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# Tumor-infiltrating lymphocytes and levels of PD-L1 and BRCA protein expression may identify patients with breast cancer with a higher rate of *BRCA1* mutations

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**Introduction.** Breast cancer (BC) is a heterogeneous disease, treated as per the predictive role of immunohistochemistry (IHC) identifiers as estrogen/progesterone and HER2 receptor proteins. Deeper molecular classification (MC) identifies molecular subtypes according to the gene-expression profiles, with different molecular genetic alterations and biological features, present in the different subtype. An overlap between IHC and MC exists, even if somewhat incomplete. We aimed to identify the overlap between IHC and MC, and identify patients with basal-like subtype of BC. We hypothesized that the rates of tumor expression of breast cancer-related protein 1 (BRCA1), the type of tumor-infiltrating lymphocytes, and the expression of programmed death ligand 1 (PD-L1) by immune cells vary among different subtypes of BC.

**Material and methods.** Parafin-embedded samples from 100 patients with primary invasive BC were analyzed and expression levels of estrogen and progesterone receptors, HER2 status, and Ki-67 were assessed *via* IHC, defining four groups – luminal A-like, luminal B-like (LumA, LumB), HER2-positive non-luminal, and triple negative (TN). The primary endpoint of our study was to identify *via* IHC with CK5/6 and 17 basal-like subtypes of BC amongst others, and to describe specific clinicopathological features together with protein expression of BRCA1 and PD-L1 and tumor-infiltrating lymphocytes, using CD20, CD3, CD4, CD8, and FoxP3.

**Results.** Basal-like BC were predominantly characterized as triple negative by IHC ($p < 0.05$) and were more frequently seen among special BC subtypes as compared to no special type (NST), with $p = 0.036$. Their immune response was represented mostly by high concentration of intratumoral cytotoxic CD8 (+) T-lymphocytes ($p < 0.05$) and stromal PD-L1-positive immune cells ($p = 0.008$). In these tumors, absence of expression of BRCA1 protein was more frequent ($p < 0.001$). Basal-like subtype of BC with absent expression of BRCA1 is associated with poorer <5-year survival ($p = 0.001$ and $p = 0.017$, respectively).

**Conclusions.** The use of IHC can establish basal-like BC, the type of its immune response and possible dysfunction in the *BRCA*-gene, reflected in the lack of expression in the BRCA-related protein.

**Key words:** breast cancer, PD-L1, BRCA1, tumor-infiltrating lymphocytes

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## Introduction

Currently, conflicting data exist about the effects of the interaction of tumor-infiltrating lymphocytes (TILs) and tumor cells, the importance of immune "checkpoint" pathways in the regulation of the immune response (IR) as well as their role in patients with breast cancer (BC), having impaired function in *BRCA1* and *BRCA2* genes [1, 2].

The complexity of the problem is due to the heterogeneity of the primary tumor in this type of neoplasm [3–5]. Different groups of BC are characterized by different molecular and genetic alterations. The defined molecular types – luminal A and B, basal, and HER2-positive – are subtypes with different prognosis and response to therapy. The basal subtypes, expressing basal cell cytokeratins such as CK5/6 and CK17, are often characterized by immunohistochemistry (IHC) as a triple negative (TN) phenotype. Basal-like (BL) subtype is characterized by the most unfavorable prognosis and genetic instability due to a multitude of mutations, including *BRCA1* and *BRCA2* genes [6]. On the other hand, mutational products are perceived by the body as neo-antigens, inducing IR and transforming these types of tumors into more immunogenic neoplasms, characterized by a more pronounced inflammatory infiltrate in the stroma, tumor, and non-neoplastic tissue. However, whether the detected in the tumor immune cells (IC) are active with an effective antitumor IR, or whether they are suppressed as a result of interaction with the tumor cells (TC), or due to the involvement of immune checkpoint inhibitory pathways, remains questionable. Further clarification of this may increase the possibility of desired immune modulation [1, 7].

Impaired function of the *BRCA1* and *BRCA2* genes due to germline/somatic mutations and/or epigenetic mechanisms is involved in the pathogenesis of some hereditary and sporadic cases of BC. Using IHC, it is possible to establish correlations in the expression of relevant proteins, reflecting the altered activity of their genes [8, 9].

The aim of our study was to determine the basal-like subtype of BC, its tumor expression of the BRCA1 protein, the predominant type of lymphocytes, and the expression of the programmed cell death- ligand (PD-L1) by IC, using the IHC method.

