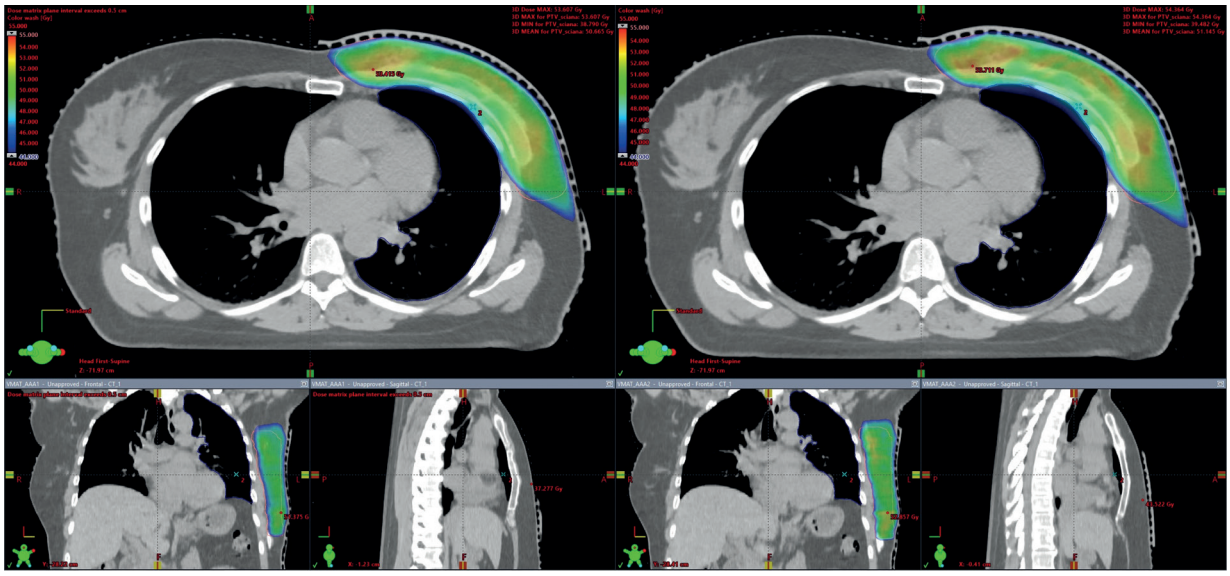

Figure 4. DVH for PTV for dose grid of 5 (A) and 1 (B) mm (AAA algorithm, eclipse, VMS). The differences between the minimum, maximum, and average doses are in the order of 1 Gy, the values are higher for a smaller dose grid

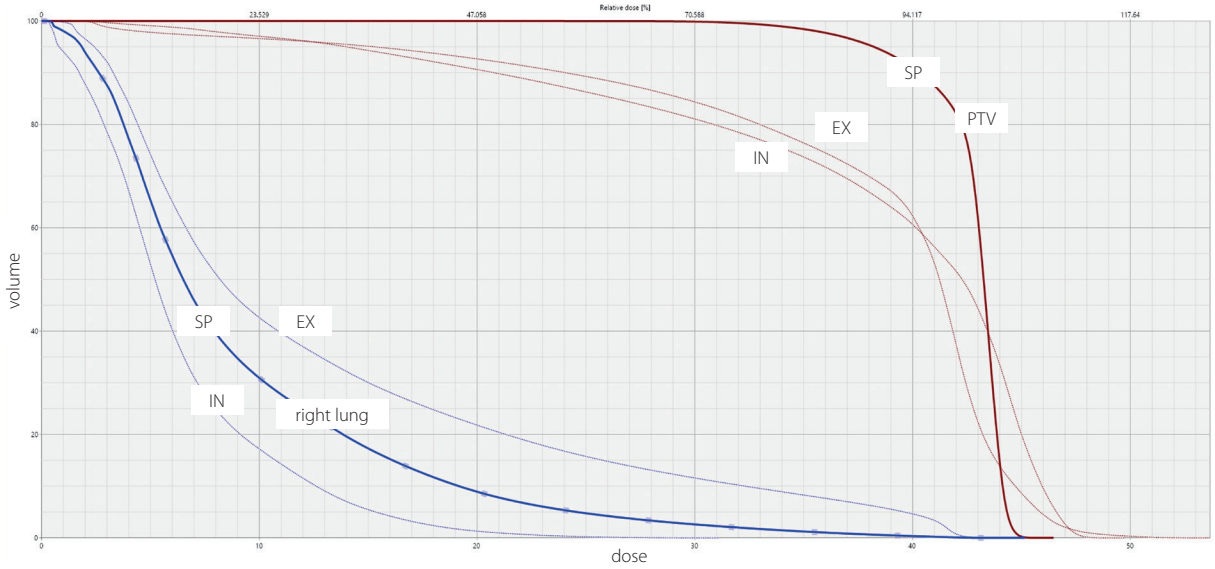

Figure 5. The simulation of chest movement associated with breathing (EX - exhale, IN - inhale, SP - stable, planned position) has a significant impact on dose distributions (without respiratory gating)

An important aspect of chest area irradiation is respiratory mobility. Figure 5 shows the DVH simulating respiratory mobility. It seems that in this anatomical location it is justified to use the respiratory gating technique (especially full inspiration) or tracking the location of the irradiated area-tracking target [11, 12].

A subcutaneous mastectomy with immediate reconstruction with an expander or prosthesis is becoming more common and sometimes replaces breast-conserving surgery in the hope that radiotherapy is not necessary. However, irradiation should be used in many patients after subcutaneous mastectomy. A very thorough diagnostic workup is demanded and proper qualification for this surgical procedure. This is also a challenge for radiation oncologists and medical physicists. Prospective trials are necessary to ensure that these new techniques do not compromise oncologic outcomes[13–16].

Conclusions

The greatest differences in irradiation and irradiation planning in patients treated for breast cancer after a subcutaneous mastectomy with the use of a prosthesis or expander between radiotherapy departments concern total and fraction doses. The irradiation techniques are mainly dynamic techniques (VMAT) and the algorithms used take into account most of the physical phenomena related to radiation absorption. The methods of normalisation do not make any significant differences in the dose distributions. The position of the patient is very similar across all RDs. Most radiotherapy departments require an expander or prosthesis with a manufacturer's certificate. This is an important aspect from a formal point of view. Most expander valves have a slightly higher density than bone. However, differences in chemical composition must be taken into consideration. They do not significantly affect the dose distributions, however, attention should be paid to the disturbances that are introduced. The actual problem is usually the lack of information from the manufacturer as to whether the material can be used in radiotherapy. We do not know if its properties change as a function of the absorbed dose. When preparing patients for irradiation, in particular when performing computed tomography, the examination protocol should be selected to minimise artifacts that may appear. Due to the mobility of this area, related to the patient's breathing. The use of respiratory gating, despite the prolongation of the therapeutic session, seems to be justified.

Conflict of interest: none declared

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Received: 29 Sep 2020
Accepted: 4 Nov 2020

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VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 153–157
DOI: 10.5603/NJO.a2021.0018

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

Skin-sparing and nipple-sparing mastectomy with a positive sentinel node in patients with breast cancer

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Introduction. A skin-sparing or nipple-sparing mastectomy is a surgical treatment that is increasingly used in the treatment of patients with breast cancer. More often women themselves decide or even ask to undergo this type of surgery. In our paper, we present the issue of combined treatment of 62 patients after nipple-sparing or skin-sparing mastectomy with a positive sentinel lymph node. Realisation of this type of surgery has further consequences in adjuvant treatment policies.
Material and methods. The group of 62 previously untreated women with positive sentinel lymph nodes took part in this analysis. The individual plan of treatment was established for every patient by the multidisciplinary team according to the rules of the breast cancer unit. All patients were treated in the Holycross Cancer Centre in Kielce (in 2015–2018).
Results. The early results show that proper qualification and realisation of oncological treatment is safe and effective. Severe complications appeared rarely.
Conclusions. Skin-sparing or nipple-sparing mastectomy is a method of surgical treatment that is increasingly used in the treatment of patients with breast cancer. It should be remembered that the qualification for this type of procedure should be careful, and adjuvant treatment should be rationally planned. Our experience shows that it is an effective and safe method.

Key words: breast cancer, skin-sparing mastectomy, nipple-sparing mastectomy, combined treatment

Introduction

In the last decade, both nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) with immediate reconstruction with a prosthesis or expander have been used in the surgical management of non-metastatic breast cancer patients, although their oncologic safety has not been established in randomised controlled trials. The literature pointed that the outcomes of the treatment with NSM, SSM and modified radical mastectomy (MRM) are similar, but, importantly, subcutaneous mastectomies preserve the patient's body shape [1–4]. NSM or SSM can be connected with sentinel lymph node biopsy in patients with clinically negative lymph nodes. In literature, data is limited about proceeding with patients after NSM or SSM with a positive sentinel lymph node. In our paper, we present the clinical implications of the treatment of women after NSM or SSM and the sentinel lymph node biopsy procedure.

Material and methods

Between 2015–2018, 290 women with NSM or SSM were treated in the Holycross Cancer Centre in Kielce. The group of

How to cite:
Kędzierawski P, Bocian A, Mężyk R. ***Skin-sparing and nipple-sparing mastectomy with a positive sentinel node in patients with breast cancer.*** *NOWOTWORY J Oncol* 2021; 71: 153–157.

62 previously untreated women with positive sentinel lymph nodes took part in this analysis. An individual plan of treatment was established for every patient by the multidisciplinary team according to the rules of the breast cancer unit. Statistical analyses were performed using MedCalc Statistical Software ver. 19.6 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). Basic statistical measures for continuous variables, as well as frequencies and percentages for qualitative and ordinal variables were calculated. The Chi-square test was used to assess the interdependence of variables in double classifications and the T-Student or Mann-Whitney test for continuous variables to examine the differentiation of the two groups studied were applied. It was assumed that p values less than 0.05 indicate statistical significance.

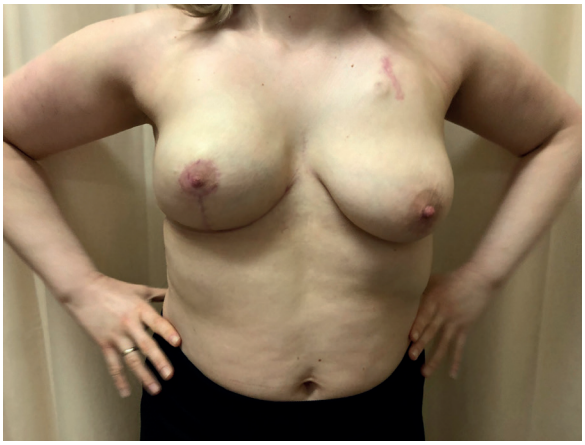

Figure 1. Patients after NSM and radiotherapy

Results

The analysed group consisted of 62 women. The mean time of observation was 46 months (min.: 11months, max.:72 months). The mean age of women was 49 years old. NSM and SSM were performed in 48 and 14 patients, respectively.

The surgical margins in all patients were negative. In 60 patients, cancer was diagnosed in the I and II clinical stages, in 2 patients in the III stages. The non-special type of cancer prevailed (51 patients). Luminal subtypes were recognised in 42 patients, both, HER2-positive and triple-negative subtypes in 7. In the analysed group, positive sentinel nodes were found in all patients. In 30 of them, an extracapsular extension (ECE) in the sentinel lymph node was diagnosed. In the group with ECE, axillary dissection (AD) was performed in 15 patients. Patients with massive extracapsular extension and a high ratio between occupied to removed sentinel lymph nodes were qualified to AD. The decision about performing AD was also taken multidisciplinary. In 8 patients after AD, additional lymph nodes with metastases were found, but the pathological nodes (pN) and stage (pN1 to pN2 or pN3) changed only in 5 women. In the group without ECE in sentinel lymph nodes, only 1 patient had axillary dissection performed. Chemotherapy, hormonotherapy and anti-HER2 therapy were implemented according to indications. Statistically, chemotherapy was applied in patients with ECE more often. The most common regimen of chemotherapy was 4 cycles of adriamycin and cyclophosphamid followed by 12 cycles of paclitaxel – applied to 28 patients. Postoperative conformal radiotherapy (PORT) was applied in 58 out of 62 patients (fig. 1).

Three patients refused radiotherapy. In one female patient micro-metastases to the sentinel lymph node were recognised. In patients with positive 1–3 macro-metastatic sentinel lymph nodes without ECE radiotherapy replaced axillary dissection. In the group with ECE for patients after SLNB and AD, radiotherapy was also applied. In patients with 1–3 positive lymph nodes we included various factors to deliver postoperative radiotherapy:

- age below 50,
- tumour diameter,
- high grading,
- lymphovascular or perineural invasion,
- Ki-67 factor,
- triple-negative or HER2 positive subtypes.

Local recurrence was not diagnosed in the analysed patients. In our group, two patients died due to the spread of the cancer. In both, triple-negative breast cancer was recognised and they were 28 and 37 years old, respectively. Sixty patients survived.

Table I. Characteristics of the analyzed group

Parameters		No extracapsular extension in sentinel lymph node No ECE	Extracapsular extension in sentinel lymph node ECE	p-value
number of patients	62	32 (51.6%)	30 (48.4%)	0.7995
age (years) • min.–max. • mean (SD) • median (Q_1–Q_3)	 28–71 49.0 (9.3) 49 (42–56)	 36–68 48.2 (8.5) 47 (41–55)	 28–71 49.8 (10.2) 50 (44–57)	 0.5077
age • <=50 • >50	 36 (58.1%) 26 (41.9%)	 21 (65.6%) 11 (34.4%)	 15 (50.0%) 15 (50.0%)	0.2165
type of cancer • no special type • lobular cancer	 51 (82.3%) 11 (17.7%)	 26 (86.7%) 7 (21.9%)	 26 (86.7%) 4 (13.3%)	0.3828

Parameters		No extracapsular extension in sentinel lymph node No ECE	Extracapsular extension in sentinel lymph node ECE	p-value
subtype of cancer				
• luminal A	35 (56.5%)	16 (50.0%)	19 (63.3%)	
• luminal B	13 (21.0%)	7 (21.9%)	6 (20.0%)	
• luminal B HER2-positive	5 (8.1%)	4 (12.5%)	1 (3.3%)	0.6963
• triple negative	7 (11.3%)	4 (12.5%)	3 (10.0%)	
• non-luminal	2 (3.2%)	1 (3.1%)	1 (3.3%)	
grading				
• G1	31 (50.0%)	16 (50.0%)	15 (48.5%)	
• G2	20 (32.3%)	10 (31.2%)	10 (33.3%)	0.9711
• G3	11 (17.7%)	6 (18.8%)	5 (16.7%)	
Ki-67 (%)				
• min.–max.	1–90	1–90	1–90	
• mean (SD)	18,1 (23.8)	20 (8.5)	16.1 (23.6)	0.3728
• median (Q1–Q3)	6 (1–20)	9 (3–23)	5 (1–20)	
Ki-67 >20				
• no	48 (77.4%)	24 (75.0%)	24 (80.0%)	0.6407
• yes	14 (22.6%)	8 (25.0%)	6 (20.0%)	
diameter of the tumour				
• min.–max.	5–55	8–55	5–50	
• mean (SD)	24.4 (10.1)	24.1 (9.9)	24.8 (10.5)	0.8055
• median (Q1–Q3)	22 (18–30)	22 (18–30)	11 (19–30)	
type of mastectomy				
• NSM	48 (77.4%)	24 (75%)	24 (80%)	0.6407
• SSM	14 (22.6%)	8 (25%)	6 (20%)	
number affected sentinel lymph nodes				
• min.–max.	1–7	1–2	1–7	
• mean (SD)	1.6 (1.2)	1.2 (0.4)	2 (1.5)	0.0009
• median (Q1–Q3)	1 (1–2)	1 (1–1)	2 (1–2)	
number effected sentinel lymph nodes				
=1	37 (59.7%)	27 (84.4%)	10 (33.3%)	<0.0001
>1	25 (40.3%)	5 (15.6%)	20 (66.7%)	
number removed sentinel lymph nodes				
=1	16 (25.8%)	11 (34.4%)	5 (16.7%)	0.1142
>1	46 (74.2%)	21 (65.6%)	25 (83.3%)	
adjuvant chemotherapy				
• no	21 (33.9%)	15 (46.9%)	6 (20.0%)	0.0267
• yes	41 (66.1%)	17 (53.1%)	24 (80.0%)	
adjuvant hormonotherapy				
• no	9 (14.5%)	4 (12.5%)	5 (16.7%)	0.6443
• yes	53 (85.5%)	28 (87.5%)	25 (83.3%)	
adjuvant antiHER2 therapy				
• no	54 (87.1%)	27 (84.4%)	27 (90.0%)	0.5125
• yes	8 (12.9%)	5 (15.6%)	3 (10.0%)	
radiotherapy				
• no	4 (6.5%)	3 (9.4%)	1 (3.3%)	0.3371
• yes	58 (93.5%)	29 (90.6%)	29 (96.7%)	
recurrence				
• no	60 (96.8%)	32 (100%)	28 (93.3%)	0.1408
• yes	2 (3.2%)	0	2 (6.7%)	
death				
• no	60 (96.8%)	32 (100%)	28 (93.3%)	0.1408
• yes	2 (3.2%)	0	2 (6.7%)	
observation time (months)				
• min.–max.	11,5–71,6	26,3–71,6	11,5–71.5	
• mean (SD)	45.7 (14.8)	47.6 (15.0)	43.7 (14.5)	0.3941
• median (Q1–Q3)	45 (31–58)	45 (35–62)	45 (31–53)	

During follow-up, 8 patients revealed capsule contractions of the prosthesis connected with the removal of the capsule contracture and exchange of prosthesis; in 1 patient partial skin necrosis was diagnosed and needed local removal. In table I, we present the group characteristics with a division into 2 subgroups: without ECE and with ECE in sentinel lymph nodes.

Discussion

At present NSM or SSM is performed in women with breast cancer more often than a decade ago. Many studies report that NSM or SSM is safe and equivalent to MRM, regarding local control rates [4–8]. A systematic review and meta-analysis of non-randomised studies did not show any statistically significant differences in local recurrence between MRM and SSM [9]. The approach to breast cancer patients should be interdisciplinary and the decisions about detailed treatment should be taken by the multidisciplinary team. Indications to systemic therapy (chemotherapy, hormonotherapy, or anti-HER2 therapy) are very well established for breast cancer patients [10]. In triple-negative and HER2-positive cases, this type of treatment is obligatory.

More uncertainties are encountered in patients with luminal subtypes. The best tool to help in the decision are genomic tests, but for many patients it is not achievable. Recommendations point out that adjuvant chemotherapy should be taken into consideration in patients with metastases to lymph nodes, but other clinical factors i.e. a young age, the diameter of the primary tumour, its grade, Ki-67 factor, vascular or perineural invasion and metastases to lymph nodes are important also. In our group, luminal subtypes were recognised in 48 patients, and chemotherapy was applied in 28, apart from hormonotherapy. Most of them were in the group with extracapsular extension in the sentinel lymph nodes. Thus extracapsular extension in a sentinel lymph node can play a role in the therapeutical decisions and prognosis, but its role is rarely considered [11].

More problems were encountered qualifying patients to radiotherapy. Indications to postoperative radiotherapy in patients after NSM or SSM are the same as in post radical mastectomy. So far, there are no controlled clinical trials that assessed who will benefit from PORT after NSM or SSM. The knowledge we have is based on retrospective analyses [12–13]. The Early Breast Cancer Trialists' Collaborative Group's meta-analysis suggests that all node-positive breast cancer patients should receive PORT [14]. In the international multidisciplinary questionnaire by Marta et al., this problem is presented broadly [15]. Responders – both surgeons and radiation oncologists – affirmed that PORT is recommended for patients with early-stage breast cancer in the presence of standard risk factors for recurrence: a young age, positive surgical margins, triple-negative tumour, lymphovascular space invasion, multicentricity, large tumour size, lymph node involvement and extracapsular extension. Other analyses pointed to similar conclusions [16–17]. It is very well known and proven that in patients with positive sentinel nodes undergoing breast-conserving treatment, axillary lymphadenectomy can be abandoned in the case of irradiation of the axilla.

The problem can be seen similarly in patients after a subcutaneous mastectomy and sentinel node biopsy. In our group, we did not perform a lymphadenectomy in patients with no extracapsular infiltration – apart from one woman. What remains important is that in almost half of patients undergoing axillary dissection, additional metastatic lymph nodes were not found. Literature shows that surgery should be limited in the axilla region and rationally replaced by radiotherapy [18–20]. We must remember that PORT should be realised with conformal techniques, and the preparation of patients should be made after international consensus and recommendations [21–22]. Complications after PORT are frequent. It is associated with the formation of a fibrous capsule or damage of the prosthesis. In our group, complications occurred in 9 patients and frequency was similar to that in the cited literature. Damage of the prosthesis was associated with its replacement [23–26].

Conclusions

A skin-sparing or nipple-sparing mastectomy is a method of surgical treatment that is increasingly used in the treatment of patients with breast cancer. More often women themselves decide or even ask to undergo this type of surgery. It should be remembered that qualification of patients for this type of procedure should be cautious, and adjuvant treatment should be rationally planned. Our experience shows that it is an effective and safe method. Randomised trials with the recruitment of patients are also necessary to assess its effectiveness as well as the potential complications arising after this type of surgery with the usage of additional methods.

Conflict of interest: none declared

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Received: 25 Dec 2020
Accepted: 13 Jan 2021

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VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 158–161
DOI: 10.5603/NJO.a2021.0016

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

The role of comprehensive nutritional care in cancer patients

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Cancer patients often have inappropriately low energy intake, exhibit an increased loss of muscle proteins and generalized inflammatory status. Nutritional support aims to reverse these processes. Covering energy requirements is necessary for safety of anti-cancer treatments: radiotherapy, chemotherapy, surgery. Nutritional support and nutritional status monitoring should be managed at every stage of the disease. Nutritional intervention is most important in malnourished patients. Comprehensive, individualized nutritional care improves the results of treatment in cancer patients. Nutritional therapy is essential in obtaining the best results from anti-cancer treatment; however, it will be effective, if should completely cover nutrient requirements.

Key words: nutrition, cancer therapy

Covering energy requirements as an element of anti-cancer therapy

Deficiencies in nutrition state are commonly observed in patients with diagnosed cancer. The state of the organism's nutrition is one of the most essential elements that determines the overall condition of the body.

Malnutrition is a state resulting from malabsorption or ingestion of nutrients followed by changes in body composition. It can lead to the impairment of broadly understood organism activities – both physical and mental [1]. The causes of malnutrition include insufficient oral nutrition, increased loss of nutrients and increased energy expenditure; these can all be related to the development of cancer. For malignant cancer patients, a negative protein and energy balance can additionally be escalated by lower food consumption as a result of anorexia and/or impaired absorption [2–4].

The body mass index (BMI), i.e. a measure of relative body mass based on the weight and height of a patient is one of

How to cite:

Jankowski M, Qelaj A, Klek S, Murawa D, Nartowicz M, Patela Z, Mańkowska-Wierzbicka D, Kapała A, Kuczyńska B, Zegarski W. ***The role of comprehensive nutritional care in cancer patients.*** *NOWOTWORY J Oncol* 2021; 71: 158–161.

the primary parameters used for the assessment of nutritional status. BMI was identified as a prognostic factor for many types of cancers [5], i.e. a weight loss by >10% over six months and/or a BMI below 20 kg/m^2 are identified in 75% of patients with newly diagnosed malignant cancers of the head and neck area [3].

Cancer patients have inappropriately low energy intake, exhibit an increased loss of muscle proteins and generalized inflammatory status that enhance the intensity of catabolic reactions in the body [2]. In those patients, we can observe an increased level of basic metabolic rate (BMR) that frequently co-exists with body mass loss, and is particularly exacerbated in lung and pancreatic carcinoma patients. It seems that the total metabolic rate (TMR) level in advanced cancer patients is lower when compared to healthy persons, which is associated with a reduction of the patients' physical activity [2, 6, 7].

Similarly to healthy persons, nutritional therapy conducted in cancer patients should include an assessment of the TMR level. Nevertheless, we should note the potential risk for over- and underestimation of calorie intake in overweight and malnourished patients, respectively. We also have to remember that nutritional therapy in cancer patients is only valid when a patient receives all their essential nutrients, especially a high protein intake of 1–1.5 g/kg of body weight (BW) per day. The energy intake should amount to 25–30 kcal/kg BW/day [2, 4].

Despite contradictory reports on the role of immunonutrition, it is believed that it has a particular significance in the perioperative period in patients with upper digestive tract cancer [8]. The nutrition is preferably administered *via* the oral or enteral route [9]. The diet prepared for cancer patients should also include eicosapentaenoic acid (EPA), an essential substrate for cyclooxygenase that limits an inflammatory response in the patient's body [2, 10].

The nutritional intervention used during radiochemotherapy in head and neck cancer patients positively impacts their nutritional status and quality of life [11]. Moreover, it results in markedly lower body mass loss compared to patients who do not receive such support [12].