## Material and methods

### *Patients*

This project was approved by the Ethics Commission at the Medical University, Pleven. After anonimization and coding of patient data, no personal information of the studied patients can be identified.

We retrospectively analyzed 25 IHC characterized as luminal A-like, luminal B-like (LumA; LumB), HER2-positive, and TN primary breast cancer samples – a total of 100 BC samples. A random selection from a list of archival tumor blocks at the University Hospital Georgi Stranski and the department of pathology was undertaken. All paraffin-embedded tumor blocks were rechecked in order to confirm the availability of sufficient quantity of tumor tissue. Tumor blocks that had enough remaining tissue with no risk of tumor depletion after the planned research were selected for the analysis.

The list of patients consisted of two hundred and ninety samples with a diagnosis of primary BC for the period 01.01.2011–05.01.2015. Clinical description of inflammatory BC or other inflammatory or inflammation reactions or conditions within the breast were not considered eligible. Core biopsies or tumor samples after systemic therapy were also considered ineligible for the purposes of our analysis. The selected patients of each subtype of breast carcinoma are few, because a small number of cases diagnosed during the indicated period met the study's inclusion and exclusion criteria. We followed the overall 5-year survival of all of them, but we did not have access to information on their progression-free survival.

Standard stained by hematoxylin/eosin (HE) slides from the archival tissue were examined with additional IHC tests, consisting of staining for estrogen receptor (ER), progesterone receptor (PR), HER2, and proliferation index Ki-67. One slide per each tumor was selected to assess the expression of CK5/6, CK17, BRCA1, PD-L1 and TILs subtypes (B-lymphocytes – CD20(+), T-lymphocytes – CD3(+), T-helpers – CD4(+), T-cytotoxic cells – CD8(+) and regulatory cells – FoxP3(+)) in staining with IHC. In our cases, the BRCA status determined by genetic analysis is was done and we cannot correlate it definitely with the protein expression.

A formulary, listing the anonymized data, was specifically elaborated for this analysis. We collected and filled in data for demographics (sex and age), clinical characteristics (type of surgical intervention and clinical staging), pathological description (grade of differentiation [G], morphological description, lymph node [LN] involvement, lymphovascular invasion [LVI] and IHC for ER/PR, HER2 and Ki-67), and 5-year survival.

### *Histological examination as per the current recommendations for the period of the diagnosis*

Classification of the BC was done as per the 4$^{th}$ edition of the WHO histology classification [10]. The Nottingham grading system (Ellston and Elis, 1991) was applied in order to assess the grade (G) of the invasive cancers [11]. Staging of the disease was done as per the 7$^{th}$ edition of the Tumor-Node-Metastasis (TNM) classification by the American Joint Committee on Cancer (AJCC) staging manual and the 2010$^{th}$ Union for International Cancer Control (UICC) [12].

IHC and expression of proteins for ER/PR, HER2, and Ki-67 was used to histologically classify among the four pathological subtypes of BC as per the 2013 St. Gallen's expert recommendations for the management of early BC [13]. IHC assessment of ER/PR and HER2 was done as per the ASCO/CAP recommendations [14, 15]. The IHC levels of Ki-67 expression were interpreted as per the Working Group on BC recommendations [16].

### *Immunohistochemistry*

Silanized microscopic slides 7109-A from sections with a 3–4 µm thickness were done from the identified for the analysis formalin-fixed (in 10% neutral buffered formalin) and paraffin-embedded (FFPE) tumor blocks.

A visualization EnVision™ FLEX, High pH (DAKO) system and AutostainerLink 48 technique (DAKO) were used for the preparation of the IHC slides. All tissue samples were stained using the following primary antibodies:

- CD3 (polyclonal antibody, Rb, dilution 1:50, Dako, DK),
- CD4 (4B12 clone, mo, dilution 1:50, Dako, DK),
- CD8 (C8 /144B clone, mo, dilution 1:50, Dako, DK),
- CD20 (L26 clone, mo, dilution 1:200, Dako, DK),
- CK17 (E3, clone, mo, RTU, Dako, DK),
- CK5/6 (D5/16 B4 clone, mo, RTU; Dako, DK),
- FoxP3 (236A/E7 clone, mo, dilution 1:100, Bioscience, California, USA),
- PD-L1 (Clone 22C3, monoclonal mouse anti-human PD-L1, dilution 1:50, Dako, DK),
- BRCA1 (MS110 clone, mo, dilution 1:100; Abcam, UK).