Regarding chemotherapy, treatment results depend on the stage of cancer as well as on the level of body mass loss and the patient's nutritional status. A lower body mass loss during chemotherapy is associated with better results of anticancer therapy and improved survival of patients – even those with inoperable and unresectable lesions. On the other hand, a higher body mass loss and lower BMI are linked with a higher risk of complications. A normal nutritional status increases the chances of completing systemic therapy at the scheduled time and doses. [13–15].

Nutritional intervention is particularly important in the context of prevention and delay of cancer cachexia development. Cachexia is most often defined as a body mass loss >5% in the previous six months or more than 2% when the patient's BMI is <20 kg/m^2. Cachexia is defined as a multi-factor syndrome characterized by a permanent loss of skeletal muscle mass with a loss of body fat (or without it), which cannot be fully reversed by conventional nutritional support [16]. According to Fearon, cachexia is a multifactorial, dynamic and progressing process divided into 3 phases: pre-cachexia, cachexia and the final one: treatment-resistant cachexia (refractory cachexia) with an expected survival time below 3 months [17].

The pathophysiology of the syndrome is characterized by a negative protein and energy balance, affecting the overall quality of life in a negative way, reducing tolerance to treatment and decreasing the overall survival of cancer patients. In cancer patients, cachexia syndrome is one of the major causes of morbidity and mortality. The progressing cachexia indicates a poor prognosis with a shorter survival time and it accompanies nearly 20% of all deaths caused by cancer [18].

Nevertheless, it should be remembered that cancer patients with concurrent metabolic disorders and body mass loss receiving hypercaloric nutrition often do not gain bodyweight. Therefore, such an intervention is not recommended.

Malnutrition and muscle atrophy are often observed in cancer patients; they have a negative impact on the result of clinical treatment and lead to prolonged hospitalization. The most frequent causes include an increase in energy and protein demand resulting from the catabolic and physiological effects of cancer cachexia, inadequate dietary intake and decreased physical activity [19].

The fundamental nutritional problem experienced by patients suffering from cancer – and likely the one with the greatest influence on prognosis – is muscle atrophy (sarcopenia). A low muscle mass is common regardless of the stage of cancer (curative to palliative) and is an independent predictor of poor physical function, lower quality of life, surgical complications, cancer progression and decreased chances of survival [20].

Nutritional intervention enables the prevention and treatment of anti-cancer therapy-related complications, including surgery, as well as improves its efficacy and extends patients' survival.

In order to face the deterioration of the nutritional state, it is of great significance to collect data on nutritional status and its evolution over the course of the disease. Various types and sites of cancer present distinct nutritional models which require adjusted nutritional therapy. The deterioration of the state of nutrition is multifactorial – it can be a result directly related to cancer, nutrition and/or metabolism [21]. Nutritional interventions will differ depending on the medical history of patient, type and stage of cancer and response to therapy. If a patient can eat and has an efficient digestive tract, nutritional counseling with or without ONS should be the selected intervention in order to take account of the amended nutritional requirements caused by treatment or disease [21, 22]. All cancer patients should be regularly controlled in terms of the development risk or presence of malnutrition. In all patients except for those provided with end of life care, it is necessary to meet all requirements regarding energy and

protein to order nutritional interventions in a gradual way starting from counseling to parenteral nutrition. Nevertheless, the benefits and risk of nutritional interventions need to be well-balanced with particular reference to patients with advanced disease [22].

Pharmacoeconomic aspects of nutritional therapy in cancer patients

Anti-cancer treatment initiation in emaciated patients is associated with a mortality and infectious complications rate of 30% and 75%, respectively. It should be remembered that a loss of lean body mass (LBM) and a reduction in physical capacity are signs accompanying both chemotherapy as well as advanced cancer. Body mass loss during chemotherapy has a direct impact on the therapeutic effect, among others resulting in a reduction of chemotherapy duration and the need to decrease doses of cytotoxic drugs. Moreover, it is associated with a decrease of the overall survival rate, the duration of the treatment response, a deterioration of patients' quality of life and performance status as well as with the worsening of general health conditions [15, 24, 25]. Comprehensive nutritional care should be proposed to every patient aimed at not only extending survival but also improving the quality of life. Nutritional support should be individualized and adjusted to the cancer stage.

In the preoperative preparation of patients at high nutritional risk, nutritional therapy is particularly important [26]. Oral nutritional supplements (ONS) facilitate an increase in nutrient intake and thus allows for stabilization or improvement in nutritional status. The patient should receive an appropriate intake which in case of immunonutrition consists of 3 x 250 ml of products containing arginine, n-3 fatty acids, or nucleotides [4]. Such supplementation is not reimbursed by the National Health Fund (NFZ) in Poland, even though it brings measurable benefits such as an improvement in the general health condition and also shortens the duration of the hospital stay [4, 9, 8]. It was demonstrated that the use of ONS as an intervention aiming only to improve nutrient intake resulted in a reduction of the re-hospitalization rate by 27.1% [27]. However, it is believed that the addition of immunomodulatory substances may boost that effect.

The pharmacoeconomic aspects of nutritional therapy in cancer patients illustrate the fact that two out of three surgical patients demonstrate nutritional status disorders. These disturbances are linked to a three fold increase in the risk of complications and a five fold increase in the risk of death compared to normally nourished persons. Unfortunately, despite the data mentioned above indicating the role of nutrition in cancer, only three out of four surgeons believe that peri-operative nutrition has a real impact on the number of complications. Moreover, only a small number of patients receive preoperative nutritional intervention despite the availability of sufficient evidence supporting the fact that the financing of nutrition therapy during the hospital stay results in the reduction of total treatment costs . This is confirmed by data showing that, on average, malnourished patients stay at the hospital for 17.2 days while patients without malnutrition only 9.7 days [28].

Elements of nutritional care are included and regulated by the comprehensive perioperative care protocol ERAS. Its use results in the average shortening of patients' hospital stay by 2.5 days, a reduction in the risk of complications by 40%, non-surgical complications by 60% and respiratory and cardiovascular complications by 60% and 50% respectively [29]. Furthermore, it markedly increases the rate of 5-year survival [30]. Regardless of the amount of data indicating the importance of the ERAS protocol, its recommendations are implemented in only 1% of patients. Should this data not be sufficiently convincing, it is worth adding that the profitability of enteral, parenteral nutrition and PEG amounts to >40%, >30%, and 30–40% respectively [29].

Discussion

The above-mentioned considerations provoke discussions concerning several topics. The first topic concerns the patient's access to information. Emphasis was placed on the need to provide cancer patients with complete and understandable information about the desired mode of nutrition. Such information should also describe the possibility of using ONS to improve the patient's nutritional status. It is also essential to present this information to the patient at the moment of diagnosis in order to create the possibility of implementing nutritional therapy early on as a part of the comprehensive anti-cancer treatment [2, 28, 31].

Particular attention was also paid to the fact that the frequency of patients referred to a nutritional consultation is increasing. However, those referrals are often delayed and in the majority of cases take place when anti-cancer treatment related complications emerge (for example, when chemotherapy cessation or surgery deferral is needed). The fact that hospitals only employ a small number of dietitians and that the estimated duration of a dietetic consultation, including the measurement of lean body mass (LBM) and a nutritional interview, is 30 minutes is vital as well. Taking into account the benefits of using nutritional support, we should also consider of funds relocation and enabling the patient to access this type of services.

No published randomized trials evaluate the role of nutritional care in cancer patients. However, a report by Schuetz demonstrates that the use of an appropriate, ESPEN guidelines-compliant model of nutritional care results in a reduction of complication rates and 30-day mortality rate of inpatient non-surgical patients compared to a control group receiving standard care [32].

Conclusions

Nutritional support and nutritional status monitoring should be managed at every stage of cancer. Comprehensive, indivi-

dualized nutritional care improves the results of treatment in cancer patients. Nutritional intervention is most important in malnourished patients. Nutritional therapy is essential to obtain the best results from anti-cancer treatment; however, it should completely cover all nutrient requirements.

Conflict of interest: none declared

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Received: 24 Oct 2020
Accepted: 19 Jan 2021

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VIA MEDICA

Case report

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 162–164
DOI: 10.5603/NJO.a2021.0017

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

Pregnancy-associated breast cancer as a screening and diagnostic challenge: a case report

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Pregnancy-associated breast cancer (PABC) is the most common malignancy of pregnancy, affecting 1 in 3000 women. Due to the increased size and density of the breast tissue during pregnancy and lactation, diagnosis and treatment are commonly delayed. A 37-year-old woman, gravida 1 para 0, at the 27th week of gestation presented with two tumors of approximately 2 cm in the right breast with ipsilateral lymph node involvement on the ultrasonography. HER2–, ER+, PR+, a poorly differentiated ductal carcinoma was identified by the core biopsy and immunohistochemistry. The diagnosis of PABC was made, the tumor's clinical stage was cT2, N1, Mx. She underwent a total mastectomy with axillary node dissection on the right side and was started on adjuvant therapy with paclitaxel. Our report highlights the importance of proper breast oncology surveillance during pregnancy, using safe and inexpensive methods including ultrasonography and biopsy of suspicious masses, to avoid cancer development and progression.

Key words: breast neoplasms, pregnancy, diagnosis

Introduction

Pregnancy-associated breast cancer (PABC) is a subtype of BC diagnosed in women during pregnancy, first year postpartum, or during the breastfeeding period [1]. Although PABC is thought to have a high mortality rate due to high metastasis rates, potentially related to delays in diagnosis, other factors should be considered. Pregnancy per say does not worsen the prognosis of breast cancer. When matching pregnant and non-pregnant breast cancer patients based on age and tumor advancement, the two populations had similar prognosis given patients were treated with standard BC treatment [2]. With that said, BC patients diagnosed within 2 years postpartum were more likely to present with cancer subtypes associated with poor prognosis (i.e. HER2+, and cancer with basal-like features) compared to both nulliparous controls and patients diagnosed more than 2 years postpartum [3]. Another study reports PABC to have different biological features compared to non-PABC, with poor prognosis reported in PABC patients with luminal B (HR+ HER2– high Ki-67) and HER2+ cancer subtypes [4].

It has become the most common malignancy of pregnancy, with 1 in 3000 pregnant women affected every year. Of all women diagnosed with breast cancer under 40 years of age, 10% of women are diagnosed with PABC. Incidence of PABC is expected to increase over the next years, which may be attributed to delayed conception and family planning, putting women at risk of malignancy due to their increased age. Mortality rates with PABC are also expected to rise due to the relationship of delayed childbearing. Other important risk factors include no history of breastfeeding, and a family history of BC [5].

The most common presentation of PABC in pregnant women is a palpable lump identified during self-examination,

How to cite:

Kalantarova A, Zembol NJ, Kufel-Grabowska J. ***Pregnancy-associated breast cancer as a screening and diagnostic challenge: a case report.*** *NOWOTWORY J Oncol* 2021; 71: 162–164.

which is similar to other young women with BC [6]. Unlike BC, the detection of PABC during pregnancy and lactation is possibly confused with normal breast changes, such as an increase in the density and size of the breast parenchyma [7]. Thus, PABC is commonly diagnosed at a more advanced stage and more often with metastasis to the lymph nodes than BC. The delay in diagnosis in PABC was reported to be between 1 to 13 months [8]. A clinical breast exam, mammography, breast MRI and ultrasound are all methods available for BC screening [9].

The screening and diagnosis of PABC pose special challenges due to the physical changes in the breast during pregnancy and breastfeeding, and the fetus's risks. As mentioned above, many methods are available for screening, and all vary in their degree of accuracy and safety. The screening method's decision is ultimately at the clinician's discretion and involves combining information about the clinical presentation with patient risk factors. Thus, the lack of a universal screening method for suspected PABC commonly results in a presentation at a more advanced stage and subsequently a poorer prognosis [10].

Case study

A 37-year-old woman, gravida 1, para 0, presented to an oncology clinic at 27 weeks of gestation. She complained of painless nodules in the right breast detected during self-examination. There was no previous history of nipple discharge or breast disorders and no family history of breast or ovarian cancer. The initial ultrasound investigation was ambiguous. Three months later, a follow up clinical breast examination revealed enlargement of previously suspicious nodules and the appearance of new nodules in the axillary region. An exploratory ultrasonography revealed two spiculated nodules measuring 22 x 11 mm and 18 x 15 mm in the right breast along with two hypoechoic ipsilateral lymph nodes. There were no nodules in the left breast, aside from a solid cystic focal lesion. A core needle biopsy was performed to confirm the central and upper quadrants of the right breast, and an invasive ductal carcinoma of non-specified type was observed in the central portion of the breast, with an invasion of the nerve trunk. A core biopsy and immunohistochemistry of the lump confirmed HER2–, ER+ and PR+ tumor cells positive for E cadherin.

The tumor's clinical stage was determined to be cT2N1, Mx. Metastatic status to the patient's bones and lungs was not assessed due to the high fetal risk associated with an X-ray and scintigraphy. The clinical presentation of this patient necessitated a right-sided mastectomy and lymphadenectomy. The pre-operative consultation with an obstetrician confirmed that the pregnancy was normal, and there were no alterations in fetal development. The post-surgical pathomorphology confirmed invasive ductal carcinoma diagnosis located in the central portion of the right breast. The pathomorphological report, post-mastectomy, confirmed an invasive ductal carcinoma of non-specified type and the immunohistochemical report verified the HER2–, ER+ and PR+ status of tumor cells.

The results of genetic counseling and testing for *BRCA1/2* gene mutations are not yet available. The patient started adjuvant therapy with paclitaxel shortly after the surgery. Recently, our patient gave birth to a healthy baby with no apparent malformations and an APGAR score of 10. A subsequent assessment with a scintigraphy and X-ray post-delivery did not reveal any metastatic lesions.

Discussion

The attending physician must be highly trained to recognize the wildly under-diagnosed PABC versus the more common hormone-induced breast changes related to pregnancy. A multidisciplinary approach should be used if a woman is diagnosed with PABC to manage her condition while carefully considering the effects on the fetus. This entails psychological counseling due to the intricacy of the issue. Multiple medical specialties should be involved in the treatment plan, including oncology, obstetrics, pediatrics and genetics. A committee should also be available for the patient to discuss any issues relating to psychological impact, religion, or ethics [11]. Having an active group of clinicians and support personnel is a valuable asset for the patient, spouse, family and unborn child.

A clinical breast exam (CBE) is a safe tool for cancer screening during pregnancy and lactation and is routinely performed during a gynecological examination [9]. However, a follow-up assessment with a different radiological technique is often required due to CBE's low sensitivity, especially in high-risk patients [12]. The sensitivity of CBE is likely to increase in breastfeeding women if the examination is performed after pumping or breast-feeding [9]. It is a general recommendation for high-risk women (e.g., older age during pregnancy) to undergo CBE every 6 months during pregnancy and lactation.

A breast MRI is the most accurate BC screening technique with a sensitivity of 71–100% and a specificity of 89% [9]. Generally, an MRI is safe to use in pregnant and breastfeeding women since it does not utilize ionizing radiation. The use of MRI in PABC screening is not always advised due to gadolinium's high ability to produce an allergic reaction in the patient. A breast MRI poses little to no safety risk during breastfeeding due to the minimal gadolinium excretion in milk and minimal absorption into the child's digestive system [13]. Generally, a breast MRI is not recommended as a screening tool during pregnancy but is considered safe during breastfeeding, assuming the woman intends to breastfeed more than 6 months postpartum [9].

A mammography is characterized by fairly low sensitivity in pregnant and lactating women [6]. There is limited data available on mammography as a screening tool in pregnancy and breastfeeding [9]. Increased breast density and changes in vascular flow are likely to result in difficulty interpreting the radiographic results [9]. Concerning the developing fetus, mammography poses some risks due to radiation. However, those risks have not been adequately quantified as yet [14]. According to a study conducted in Sweden, a digital mammography can be safely

used in pregnant women, however only in addition to widely recommended ultrasounds and biopsies [6]. With that said, there are recommendations to evaluate symptomatic women who are younger than 30 years (without regard to pregnancy status) using ultrasonography; the use of mammography is reserved for situations in which ultrasound does not visualize a lesion or the lesion observed is suspicious [15].

A retrospective study conducted in Sweden concluded that PABC patients underwent initial examination with ultrasonography and biopsy more often than mammography [6]. Ultrasound has a diagnostic sensitivity of 100% with an 86% specificity when a palpable mass is detected [16]. Although ultrasound has a weak screening sensitivity (29–52%) in patients not presenting with a palpable mass, many clinicians continue to use it for regular screening in high-risk women during pregnancy and breastfeeding for safety reasons.

A multidisciplinary interplay is especially critical, not only in initial diagnosis, but also in follow up counseling. Some recent studies recommend counseling patients to wait two years after PABC diagnosis and treatment before planning their next pregnancy due to recurrence risk during pregnancy [1, 17]. Additionally, a study conducted by Clark and Reid of 330 patients concluded that women who waited two years after BC treatment to conceive had a significantly increased five-year survival rate compared with those who waited six months to conceive [18]. While pregnancy appears to confer no increased risk for recurrence of BC, there is no recent data regarding the outcomes of subsequent pregnancy for women with initial PABC. Recurrence of PABC in subsequent pregnancies is an area where future research is essential and can be beneficial in women previously affected with PABC.

Conflict of interest: none declared

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Received: 2 Nov 2020
Accepted: 1 Dec 2020

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VIA MEDICA

Oncogeriatrics

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 165–168
DOI: 10.5603/NJO.2021.0031

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

Treatment of rectal cancer in the older population

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The majority of rectal cancer patients are elderly. Biological age, not chronological age alone, is the main risk factor of postoperative morbidity in this group. Therefore, based on the Comprehensive Geriatric Assessment, we can differentiate three groups of patients: fit, pre-frail and frail. In the fit group, a standard multimodal oncologic treatment can be offered. In the pre-frail group, prerehabilitation should be recommended to improved resilience to surgical stress. In frail patients, a tailored approach should be discussed in a geriatric multidisciplinary team meeting. At present, a whole range of multimodal tailored approaches can be offered to rectal cancer patients. In this group, of much more importance is postoperative functional recovery, including both organ-specific outcomes and the ability to regain independence than currently used outcome indicators. Therefore, as important as cancer staging and tumour biology, it is crucial to understand the health status of an older patient with rectal cancer.

Key words: rectal cancer, older patients, frailty, elderly

The majority of rectal cancer (RC) patients are elderly, diagnosed at a median age of 70 years. However, the risk of developing rectal cancer still increases with age, so octo- and nonagenarians with rectal tumours are, currently, also not a rarity [1].

The major problem in tailored treatment of RC in older patients is still the lack of good research data. Older patients are still not sufficiently included in studies. In 2019, Abbasi et al. demonstrated that the proportion of older patients in clinical trials is <25% (age 65–74 years) and <10% (age 75 and more), respectively [2]. In turn, Schiphorst et al., analysing the participation of older patients in laparoscopic surgery for colorectal cancer, showed that the median age was less than 65 years in 86% of the studies, and 44% of the studies excluding the elderly [3]. This shows that the guidelines for the treatment of the elderly are still based on the extrapolation of evidence obtained from studies including patients from younger age groups or older patients who were completely healthy. Therefore, older patients with RC are often under-treated due to their chronological age or poorly evaluated co-morbidities, or over-treated due to failures in recognising the frailty status of the patient [4].

Due to improvements in anaesthesia, surgical techniques and perioperative care in developed countries, significant decreases in perioperative morbidity and mortality are observable. However, the 5-year absolute survival and disease-free survival of older patients are still significantly poorer in comparison to younger patients. Therefore, increasing the awareness of physicians treating RC is one of the main goals of this mini-review based on recently published studies and the expert recommendations of the European Society of Surgical Oncology, the European Society of Coloproctology, the International Society of Geriatric Oncology, and the American College of Surgeons Commission on Cancer [5–9].

How to cite:
Kenig J. ***Treatment of rectal cancer in the older population.*** *NOWOTWORY J Oncol* 2021; 71: 165–168.

Preoperative assessment and treatment decisions

As was mentioned in our previous publications, the population of older patients is very heterogeneous in terms of co-morbidity, physical reserve, cognitive function and social support [10, 11]. Current routine preoperative assessment also cannot adequately identify patients at risk. Therefore, the comprehensive geriatric assessment (CGA) was introduced to help determine the primary status of the older patient, to diagnose frailty syndrome (surrogate of biological age) and to identify how to optimise the patient's condition before the start of the treatment. A standardised preoperative diagnostic approach, individualised surgical technique selection and tailored postoperative care are essential for the successful treatment of older patients [6, 12]. In general, based on the CGA, we can differentiate 3 groups of older patients:

1. **Fit:** patients without any deficits in the CGA domains and less than 80 years old. In this group, the standard oncologic treatment can be offered and the postoperative outcomes are comparable with younger patients.
2. **Pre-frail:** patients with 1 or 2 deficits in the CGA domains or more than 80 years old. In these patients, pre-rehabilitation should be recommended to improve resilience to surgical stress by, at least, augmenting functional capacity and nutritional status before surgery.
3. **Frail:** patients with 3 or more impaired domains in the CGA or 80 years old with 2 deficits in the CGA. A tailored approach should be discussed in a geriatric multidisciplinary team meeting [6].

Important treatment outcomes for older patients

The outcomes of cancer treatment in older patients should be evaluated differently and should be discussed with the patient before surgery. The 5-year overall survival, the disease specific survival, or the progression-free survival are well established indicators to define cancer control. However, these indicators have limited value for patients aged 80+ years, and particularly, for frail patients independent of their chronological age. In this group, of much more importance is the functional recovery indicators, including both organ-specific postoperative outcomes and the ability to regain independence. In the case of rectal cancer, organ-specific' outcomes should include evaluation of urinary, sexual, bowel function, faecal incontinence and, in the case of a diverting loop ileostomy, its closure after primary operation. Similarly, we need more studies on the time and level of posttreatment independence restoration. Good quality data on these topics in frail patients are still not available [5].

Treatment of rectal cancer in older patients

Table I presents the therapeutic options for rectal cancer patients depending on the risk group based on guidelines, supplemented by information on possible treatment options for frail patients [7]. However, it must be stressed that diagnosing frailty in a patient is not a contraindication for surgery. It is a sign that standard oncologic treatment can lead to unacceptable results; major morbidity, permanent disability, institutionalisation and death. Moreover, frailty is not a qualitative indicator (present or not). It can be quantified and there are significant differences between mild and severely frail patients.

Table I. Therapeutic options for rectal cancer patients depending on the risk group [7], including options for frail older patients

Risk group	Stage factors	Fit patients	Frail patients
very early	cT1 sm1–2, N0	local excision TME in case of sm3, IMVI(+), G3–4	• local excision
early	cT1–2 cT3aN0, middle or high rectum, MRF(–), EMVI(–) CT3aN1 high rectum, MRF(–), EMVI(–)	TME in case of CRM(+), N2: adjuvant treatment	• local excision +/– adjuvant treatment • prerehabilitation followed by TME • neoadjuvant CRTh with watch-and-wait strategy in case of complete clinical response • palliative care in sever frailty
intermediate	cT3a/b in low rectum, levators clear, MRF(–) cT3a/b in mid- or high rectum, cN1–2, no EMVI	neoadjuvant RTh (5 x 5 Gy) or CRTH followed by TME	• neoadjuvant rth 5 x 5 with longer time interval (in the mean time prerehabilitation) and TME • neoadjuvant CRTh with watch-and-wait strategy in case of complete clinical response (in the mean time prerehabilitation) • prerehabilitation followed by TME • palliative care in sever frailty
advanced	cT3 with MRF(+) any cT4a–b pelvic lateral N+	neoadjuvant CRTh followed by TME or more extended surgery	• neoadjuvant RTh 5 x 5 with longer time interval (in the mean time prerehabilitation) and TME or more extended surgery • neoadjuvant CRTh (in the mean time prerehabilitation) followed by TME or more extended surgery • palliative care in sever frailty

sm – submucosa; V1 – cancer cells in the vessels; G – grading; CRM – circumferential resection margin; MRF – mesorectal fascia; EMVI – presence of extramural venous invasion; IMVI – intramural vascular invasion; TME – total mesorectal excision; RTh – radiotherapy; CRTh – chemoradiotherapy

Local excision (irrespective of platform used), in experience hands, can achieve good oncologic results, sparing the rectum, while lowering morbidity (7–14%) with very good functional results (1% urinary dysfunction, <1 faecal incontinence) [5]. According to the guidelines, the rectal cancer most suitable for local excision is T1 cancer with submucosal invasion <1000 µm, without lymphovascular invasion, well-differentiated and with budding grade 1. There are several studies on its use in T1 rectal cancer with poor pathology and T2 tumours with/without neodjuvant/adjuvant treatment or its combination. This strategy cannot be regarded as a standard of treatment due to the high recurrence rate. However, it can be considered in frail patients in combination with or without neo-/adjuvant treatment. Studies clearly show that neoadjuvant treatment is connected to a higher complication rate in comparison to adjuvant treatment. [13, 14].