At the time of our study, there were no generally accepted recommendations for reporting the markers we investigated. The cut-offs for them were determined by a research team based on the average values of the results obtained for all studied patients.

Immunohistochemistry (IHC) staining with CK5/6 and CK17 antibodies was used to identify basal-like subtype of BC. IHC definition of basal-like subtype was identified when the samples of BC had a positive expression of >60% (cytoplasmic for CK5/6; cytoplasmic and/or membrane for CK17) for both cytokeratins or expression >80% of any of them.

Immunohistochemistry staining for PD-L1 (22C3 clone) was also done and the levels of PD-L1 expression were scored as per the percentage of positivity in immune cells (IC). PD-L1 staining was considered positive at magnification ×20 if membrane and/or cytoplasmic staining in lymphocytes directly associated with the response was detected in the invasive tumor. The cut-off accepted for positivity was 1%.

BRCA protein expression on tumor cells was also assessed by IHC staining with the MS110 clone antibody. Detection of nuclear staining in the tumor cells was compared to that of normal epithelial cells (in which strong nuclear staining is normal and used as an internal control) and intensity was graded as 1(+), 2(+) and 3(+). The percentage of viable cancer cells and the intensity of marking were largely variable. Negative BRCA1 expression was considered in case of detection of >20% of viable tumor cells and intensity of 1(+) or in the absence of any staining. Positive expression of BRCA1 was considered if nuclear staining was measured as 2(+) and/or 3(+) in >80% of tumor cells.

Subtyping of immune infiltrates was done by IHC staining with CD20, CD3, CD4, CD8 and FoxP3, detecting respectively B-, T- and T subtypes – helper, cytotoxic, and regulatory lymphocytes.

Immunohistochemistry expression for different lymphocyte populations was considered positive if the following expression was detected:

- CD3 – membrane and/or cytoplasmic,
- CD4 – membrane,
- CD8 – membrane and cytoplasmic,
- CD20 – membrane,
- FoxP3 – nuclear staining.

The lymphocytes were the subject of immune phenotypisation and were divided into intratumoural and stromal. Their levels were separately calculated, semi-quantitatively graded, and further analyzed. Depending on the average number of IHC positive cells, the results were recorded as: 0 (no positive cells), low and high number of TILs subsets.

Using antibodies against CD3, CD4, CD8 and CD20 and positive staining (membranous for CD4 and CD20; membranous and cytoplasmic for CD3 and CD8) identified TILs both in tumor and stroma. Their respective levels were measured and this was done at high magnification of high power field (HPF) ×400 in 5 randomly selected fields. The interpretation of the results was semi-quantitatively graded and divided into binary groups: TILs were considered as low in cases of detection of less than 25 IHC positive cells and high if ≥25 IHC-positive cells were measured. Lymphocytes in the tumor and the stroma, stained by the FoxP3 (with nuclear expression), were also differentiated into two groups semi-quantitatively and were counted in minimum 10 tumor fields at 400× HPF magnification: detection of less than 15 FoxP3-positive cells was interpreted as low lymphocyte expression and levels ≥15 were considered as high level of regulatory lymphocyte expression.

### *Statistical design and analysis*

The results of the testing of the prespecified biomarkers were summarized and data was statistically analyzed using IBM SPSS Statistics 25.0 and MedCalc software version 14.8.1. Descriptive statistics was used and categorical features were summarized with frequencies and percentages. P-values were calculated and values <0.05 were considered as significant.

## Results

### *Patient and tumor characteristics*

The median age of all 100 patients was 63.90 ± 12.17 years and most of them were over 50 years (84.0%) at the time of their diagnosis (tab. I). Included in the study were mainly tissue samples from mastectomy (78%). Invasive ductal carcinoma (IDC) of no special type (NST) was the most common histology in 80.0% of the cases, and different special morphological types of IDC were detected in 11.0%:

- mucinous: (n = 4),
- neuroendocrine features (n = 1),
- tubular (n = 1),
- with apocrine differentiation, metaplastic (n = 3),
- with medullary features (n = 1),
- adenoid cystic (n = 1).