There is still the belief that older patients cannot undergo a total mesorectal excision (TME) due to the high rate of perioperative complications. In the past, this type of operation was not advised in patients aged 75 years or more [15]. As was mentioned before, currently the chronological age alone does not determine the choice of treatment.

Similarly, advanced age had initially been viewed as a relative contraindication to minimal invasive surgery due to the physiologic influence of pneumoperitoneum on the older patient. Based on well-known trials, COLOR II, CLASICC, COST, we know that minimal invasive rectal cancer surgery is safe and has comparable oncological results as open surgery [16–18]. None of these studies excluded elderly patients based on their chronological age. However, older patients were underrepresented compared to younger patients. Li Y et al. analysed 11 studies on colorectal resection in octogenarians and proved that laparoscopy is safe and carries a lower risk of infectious complications (pulmonary and surgical site), a shorter length of hospital stay and a reduced incidence of postoperative ileus while maintaining the same cardiovascular risk as compared to open surgery [19]. These benefits are pointed out by Senagore et al., showing decreased direct costs associated with laparoscopic surgery in older patients [20]. A study of 33,000 patients in the Netherland's Cancer Registry showed that the reduction in 1-year mortality associated with laparoscopic resection was greatest in the population of patients greater than 75 years of age [21]. However, laparoscopic TME is still performed in only 10–50% of all rectal cancers with a high conversion rate (up to 30%).

A few published studies on robotic colorectal surgery in the geriatric population reported similar oncologic outcomes to the laparoscopic approach, although with increased costs and longer operative time [22–24].

Studies on Transanal TME (taTME) in older patients are not currently available. Based on data from the International taTME registry, managed by the Pelican Cancer Foundation, in 92% of the older study population, a sphincter-preserving procedure was carried out. The conversion rate was low (5%). The overall 30-day mortality and morbidity were 1% and 38%, respectively. There was no difference in the number of surgical complications between the older and younger rectal cancer patients. Therefore, age alone is not a contraindication to minimal invasive surgery. Laparoscopy seems to be the preferred option to perform TME surgery in older patients. The benefits of laparoscopy are consistent with the expectations of geriatric surgery [5].

Neoadjuvant chemoradiation

Neoadjuvant radiotherapy is the standard treatment for locally--advanced mid-distal rectal cancer to increase local control. If the radial margin is not threatened, the preoperative radiotherapy 5 x 5 Gy with immediate operation is most commonly used. In frail patients, a longer time (4–8 weeks) between the end of the radiation and the surgery is recommended to reduce the complication rate. Over this time, prerehabiliation can be carried out to improve resilience to surgical stress by, at least, augmenting functional capacity and nutritional status before surgery. In the case of a larger tumour, with a threatened radial margin, a 45–50 Gy dose of radiotherapy is given over 5 weeks. Concurrent chemotherapy is also administered. However, in older patients, the toxicity of this treatment may compromise the chance of TME surgery, which is the main treatment for local control and curative intent. In turn, in up to 25–30%, a complete clinical response can be achieved [25]. This so-called watch and wait strategy, allows to preserve rectum avoids preoperative morbidity, a permanent stoma or long-term functional problems associated with TME surgery. However, up to 30% have a regrowth. Detected early, it can be successfully treated with delayed TME surgery.

Smith et al. compared cohorts: 60-year-old men with mild co-morbidities, 80-year-olds with minor co-morbidities, and 80-year-olds with significant co-morbidities. Patients with a complete clinical response after chemoradiotherapy were followed according to the watch and wait protocol or had TME. There was no difference in absolute survival in 60-year-old patients from the watch and wait and TME group. However, in both the 80-year-old groups, there was a 10.1% survival advantage at the one year mark in those who underwent a watch and wait protocol [26, 27].

Adjuvant chemotherapy

Adjuvant chemotherapy is typically given following surgical resection with or without neoadjuvant chemoradiotherapy. Several studies have been carried out to evaluate the benefits of adjuvant chemotherapy for rectal cancer. Breugom et al. and Bujko et al. performed two meta-analyses on this topic. The first showed no difference in overall survival, disease free survival, or the rate of distant recurrence. In a subgroup analysis, the authors observed an increase in disease free survival and a decreased rate of distant recurrences in tumours between

10 and 15 cm from the anal verge [28]. The second showed no benefit for postoperative chemotherapy in improving overall survival or disease free survival [29]. Therefore, the SIOG consensus on postoperative chemotherapy in colorectal cancer in older patients advocates a risk-balanced approach [30].

Conflict of interest: none declared

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Received: 17 Apr 2021
Accepted: 21 Apr 2021

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VIA MEDICA

Genetics and oncology

NOWOTWORY Journal of Oncology
2021, volume 71, number 2, 169–175
DOI: 10.5603/NJO.2021.0032

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

Personalised medical management of patients with melanoma (part 1)

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In recent years, a dynamic increase has been observed in occurrence of melanomas, especially in young and middle-aged patients. This is the reason why curing these patients has become a priority also in the economic context. Melanomas belong to a group of neoplasms of very high genetic heterogeneity. The most common genetic alterations concern two signalling pathways: mitogen-activated pathway (MAPK) and phosphoinositide 3-kinase (PI3K) pathway. Identification of the characteristic molecular changes in the neoplastic tissue allows optimisation and individualisation of the therapy. Thus, it contributes to an increase in successful cancer treatment, reduction of treatment side effects and to improvement of the patients' quality of life. Currently, the standard management of skin melanoma patients involves – along with surgical treatment and classical chemo/radiotherapy which is now less frequently used – also introduction of targeted therapy focused on molecular changes within the tumour tissue as well as immunotherapy which relies on activating the immune system.

Key words: melanoma, *BRAF, NRAS*, targeted therapy

Introduction

Individualised oncological therapy involves therapeutic management aimed at selecting the treatment to obtain maximum benefits while minimising side effects. Effectiveness of such treatment is always associated with evaluation of the patient by a multidisciplinary team of clinicians. The objective of this assessment is to determine optimal therapeutic approach ("tailored treatment"). Implementation of such procedure is possible due to immense technological development observed in genetics and molecular biology over the last decade. It involves:

- introduction of a new classification of neoplasms,
- search for new therapeutic goals,
- assessment of the patient's response to treatment (pharmacogenomics),
- detecting treatment resistance,
- detecting recurrence at a very early stage,
- cancer risk assessment [1].

Epidemiology and risk factors

Melanoma is one of those cancers in which targeted treatment has been used for several years. It is a malignant neoplasm originating from melanocytes, i.e. cells that produce the pigment called melanin. These are cells of neuroectodermal origin [2]. The most common primary location of melanoma is the skin (over 96% of cases), especially surfaces exposed to sunlight. Other

How to cite:
Gil J, Łaczmańska I, Sąsiadek MM, Ziętek M. ***Personalised medical management of patients with melanoma (part 1).*** *NOWOTWORY J Oncol* 2021; 71: 169–175.

locations that are much less common include: the conjunctiva and uvea, oral, pharyngeal and genital mucosa, meninges and distal parts of the body (including subungual localization) [2].

The highest incidence of melanoma is observed in Australia, New Zealand and North America. In Poland, melanoma is relatively rare, and its standardized incidence rate is approximately 6.5 per 100,000. According to the National Cancer Registry of 2017, there were 3,785 cases of melanoma in Poland recorded (1,796 men and 1,989 women), and 1,410 deaths caused by melanoma [3]. Although melanoma is a rare neoplasm (about 2% of all cancers), the last dozen years witnessed a dynamic increase of its incidence, especially in the Caucasian population. This is also the case in Poland (according to the data of the National Cancer Registry, an increase of over 70% in 10 years). The relatively young age of onset (30–50 years) is also important, as it translates significantly to serious socio-economic consequences [4]. Importantly, melanoma-related mortality in Poland is 20% higher that the respective number in western countries, even though the morbidity rate in Poland is lower. This is clearly reflected in statistical data concerning differences in treatment effectiveness in individual countries – among all cancers, the differences for melanoma are the highest (Poland 69.8 *vs.* Germany 93.1) [3]. It is probably related to late detection / diagnosis of the disease and ignorance and/or failure to apply prophylaxis.

The rapid growth rate and high metastatic potential place melanoma among those cancers which are the most difficult to treat and have the worst prognosis [2]. Therefore, it is very important to diagnose the disease quickly and accurately, because if the cancer is detected early (when it is locally limited to its primary focus), it is almost 100% curable – it can be removed surgically [2].

The main risk factor for development of melanoma is light skin and exposure to ultraviolet (UV) radiation, either natural (especially UV-B), or artificial (indoor tanning, especially UV-A radiation). People who have been exposed to UV radiation intensively and intermittently, and who have suffered sunburns during childhood and/or adolescence, are at an increased risk of developing this disease, compared to those who have experienced long-term and regular UV exposure. People who have suffered more than 5 severe episodes of sunburn are approximately 2 times more likely to develop melanoma [5].

There is a gradient in the incidence of melanoma in Europe – the highest rate of morbidity is recorded in the north of the continent, while in the south there are significantly fewer cases. Fewer melanoma patients in southern European populations are likely associated with chronic sun exposure (compared to periodic / sporadic exposure in the north) and characteristically darker skin phototype which provides natural protection against UV radiation [6].

Diagnostics

Most melanomas form *de novo* – about 50–60% on the skin without pigmentation changes, and about 40% arise on existing pigmentary lesions [4]. Self-observation of skin changes, especially atypical pigmented nevi, is extremely important, and any disturbing change should be reported to a specialist. Patients may use the ABCDE scale for nevus assessment and initial identification of some melanomas, with letters corresponding to lesion features:

- A – *asymmetry* of the nevus,
- B – *border* irregularity,
- C – *colour* inconsistencies,
- D – *diameter* larger than 5 mm,
- E – *evolution / elevation*, marking a change in shape or protuberance of the nevus over time [7].

Lesions may be associated with ulceration and/or bleeding. A dermatoscopy by a specialist is the basis for a clinical diagnosis of the disease. Subsequently, the suspicious lesion should be surgically removed with a minimum margin of 1–2 mm of healthy skin and subjected to histopathological analysis for diagnosis. There are 4 main histological subtypes of melanoma:

- superficial spreading melanoma – SSM (41%),
- nodular melanoma – NM (16%),
- melanoma arising from the lentigo (lentigo maligna melanoma – LMM) (2.7–14%), and
- subungual or limb melanoma (acral lentiginous melanoma – ALM) (7–10%).

Other rarer types include desmoplastic melanoma or blue nevus melanoma [7, 8]. The histopathology report should include subtype diagnosis, as well as other important features:

- macroscopic characteristics, i.e. size of the excised skin fragment with the lesion, location of the lesion on the skin, tumour dimensions and lesion description (including its colour, border, nodule or its absence, satellite foci),
- microscopic features, i.e. tumour thickness in mm (Breslow measurement), ulceration or its absence, number of mitoses per mm^2, presence or absence of microsatellites and additionally growth phases (radial *vs.* vertical), presence or absence of lymphocytic infiltration, presence or absence of infiltration of lymphatic vessels, presence or absence of infiltration of nerve trunks [7, 8].

Subsequent diagnostic tests (chest X-ray, abdominal ultrasound, lymph node ultrasound, CT or PET) allow staging of the disease advancement. Such comprehensive diagnostics enables forecasting further natural course of the disease (prognostic factor). On the other hand, molecular tests for the presence of mutations within tumours at high clinical stages allow to plan the most effective treatment (predictive factor). There are five stages of clinical tumour advancement [7]:

- Grade 0 – referred to as *carcinoma in situ* – a form that does not exceed the epidermis with no infiltration.
- Grade I – if the melanoma is ulcerated and its thickness does not exceed 1 mm, or if it is not ulcerated and its thickness does not exceed 2 mm, lymph nodes are not affected (N0) and there are no distant metastases (M0).

- Grade II – it has three subgrades, distinguished by the primary lesion's thickness:
  - IIA – if the melanoma is ulcerated and its thickness does not exceed 2 mm or if it is not ulcerated and its thickness does not exceed 4 mm,
  - IIA – if the melanoma is ulcerated and its thickness does not exceed 4 mm or if it is not ulcerated and its thickness exceeds 4 mm,
  - IIC – if the melanoma is ulcerated and its thickness exceeds 4 mm.

  In grade II, lymph nodes are not affected (N0) and there are no distant metastases (M0).
- Grade III – presence of metastases in the regional lymph nodes. There are four subgrades (IIIA–IIID) depending on the number of lymph nodes involved and the type of metastasis (micrometastases diagnosed microscopically *vs.* macrometastases found in a clinical examination). No distant metastases (M0). At this grade, skin metastases are possible in the form of satellite or in-transit foci which can be isolated or associated with metastases to regional lymph nodes.
- Grade IV – the most advanced stage of the disease, characterised by metastases to:
  - extra-regional lymph nodes, skin or subcutaneous tissue,
  - visceral organs such as the lungs and liver,
  - central nervous system – this group of patients has the worst prognosis.

Hereditary / genetic predisposition to melanoma

In addition to the most common sporadic form of melanoma, hereditary forms are also known. No single inheritance mode has been identified with respect to genetic factors determining melanoma development predisposition, and the familial cases of melanoma have multi-gene background, frequently associated with a specific complexion (light skin with freckles and red hair is associated with higher risk), as well as family habits (e.g. overexposition to solar radiation) [9]. The *CDKN2A* gene (cyclin-dependent kinase inhibitor 2A), well-studied in the Polish population, is one of the leading and most researched predisposing genes. It encodes the p16 cell cycle control protein (INK4A) and the p14 (ARF) isoform [10] . This gene is located on the short arm of chromosome 9 (9p21). The most common constitutional variant, i.e. the variant which is present in all cells of the body, is c.442G > A (p.A148T, *missense* type change, substitution of alanine by threonine), which increases the risk of melanoma 2–2.5 times, it also increases the risk of pancreatic, lung, colorectal and breast cancers and malignant tumours of the brain [10–12] . Although the alteration itself does not cause dysfunction of the protein encoded by this gene, it has been suggested that it may be inherited together with another variant that has negative impact on the protein and thus modulates the risk of developing the disease [10]. Interestingly, the data in the ClinVar database do not support the pathogenicity of this lesion and classify it as a *benign* variant which is not related to a disease. Therefore, the diagnostic result obtained for a given patient should be interpreted in relation to clinical data (including data on the ethnicity of the patient), literature data and emerging new guidelines.

Selected genetic syndromes with an increased risk of melanoma

There are various genetic syndromes which are associated with the increased risk of development of skin cancers, including melanoma. The greatest risk is observed in *xeroderma pigmentosum* (XP) and dysplastic nevus syndrome. Li-Fraumeni syndrome predisposes to the development of this cancer to a smaller extent.

Xeroderma pigmentosum is a very rare heterogenic disease characterised by autosomal recessive inheritance. In this disease, the skin displays characteristically increased susceptibility to ultraviolet radiation, which involves high risk of early-age development of skin cancers. The genetic background of XP involves mutations in the genes which encode enzymes responsible for repairing DNA damage caused by UV radiation. These mutations consist in *nucleotide excision repair* (NER). The exception is the XPV subtype, in which the disease is caused by mutations in the polymerase η. There are several sub-types of XP depending on the gene affected by the mutation (*XPA*, *XPB*, *XCP*, *XPD*, *XPE*, *XPG*, *ERCC4*, *DDB2* and *POLH*). XP prophylaxis involves avoiding exposure to UV radiation, frequent dermatological check-ups and removal of precancerous lesions [13].

Dysplastic nevus syndrome (familial atypical multi mole melanoma syndrome – FAMMM) is inherited in an autosomal dominant manner with variable expression and incomplete penetrance [14]. Apart from melanoma, increased risk of other malignancies is observed, including pancreatic cancer. The risk of developing melanoma in patients with dysplastic nevi is primarily related to the total number of nevi and family history of melanoma [15]. The syndrome is caused by the mutations in genes encoding proteins that regulate the cell cycle, including *CDK2A* and *CDK4* (cyclin-dependent kinase 4) [15].

Li-Fraumeni syndrome which is the hereditary predisposition to a broad spectrum of neoplasms, is based on a mutation in the suppressor gene (anti-oncogene) TP53 (tumour protein p53). This is an autosomally dominantly inherited syndrome. About 50% of mutation carriers develop tumours by the age of 30, often multifocal or bilateral lesions. The most common neoplasms associated with Li-Fraumeni syndrome are sarcomas and osteosarcomas, as well as breast cancer, adrenal cortex cancer and malignant tumours of the brain. Melanoma does not belong to the main spectrum of neoplasms found in this syndrome, but the risk of its development is increased. Therefore, prophylaxis should include the analysis of any new skin lesion / nevus by a dermatologist and limitation of exposure to UV radiation [16].

Genetic counselling in patients with hereditary melanoma predisposition

Patients with oncological diseases should be consulted by a clinical geneticist, who should assess whether the disease meets the hereditary cancer syndrome criteria. There are features allowing for such diagnosis even without finding the germline mutation, e.g. diagnosis of the hereditary breast cancer syndrome (HBC-syndrome).

The case is similar for patients with clinical history of melanoma. In families with hereditary predisposition, cancers are diagnosed in young patients (below 40 years of age) and in several close relatives. In the case of melanoma, it should be remembered that development of this cancer may be also associated with shared environmental risk.

As it has been mentioned before, the genetic background in families with accumulation of melanomas is not easily found. Apart from the already mentioned *CDK2A* and *CDK4* genes, involvement of other genes, of moderate penetrance, has been suggested, too: *TERT* (*telomerase reverse transcriptase*), *MITF* (*microphthalmia-associated transcription factor gene*), *POT1* (*protection of telomeres 1*) or *BAP1* (*BRCA1 associated protein 1*) [17]. Additionally, genetic counselling should take into account the increased risk of pancreatic cancer (in carriers of *CDKN2A* mutations). The patient's skin phenotype and geographic origin are important, too, as the risk can differ between particular populations, even in carriers of the same genetic variant. Genetic tests which can be applied to analyse the genetic burden may concern only the c.442G > A (p.A148T) variant in the *CDKN2A* gene (especially for the Polish population). The gold standard in this type of testing involves sequencing with Sanger method, especially that this method is not very expensive, but has very high sensitivity. The gene fragment that contains the change is amplified by PCR (polymerase chain reaction) and then every nucleotide in the sequence is read by the sequencing reaction. In families with hereditary predisposition, if the p.A148T variant is not detected, sequencing should cover the entire *CDK2A* gene including promoter sequence. If no variants are found in the *CDKN2A gene,* then a test is typically performed for mutations in the *CDK4* gene and other genes of potential relevance in melanoma. However, these are informal recommendations, as so far, no guidelines for the analysis of genes other than *CDKN2A* have been published [18, 19]. Also in other cancer syndromes, such as Lynch syndrome type II, Cowden syndrome, familial retinoblastoma, one should remember about the increased risk of melanoma [18].

Most common molecular changes in melanomas

Melanomas are a very heterogeneous group of cancers in terms of the molecular changes occurring in their development; and compared to other malignancies, they are associated with a high rate of somatic mutations [20]. Therefore, characterising molecular changes allows implementation of individualised clinical approach, and it may have prognostic significance.

There are 3 levels within a cell where defined genetic changes may occur. The first level is called the input layer and it is integrated into the cytoplasmic membrane, which consists of ligands and surface receptors. These are for example the receptor tyrosine kinases (RTKs), including KIT and ALK. After the receptors are activated, the next level is launched, i.e., signal transmission pathways. This level consists of two main trails: MAPK (mitogen-activated protein kinase) and PI3K / AKT / mTOR (phosphatidylinositol-3-kinase pathway). The signalling cascade ends at the last effector level in the cell nucleus (e.g., the *TERT* gene) with the activation or inhibition of transcription factors [20].

One of the most commonly observed and characteristic pathomechanisms in melanomas involves activation of the MAPK pathway with its main components of RAS / RAF / MEK / ERK kinases. This activation occurs as a result of mutations in the genes which encode proteins involved in the signalling pathway. The most commonly mutated proto-oncogenes are *BRAF* and *NRAS*.

BRAF

BRAF gene (*B-Raf proto-oncogene, serine / threonine kinase*), located on the long arm of chromosome 7 (7q34), encodes the serine-threonine kinase which activates the ERK pathway. *BRAF* mutations are seen in approximately 50% of advanced melanoma cases and are common in patients with no history of sun damage to the skin. These mutations are very rarely found in melanomas of the mucous membranes or oral cavity [21]. Despite identification of many different mutations in the two segments of the kinase domain, the most common one is a substitution of valine for another amino acid at position 600 of the amino acid chain (more than 97% of the mutations) [22]. The most common change involves substitution of glutamic acid (V600E, 70–80%). This, in turn, activates *BRAF* and causes a more than 800-fold increase of the phosphorylation capacity of the substrate MEK [23].

The next most common alteration concerns V600K (lysine substitution, 10-20%). Less common changes are V600R, V600D, and V600M (substitutions for arginine, aspartic acid, and methionine, respectively) [21]. *BRAF* mutation leads to an increase in the cell proliferation index independent of external signals (activation of the MAPK / ERK pathway).

Melanomas with the *BRAF* mutation have poor prognosis. The disease has an aggressive course associated with shorter survival time in patients with high (IV) stage cancer compared to patients without the *BRAF* mutation (wild type – WT). Further, *BRAF*+ melanomas are more common in younger people and, unlike wild-type melanomas, they are characterised by superficial tumour spread or nodular type [22]. Mutations of the *BRAF* gene in melanoma always coexist with inactivation of the suppressor gene, e.g. *PTEN* or *TP53* (oncogene / tumour suppressor gene effect) [24].

NRAS

NRAS gene (*NRAS proto-oncogene, GTPase*) encoding small--molecule GTPase is located on the short arm of chromosome 1 (1p13.2). *NRAS* is the next most commonly mutating protein in melanomas, and the MAPK pathway is one of its several effector pathways. It is estimated that approximately 15–25% of melanoma cases have activating mutations in *NRAS* [25]. The most common *NRAS* mutation in melanoma is substitution of glutamine with other amino acids at codon 61 (Q61). Typically, these are arginine (R), leucine (L), lysine (K) and histidine (H) [26]. *NRAS* and *BRAF* V600 mutations are mutually exclusive. Inactivation of p53 or p16 and coexistence of the *NRAS* mutation are factors that trigger the process of neoplastic transformation [24]. The NRAS protein is a GTPase responsible for the hydrolysis of GTP to GDP. Mutations commonly found in melanoma interfere with the hydrolysis process and NRAS is permanently bound to GTP, causing its continued activity independent of external signals. NRAS activates the MAPK pathway by CRAF kinase (BRAF independent pathway activation), which translates into increased proliferation. In addition, it also activates the PI3K / AKT pathway. This, in turn, is associated with modulating the growth and survival of cancer cells [27].

The *NRAS* mutations are most common in elderly patients who are chronically exposed to UV [28]. Presence of a *NRAS* mutation is an independent negative prognostic marker associated with higher risk of nodal metastases and lower median survival compared to patients without this change [29].

NF1

In 2015, The Cancer Genome Atlas (TCGA) published a sequence analysis of the exome in 333 patients with primary and/or metastatic melanoma. The data showed that skin melanomas can be divided into 4 genomic subgroups, which include cancers:

- with *BRAF* mutation,
- with *NRAS* mutation,
- with *NF1* (neurofibromin 1),
- *triple wild type*, i.e. tumours without mutations in the above genes [30].

However, clinical implications concerning prognosis and forecasting response to treatment are still equivocal with respect to the group with *NF1* gene mutations. Therefore, further studies are necessary to introduce guidelines for management of patients with this mutation [8].

PTEN

PTEN gene (*phosphatase and tensin homolog*), located on the long arm of the chromosome 10 (10q23.31), encodes phosphatase which acts as a tumour successor by blocking the PI3K signalling pathway through lipid phosphatase activity and by negatively regulating the MAPK pathway through protein phosphatase activity (double specificity).

In about half of melanomas with *BRAF* mutations, loss of expression of PTEN protein is detected. This loss reflects homozygous deletion of the gene and other genetic and epigenetic changes which lead to reduction/loss of protein expression. Further, a subgroup of melanomas can be identified with amplification of AKT3 (*AKT serine/threonine kinase 3*) – effector of PI3K pathway. This amplification is an independent mechanism that leads to activation of the PI3K pathway in tumours with present mutations that activate *BRAF* [31]. The consequences of the loss of PTEN function associated with AKT3 amplification still need to be clarified. However, it is suggested that activation of the PI3K pathway affects the expression of the porapoptotic protein BCL2L11. Lack of PTEN activity inhibits expression of BCL2L11, which translates into increased resistance of cells to apoptosis. The moment of loss of PTEN activity remains unresolved – whether it occurs in the initial or later stages of carcinogenesis [31].