**Table I.** Percentage distribution of clinico-pathological data in all studied patients and in different subtypes of BC

| Variables | LumA | LumB | HER2 | TN | All patients |
|---|---|---|---|---|---|
| | % | % | % | % | % |
| **age (yr)** | | | | | |
| ≤50 | 24.0 | 20.0 | 16.0 | 4.0 | 16.0 |
| >50 | 76.0 | 80.0 | 84.0 | 96.0 | 84.0 |
| **5 years** | | | | | |
| no | 8.0 | 36.0 | 72.0 | 64.0 | 45.0 |
| yes | 92.0 | 64.0 | 28.0 | 36.0 | 55.0 |
| **grade** | | | | | |
| G1 | 32.0 | 8.0 | 4.0 | 0.0 | 11.0 |
| G2 | 68.0 | 44.0 | 24.0 | 28.0 | 41.0 |
| G3 | 0.0 | 48.0 | 72.0 | 72.0 | 48.0 |
| **stage** | | | | | |
| I | 36.0 | 12.0 | 8.0 | 8.0 | 16.0 |
| II | 48.0 | 56.0 | 56.0 | 64.0 | 56.0 |
| III | 16.0 | 32.0 | 32.0 | 28.0 | 27.0 |
| IV | 0.0 | 0.0 | 4.0 | 0.0 | 1.0 |
| **metastatic lymph nodes** | | | | | |
| no | 76.0 | 36.0 | 36.0 | 64.0 | 53.0 |
| yes | 24.0 | 64.0 | 64.0 | 36.0 | 47.0 |
| **LVI** | | | | | |
| no | 96.0 | 72.0 | 60.0 | 76.0 | 76.0 |
| yes | 4.0 | 28.0 | 40.0 | 24.0 | 24.0 |
| **tumor size** | | | | | |
| ≤3 cm | 36.0 | 12.0 | 12.0 | 24.0 | 21.0 |
| >3 cm | 64.0 | 88.0 | 88.0 | 76.0 | 79.0 |
| **samples** | | | | | |
| excision biopsy | 28.0 | 12.0 | 24.0 | 24.0 | 22.0 |
| mastectomy | 72.0 | 88.0 | 76.0 | 76.0 | 78.0 |
| **histological type** | | | | | |
| NST | 68.0 | 80.0 | 92.0 | 80.0 | 80.0 |
| lobular carcinoma | 12.0 | 20.0 | 4.0 | 0.0 | 9.0 |
| other special type | 20.0 | 0.0 | 4.0 | 20.0 | 11.0 |
| **basal-like subtype** | | | | | |
| no | 96.0 | 92.0 | 88.0 | 52.0 | 82.0 |
| yes | 4.0 | 8.0 | 12.0 | 48.0 | 18.0 |

Lobular type of histology was identified in 9% of the BC samples. Low and intermediate grade (G1–2) tumors was the most common differentiation degree, detected in 52% of the tumor samples, whereas the remaining samples were G3 tumors (48%). 79% of all patients had tumors larger than 3 cm in size, with most (88% each) having LumB and HER2 subtypes.

The highest percentage (36%) of tumors ≤3 cm were from the LumA subtype group. The majority of patients (72%) were diagnosed in stage I–II, the remaining were stage III (27%) and stage IV (1%). The axillary lymph nodes were not involved by metastatic dissemination in 53% of the patients (pN0) and were positive in the remaining 47%. Lymphovascular invasion (LVI+) was observed in 24% LVI, and it was present in 16.9% of the pN0 patients. The 5-year survival rate of the cohort of all 100 patients was 55%. All patients included in our study were not treated preoperatively. However, we did not have access to the ongoing therapy of most of them, therefore we did not include this type of information in the clinical data studied.

### *Rates of basal-like subtype among groups*

Basal-like subtype of BC (BLBC) was identified by positivity in CK5/6 and/or CK17 as described above and was found in 18% of all 100 cases with BC. Most BLBC were detected in the group of TNBC (48%) – 12 out of 25 patients, followed by 12% in the HER2-positive group (3 out of 25), 8% in the luminal B-like group (2 out of 25) and the smallest percentage – 4% was in luminal A-like type (1 out of 25) and this distribution of BL cancers was statistically significant ($p < 0.05$) (fig. 1).

If analyzed by BC subtype, patients were divided into NST (80%), ILC (9%), and special type IDC (11%). Within the special type the relative rate of BL subtype was significantly higher ($p = 0.036$) compared to those of non-BLBC. With other words, patients with IHC for TNBC have a significantly higher percentage of non-BL subtype in the presence of the NST histological type, while in the spacial type the relative proportion of those with basal subtype is significantly higher ($p = 0.036$).

### *Assessment of immune response in BLBC – lymphocyte subtypes and PD-L1 expression*

Immune response (IR) in BLBC was more represented and consisted predominantly of significantly higher rates of intratumoral cytotoxic CD8(+) T-lymphocytes ($p < 0.05$) and stromal PD-L1-positive immune cells ($p = 0.008$) (fig. 2).

### *Type of BRCA1 protein expression in BLBC*

In BLBC, absent expression of BRCA1 protein from the tumor cells was more frequently noted ($p < 0.001$) (fig. 3).

### *Prognostic significance of the results*

Patients with BLBC (18%) and IHC negative expression of BRCA1 protein (26%) had poorer 5-year survival ($p = 0.001$ and $p = 0.017$, respectively) (tab. II and III).

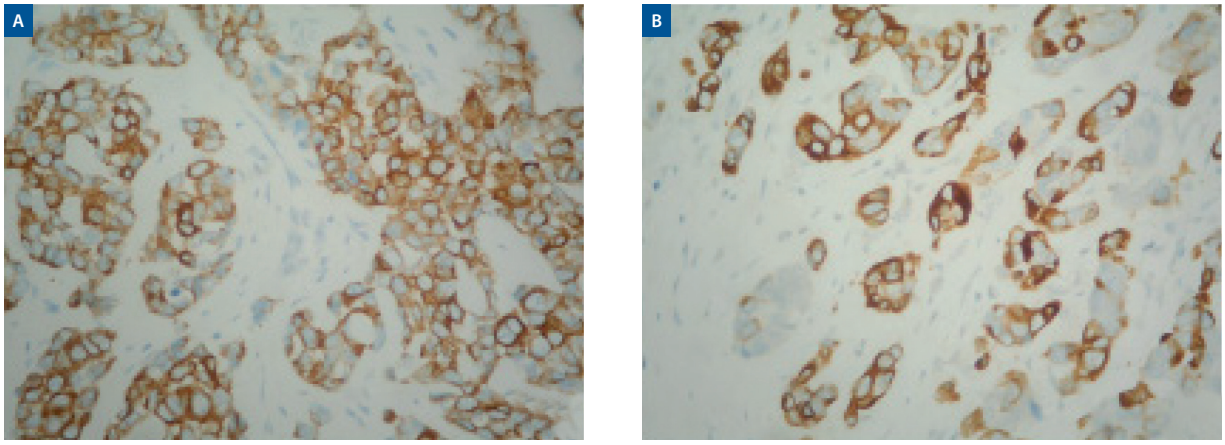


**Figure 1.** IHC expression model of CK5/6 (**A**) and CK17 (**B**) in basal-like TNBC (×400)

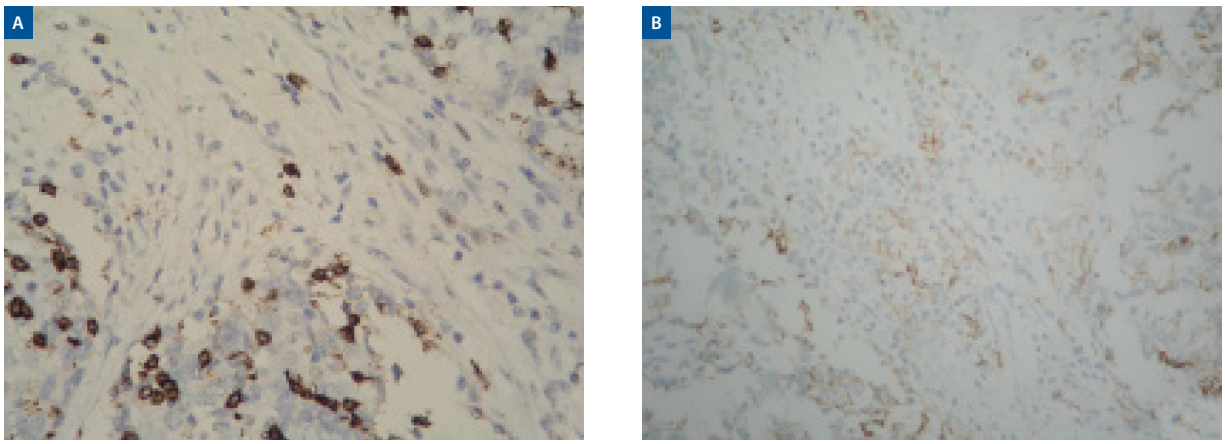


**Figure 2.** IHC staining for CD8 (**A**) and PD-L1 (**B**) in basal-like TNBC (×400)

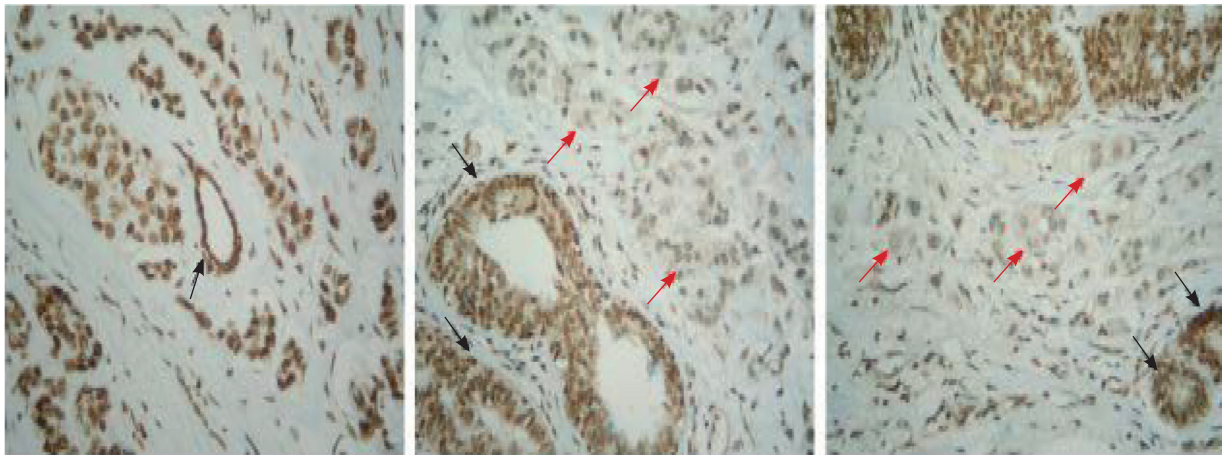

**Figure 3.** IHC staining for BRCA1 protein in BL TNBC – positive and negative expression in normal epithelial cells of breast (black arrow) and tumor cells of BC (red arrow), respectively (HPF ×400)

**Table II.** Comparative analysis of 5-year survival according to basal/non-basal-like BC (all patients)

| Indicator | Non-basal-like | | Basal-like | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **5-year survival** | | | | | 0.017 |
| no | 32 | 39.0 | 13 | 72.2 | |
| yes | 50 | 61.0 | 5 | 27.8 | |

**Table III.** Comparative analysis of 5-year survival according to BRCA1 expression (all patients)

| Indicator | Negative | | Positive | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **5-year survival** | | | | | 0.001 |
| no | 19 | 73.1 | 26 | 35.1 | |
| yes | 7 | 26.9 | 48 | 64.9 | |