KIT

Mutations which lead to function loss, activation and/or amplification of *KIT* (*KIT proto-oncogene, receptor tyrosine kinase*), are relatively common in rare (1–3% of all melanoma cases) melanomas of the mucous membranes and subungual tissues (10–40%). Further, unlike the *BRAF* mutation, they occur in people who are chronically exposed to skin damage caused by solar radiation [32, 33]. Mutations / amplifications of the KIT protein lead to constitutive activation of various intracellular pathways, including MAPK / ERK and PI3K / AKT, which play key roles in melanoma development. *KIT* gene mutations in melanoma are most commonly (about 70%) located in:

- exon 11 – most commonly substitution of proline for lysine in codon 576 (L576P), and
- exon 13 – most commonly substitution of glutamic acid for methionine in codon 642 (K642E) [33].

These mutations cause enhanced proliferation which translates to increased expression of Ki-67 protein (proliferation biomarker) in immunohistochemistry testing of patients with a mutation as compared to patients with the unchanged gene. The presence of a mutation in the *KIT* gene is a prognostic marker associated with a worse prognosis as compared to melanomas without this change [34].

GNAQ/GNA11 and BAP1

The genetic profile of uveal melanomas turned out to be completely different from that of the skin or mucous membranes melanomas, because in these cancers there are no mutations of proto-oncogenes and suppressor genes crucial for development of skin melanomas. However, they have characteristic mutations in two proto-oncogenes: *GANQ* (*G protein subunit alpha q*) and *GNA11* (*G protein subunit alpha 11*) which are mutually exclusive. Both genes encode the α-subunit of a G protein with GTPase activity involved in the activation of various signal transmission pathways [35]. Mutations of these

genes lead to the inactivation of the GTPase function. This is associated with constitutive binding of protein with GTP and – similar as in the case of NRAS – it leads to its constant activity.

Further, beside mutations of the listed protooncogenes, point mutations of the BAP1 suppressor protein-encoding gene were found in uveal melanomas. The biggest number of mutations are present in the domains binding BAP1 to BRCA1 and BARD1 [19, 35, 36].

Genetic analysis of somatic changes

Somatic changes are characteristic and present only in the patient's cancer cells. Their identification allows introduction of treatment targeted at these changes. Consequently, the applied therapy may be much more effective than the classic chemotherapy.

The most commonly analysed material is DNA isolated from paraffin blocks. The key step before isolating the genetic material is to assess the percentage of neoplastic cells (which should be higher than 50%). This is a precondition for selection of the tissue fragment to be tested. *BRAF* V600 mutation status is the only biomarker currently considered important in the treatment of advanced metastatic cutaneous melanoma. Therefore, assessment of this status has become a priority in selecting therapy and has been included in guidelines by both the European Society for Medical Oncology (ESMO) and American National Comprehensive Cancer Network (NCCN) [17, 37, 38]. So far, several methods have been developed that can be used to detect BRAF mutations. These include:

- Sanger sequencing, immunohistochemistry (IHC),
- pyrosequencing,
- mutation-specific PCR,
- mutation specific real-time PCR / qPCR,
- digital PCR,
- high-resolution melting curve analysis (HRM),
- next-generation sequencing (NGS) [39].

Recommendations for identification of BRAF mutations in clinical practice indicate sequential analysis using two methods. The first step is to perform screening by IHC with monoclonal VE1 antibodies (specific for the mutant version of the BRAF protein with the V600E mutation). Secondly, the presence of the mutation must be confirmed by one of the methods of molecular biology. These recommendations are associated with the risk of false negative results and/or failure to detect presence of other mutations than V600E by IHC. If there is not enough material for genetic testing, then IHC remains the method of choice.

It should be remembered that sensitive molecular methods, e.g., real-time PCR may detect *BRAF* mutations which occur in a small percentage of tumour cells (even >5%), mostly wild type. However, it is not actually of clinical relevance in response to targeted therapy. Therefore, it seems that the NGS method is currently the best molecular method [39]. It allows simultaneous analysis of all genes which are relevant in melanoma (there are commercially available panels), and apart from high sensitivity, it indicates the percentage of mutated alleles.

Nowadays in Poland and worldwide, there are many commercial tests available which allow fast and unequivocal determination of *BRAF* mutation status. Most commonly, these are tests based on real-time PCR and – more importantly – optimised for DNA from paraffin blocks. Reference laboratories should use tests certified for diagnostic purposes (e.g., CE IVD certificate or recommendations by the American Food and Drug Administration [FDA]). Further, to ensure high level of performance of the tests, such laboratories should regularly undergo international inspections for external quality control. They should also promptly implement the latest recommendations.

Liquid biopsy is another way to obtain material for tests. It is gaining clinical significance with respect to analysing mutations in neoplastic tumours (especially inoperable ones), as well as treatment and resistance monitoring. This method involves identification of circulating tumour cells (CTCs), circulating tumour DNA (ctDNA) or circulating tumour RNA (ctRNA) in the patient's blood, as they hold characteristic mutations of prognostic importance [40].

Conflict of interest: none declared

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Received: 24 Mar 2021
Accepted: 25 Mar 2021

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Preliminary report

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 176–178
DOI: 10.5603/NJO.2021.0033

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

Smoking cessation help for cancer patients – a pilot project "Quitting Supports Treatment"

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Available data suggest that up to 50% of cancer patients, who were smoking before diagnosis, continue to smoke during treatment, unaware of the damage caused due to continued tobacco use and the undervalued benefits of quitting smoking after a cancer diagnosis. Structured initiatives aimed at helping cancer patients give up smoking was undertaken at the M. Sklodowska-Curie National Research Institute of Oncology in Warsaw (Poland) within the pilot project "Quitting Supports Treatment (QST)". QST was launched in September 2019 and was a joint initiative of two departments: 1. The Cancer Epidemiology and Primary Prevention Department and 2. The Soft Tissue/Bone Sarcoma and Melanoma Department. Moreover, QST works with the significant support of Department of Nurses and Midwives Professional Development. The preliminary results suggest the need for several organizational improvements in order to increase QST participation rates. Revision of previous experiences could bring valuable conclusions with regards to the effectiveness of QST, but also for other similar projects.

Key words: smoking cessation, cancer patients, tobacco, cancer prevention, Poland

Tobacco smoking is known to cause a number of malignancies, and it remains the single main cause of premature death worldwide, with over 480,000 deaths each year [1]. It has been linked to more than 15 types of cancer, including lung, bladder, and esophageal cancer [2], with ongoing detrimental effects of continued cigarette smoking on patients' health after cancer diagnosis. These effects include decreased overall and cancer-specific survival and increased risk of cancer recurrence, treatment toxicity, secondary malignancy, depression, stress, and reduced quality of life [3]. Smoking cessation is especially important for patients with cancer because tobacco use can compromise the effects of their cancer treatment, shorten patients' survival, increase mortality and toxicity from therapeutic interventions, and even in some cases result in an increased incidence of recurrence and secondary malignancies [4]. Furthermore, smoking in the perioperative period can increase the risk of pulmonary embolism and poor wound healing, diminish the efficacy of chemotherapy, impair the function of the immune system, thus resulting in an increased risk of infection.

How to cite:

Koczkodaj P, Cedzyńska M, Rutkowski P, Janiak A, Przepiórka I, Ciuba A, Mańczuk M, Przewoźniak K, Didkowska J. ***Smoking cessation help for cancer patients – a pilot project "Quitting Supports Treatment".*** *NOWOTWORY J Oncol* 2021; 71: 176–178.

Available data suggest that up to 50% of patients who were smoking before a cancer diagnosis, continue to smoke during treatment [5], unaware of the harm related to continued tobacco use and the undervalued benefits of quitting smoking after a cancer diagnosis. Such benefits include a reduced risk of death by 30% to 40% [6], longer survival, improved chances of successful cancer treatment, less serious adverse events, increased energy and a better quality of life [7].

Moreover, health care professionals do not always encourage their patients to quit smoking and do not provide tobacco cessation assistance for continuing tobacco users [8], with about 62% of smoking cancer patients receiving smoking cessation counseling from their physicians in a sample from a study conducted by Lola Burke et al. [9]. Interventions to achieve tobacco abstinence include pharmacotherapy and counseling, and these often require repeated attempts, as helping patients with cancer to quit smoking cigarettes is far from an easy process [10]. Nevertheless, the accumulation of evidence provides strong grounds for incorporating smoking cessation as a standard component of treatment within all cancer centers. Consequently, all cancer patients should be advised of the health benefits of cessation and provided with help in quitting. Support should also be given to patients who have recently quit smoking, due to the high probability of relapse [11].

A structured initiative aiming to help in smoking cessation for cancer patients was undertaken at the M. Sklodowska-Curie National Research Institute of Oncology in Warsaw (Poland) within the pilot project "Quitting Supports Treatment (QST)". QST started in September 2019 and was a joint initiative of two departments: the Cancer Epidemiology and Primary Prevention Department and the Soft Tissue/Bone Sarcoma and Melanoma Department. Moreover, QST works with the significant support of the Department of Nurses and Midwives Professional Development.

The program consists of three main elements.

- **Stage 1:** all patients admitted to cancer hospitals are given a questionnaire about smoking and their willingness to stop. Additionally, all patients receive a leaflet on the benefits of quitting smoking after cancer diagnosis, prepared specifically for QST needs.
- **Stage 2:** if they are smokers and they declared a willingness to stop smoking, their data are transferred to the National Quitline. The quitline counselors arrange a telephone consultation and provide a support call to them. The number of calls depends on the individual needs of the patient.
- **Stage 3:** in the case if the patient declares that she or he smokes and does not want to quit, the anti-tobacco minimal intervention (MI) is provided by a nurse in a medical ward. If as the results of MI patient changes his mind, the quitline counselors provide a proactive call (counselors initiate a contact with a given patient).

Looking at the preliminary data from the months which were not affected by the SARS-CoV-2 pandemic (September–December 2019), we can assume that even before this specific event, in regular hospital admission circumstances, cancer patients were not eager to quit smoking. In the analyzed period, 296 patients expressed initial interest in QST and received a quitline call. Only about 13% (40) of them wished to have a second call and to receive help in quitting. Furthermore, 65% (26) of them changed their smoking habits: 40% (16) decreased smoking substantially and 25% (10) quit smoking completely.

Undoubtedly, cancer disease is connected with a particular physical and psychological burden for patients. However, some lessons on QST functioning have also been learned since the start of the program. The most important one is that in the face of health professional shortages in Poland (including nurses), as well as the constantly increasing incidences of cancer, there is a need to consider the introduction of additional health educators on medical wards. This solution could bring about higher effectiveness in smoking cessation among cancer patients, however, it demands extra funding and further organizational facilities (additionally, it could be difficult in the current epidemiological circumstances). In contrary to the enlargement of human resources needed to QST implementation and conduction, it should also be considered a modification of the QST promotion – focusing on more tailored and efficient communication regarding the health benefits of quitting. Finally, changes in QST methodology should be taken into consideration as well.

Conflict of interest: none declared

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Received: 18 Oct 2020
Accepted: 19 Oct 2020

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NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 179–182
DOI: 10.5603/NJO.2021.0034

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

Infringement of the personal rights of a doctor and medical institution

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Health and life constitute a special value for everyone. Therefore, parties involved in providing medical services are subject to exceptionally high expectations, and the activities of doctors and medical institutions are subject to social control. Such control is carried out with the participation of patients and journalists using mass media, particularly the Internet. Even though such control is allowed and freedom of speech and freedom of the press allow for public expression of opinions (including critical and negative ones), presenting one's position – even on important social issues – does not entitle one to infringe upon the personal rights of medical personnel and health care institutions. Meantime, criticizing and defaming doctors has become increasingly common in recent years due to the growing popularity of internet portals evaluating doctors, social media disseminating information, as well as the social tensions related to the overburdened health service and limited access to some health services due to the COVID-19 pandemic. Furthermore, patients exposed to stress about the health or hospital treatment are more likely to manifest their emontions by verbal aggression (insults or slanders) towards the medical personnel [1].

In the case of a threat to or infringement of personal rights, civil and criminal remedies are available to the doctor and the medical establishment, which protect against the negative consequences of an infringement of reputation or good name in the personal, professional and social sphere.

Key words: infringement of a doctor's personal rights, defamation, violation of good name, violation of the reputation of a medical institution

The limits of protection of the personal rights of doctors and medical institutions

In the case of the dissemination of insulting, untrue content or comments about a particular doctor, the limits of permitted criticism may be exceeded, and the doctor's personal rights violated (Article 24 in connection with Article 23 of the Civil Code of 23 April 1964, hereinafter the "Civil Code") [1].

Whether the negative opinions made public or disseminated are considered as a threat of infringement is determined by the assessment of the specific case and the accompanying circumstances. These are verified in the light of the general conditions for the application of these provisions, which include:

- identification of the personal good which has been infringed,
- individualization of a natural or legal person as a holder of a right,
- a threat or infringement of the right,
- establishing unlawfulness of interference into the sphere of protection of personal right.

How to cite:

Ożegalska-Trybalska J. ***Infringement of the personal rights of a doctor and medical institution.*** *NOWOTWORY J Oncol* 2021; 71: 179–182.

The most frequently violated personal rights are the good name and dignity of a doctor. Violation of this right may take place when a doctor is accused of improper conduct in carrying out their profession (e.g. lack of proper qualifications, malpractice, ignoring patients' rights, corruption, etc.). Such allegations may put him at risk of losing the trust necessary to carry out the profession of public trust changes in a behavior of patients or loss of them (e.g. the judgment of the Supreme Court of 29.10.1971, II CR 455/71).

If a medical institution (hospital, medical clinic, health center) is the subject of pejorative opinions or harassment, its reputation (good name) may be threatened or infringed (Article 43 in conjunction with Article 24 of the Civil Code), which shall be understood as patients' good opinion about its activity in the field of medical services. Infringement of this personal right of a legal person may consist in unjustified attributing to an institution of inappropriate, reprehensible operation accusing (e.g. low quality of services, negligence towards patients, abuses in providing medical services, bullying of employed personnel, etc.) negatively influencing its assessment by patients, including losing the trust necessary to perform its statutory tasks as a medical institution. The breach of reputation may also consist in untrue information being made public about irregularities in the work of hospital staff (in particular towards patients), which do not fall within the bounds of acceptable criticism as far they are not based on facts. As a rule, in such a case, a statement of the infringement of the personal interests of a medical institution does not, at the same time, constitute an infringement of the personal interests of its employees. However, there may be situations in which allegations against the employed personnel (doctor) may objectively affect the reputation of the institution and infringe its good name.

Apart from indicating the personal right that has been violated, it is also necessary to prove that the actions violating the personal right are not anonymous, which means that the questioned statements, opinions or negative comments shall explicitly refer to an individual person or institution.

The decisive factor for determining a violation of a personal right is not the subjective feeling of the doctor (institution) but the objective perception of specific behavior and the reaction it causes in public perception [2]. A required assessment is needed as regard the context of the allegedly infringing statements, their possible connotations, references, the situational context, the group of recipients, etc.

Demonstrating the severity of a threat or infringement may be difficult because the boundaries of acceptable criticism and the means used for this purpose are in case of doctors exercising a profession of public trust – significantly shifted. As confirmed by the court rulings, due to the specificity of their profession, a doctor who provides health services must take into account the fact that their activity may be openly criticized, and their personal rights (in particular their name) to the extent related to their profession are subject to weaker protection (the judgment of the Supreme Court of 18 January 2013, IV CSK 270/12).

However, the presumption of unlawfulness makes it easier to enforce claims for the threatening or infringing of personal rights. It means that each infringement of personal property is treated as unlawful, unless there are special circumstances justifying interference in the sphere of personal rights. These include:

- acting as allowed by the applicable provisions of law,
- exercising one own's right,
- the wronged party's consent, and
- acting in defense of a justified interest (see the judgment of the Supreme Court of 4 June 2003, I CKN 480/01; the judgment of the Appeal Court in Kraków of 3 June 2020, I ACa 1315/19).

Freedom of speech and freedom of expression of opinions (Article 54 paragraph 1 of the Constitution of the Republic of Poland) and acting in defense of legitimate interests are usually invoked in disputes about the infringement of personal rights of doctors and medical institutions. However, one may exercise these rights as long as third parties' personal rights are not affected. Although patients and other persons have the right to express negative or unflattering opinions about a doctor, the limit of criticism is set by the doctor's right to protect their personal rights. Objective criticism may be regarded as socially useful, but it should not exceed the limits permitted by the law. When setting the limits, the court should balance the rights and interests of both parties, assuming that in comparison with the protection of personal rights, freedom of speech and the protection of personal rights are equally protected. On the one hand, the court may find that an evaluative or critical opinion or judgement leads to the infringement of personal rights if it is not based on an objective circumstances and facts and does not have the features of reliability and accuracy. That is because only the adequacy of the assessment to the described actual event repeals the unlawfulness of the utterance, even when it contains formulations that violate personal dignity or the good name of the doctor or the medical institution (judgment of the Supreme Court of 23.2.2017, I CSK 124/16). It is considered unlawful to disseminate false information (cf. judgments of the Supreme Court of 22.12.1997, II CKN 546/97 and 23.06.2004, V CK 538/03) or true information presented in a manipulated context (cf. the judgment of the Appeal Court in Białystok of 25.2.2016, I ACa 981/15). On the other hand, the use of even controversial forms of expression may fall within the permissible framework (as an action devoid of unlawfulness) because it concerns issues of major social importance (e.g. a doctor's opinion on the issue of transplantation, abortion, vaccine safety, etc.).

Infringements of personal rights of doctors on the Internet and in press articles

Special rules and circumstances relevant for the assessment of infringement of personal rights of doctors and medical in-

stitutions concern the publication of negative comments and opinions on the Internet, on portals used to evaluate doctors, as well as press articles prepared by journalists – especially in sensationalist magazines.

Regarding the prevention of potential violations of third party rights, administrators are not obliged to check, monitor and censor the content posted by users (Article 15 of the Act on rendering electronic services of 18 July 2002) [3]. Instead, content verification for infringement may result from the specific rules of the portals and be carried out by moderators.

Once an infringement is noted, it is important to notify the administrator, who is obliged to react by removing the infringing content or preventing access to it. The administrator may also be a private person who has an open public profile on their website or a forum where Internet users can post comments. To assert claims in court proceedings, upon request and subject to the provisions of the data protection law, the administrator shall make available the user's data who infringed the personal interests by his/her entries. Suppose the administrator was aware of the existence of entries on his or her website that infringes someone else's personal rights or, in the case of being notified of their unlawful nature, does not react in the indicated manner. In that case, they are liable for infringement in a similar manner to the author of the entry (judgment of the Supreme Court's of 30.9.2016, I CSK 598/15).

The effectiveness and scope of claims for infringement of personal rights are influenced by the context of the individual case (e.g. negative statements on a portal dedicated to sharing opinions about doctors), the means of communication such as the Internet and the circle of people reached by the statement that infringes the personal rights. According to court rulings and practice, posting comments on an Internet forum constituting a public space justifies higher than average consent to a stronger, even exaggerated opinions and critical comments, characterized by a dose of exaggeration or even aggression. Moreover, portals posting opinions and comments on doctors also have greater permission to proceed with the name of doctors as their personal data, since such portals are considered one of the tools with which patients can exercise social control (the judgment of the Supreme Court of 20.1.2017, I CSK 99/16, the decision of the General Inspector of Personal Data of 23 December 2009, DOLiS/DEC-1323/09) [4].

The topic of medical services and doctors also appears in the mass media, including press articles describing medical errors or pathologies in the health service, sometimes using very strong forms of expression regarding specific persons or medical institutions. On these occasions, journalists exercise their freedom of expression and the right of citizens to reliable information, openness of public life and social control and criticism (Article 14 of the Constitution and Article 1 of the Press Law of 26 January 1984) [5]. However, freedom of the press does not justify the infringement of personal rights by providing information that is inconsistent with reality, unfoundedly damaging assessments (e.g. as to allegations of violating a patient's life or health, making the provision of services dependent on financial gain, etc.).

When using press materials, presenting facts, opinions, events and comments, a journalist shall exercise high care and diligence, particularly, when verifying the truthfulness of the obtained information or indicating its source (Article 12 of the Press Law). Statements of a reliable character (even if they contain unflattering statements) must be distinguished from criticism or negative assessment based on unsubstantiated facts or journalistic fiction. Suppose a publication manipulates facts, presents them in a selective or tendentious way, which may present a doctor or a medical institution in an dishonest way, personal rights such as a good name or image may be violated. This is the case if a journalist intentionally abuses editorial and language means, adding drama to the description and thereby strengthening the negative impact on the reader (the judgment of the Regional Court in Elbląg of 23.12.2013, I C 308/13).

Claims of a doctor and medical entity in the case of infringement of personal rights

Freedom of expression, which includes the right to criticize and express negative opinions to protect important social interests to which health care belongs, does not entitle one to make false accusations, slanderous, untrue or unreliable comments about doctors and medical service providers, which may constitute an infringement of their personal rights. The following means of protection are available for claiming such damages.

1. According to Article 24 of the Civil Code, a person whose personal right is endangered by someone else's action may demand that this action be abandoned unless it is lawful. In the case of an infringement, it is also possible to demand that the person who committed the infringement perform actions necessary to remove its effects to make a statement of appropriate content and in the appropriate form. The manner of remedying the infringement of personal rights should be selected in accordance with the type, intensity and scope of the infringement. If the infringement has been committed through an Internet publication or a particular newspaper, this is an appropriate medium to publish an apology or other statement. The provision mentioned above may constitute the basis for claims against natural persons (doctors or other medical personnel) and legal persons (hospitals, public and private clinics).
2. Irrespective of other measures required to eliminate the effects of the infringement of personal rights, in the case where the infringement is culpable, the entitled person may also demand pecuniary compensation or payment of an appropriate sum of money for the indicated social purpose (Article 448 of the Civil Code). In the situation where the violation of the good name or reputation has

a real and direct impact on the loss of patients' trust and financial damage related to the loss of employment or income from providing medical services, it is possible to claim compensation on the general principles of the Civil Code (Article 24, paragraph 2, in connection with Article 415 of the Civil Code). In the case of a claim for compensation or damages, the doctor should demonstrate the extent of the harm or damage, respectively.

3. Some statements may lead to defamation (slander), which can be claimed as a criminal offense (art. 212 § 1 of the Act of 6 June 1997 – Penal Code) [6].
4. An independent tool that can be used in the case of an untrue or unreliable press publication infringing on a good name or reputation is to request the publication of free of charge, the subject-matter and factual correction of inaccurate or untrue press material within three working days of the receipt of the correction (Articles 31a and 32 of the Press Law).

Conflict of interest: none declared

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Received and accepted: 13 May 2021

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VIA MEDICA

Letter to the Editor

NOWOTWORY Journal of Oncology
2021, volume 71, number 3, 183
DOI: 10.5603/NJO.2021.0035

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

On national oncology journals in Europe

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Publishing in peer-reviewed journals is one of the main methods of disseminating research results to the scientific community. Like other disciplines, oncology has several international journals publishing research from authors all over the world. Examples of such journals are *International Journal of Cancer* and *European Journal of Cancer*. These journals are often linked to international organisations or societies. Other large journals, such as *JAMA Oncology*, are linked to a national association but have a strong international focus.

In Europe, this latter category includes journals such as the *British Journal of Cancer*. In addition, several smaller peer-reviewed national journals are available, such as *Forum of Clinical Oncology* and *Nowotwory. Journal of Oncology* linked to the Hellenic Society of Medical Oncology and Polish Society of Oncology respectively. Another category of journals is linked to several national or regional organisations, such as the *Journal of the Balkan Union of Oncology*.

Like the larger, international journals, these smaller national journals publish high-quality research for the benefit of the scientific community. There are, however, some potential differences that warrant further research. A first difference is that these journals might have a special role in disseminating research to the national healthcare professionals. This hypothesis is supported by the fact that some of these journals also publish in the local language in addition to English. This could potentially facilitate the accessibility to / and therefore the adoption of, novel techniques or knowledge by healthcare professionals. A second aspect of these journals could be that they function as a publication venue for local researchers. This is supported by a study on the *Journal of the Balkan Union of Oncology*, that found that 76.5% of the publications originated from authors in the Balkan region [1]. A third potential difference is that these journals may not always be indexed by some of the major services such as Medline, Scopus and Web of Science Core Collection. They may however be indexed by local services. It has been suggested that these journals can benefit from being indexed in the larger databases [2]. A final difference is that due to the previous points, these journals have a smaller outreach than the larger international journals. This hypothesis could be tested by comparing metrics such as the impact factor between these journals and the larger ones.

In general, it is clear that national and regional oncology journals have an essential role in publishing high-quality scientific research. There is however still a lot to discover about their specific characteristics. A study shedding more light on this could provide these journals with better insights into their position in the landscape and help them with developing a strategy to advance towards the role they want to fulfil.

Conflict of interest: none declared

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Received: 22 Feb 2021
Accepted: 2 Mar 2021

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How to cite:
Stans J, Davids E. ***On national oncology journals in Europe.*** *NOWOTWORY J Oncol* 2021; 71: 183.