## Discussion

Knowledge about heterogeneity of primary breast cancer (BC) is continuously evolving and the discrepancy between clinical behavior and the histologically, molecularly, and biologically determined subtype is being largely discussed [1, 17]. There are different risk factors for development of BC, divided into non-genetic (reproductive and lifestyle-related), genetic (mainly inherited mutations), and epigenetic (leading to genetic dysfunction) [18, 19]. Among the genes involved in the pathogenesis of this neoplasm, scientific data is mostly available for the breast cancer susceptibility genes type 1 and type 2 (*BRCA1* and *BRCA2*), located in 17q21 and 13q12, respectively. Their normal function in non-neoplastic cells is basically related to the repair of damaged DNA, regulation of the cell cycle, the processes of transcription, and replication of DNA, providing the genetic stability of the cell. The two genes function in coordination at different stages of implementation, although they are not located on homologous chromosomes [18, 20]. Molecular genetic testing has been extensively studied during the last years, but its introduction into real, daily, clinical practice will take more time due to its high financial burden. Thus, treatment decisions still remain based on IHC markers.

The function of *BRCA1* and *BRCA2* genes may be impaired due to germline/somatic mutation or epigenetic silencing mechanisms (decreased gene expression, decreased *BRCA1* mRNA levels and corresponding protein expression, methylation of the *BRCA1* promoter region, amplification of the *BRCA2* gene, etc.). Such abnormalities may cause deficiencies in the *BRCA*--dependent double-stranded DNA homologous recombination repair. Cells with *BRCA1* and *BRCA2* alterations become dependent on alternative repair mechanisms, and unresolved genetic defects lead to genomic instability with an increased risk of cancer initiation. Women with a *BRCA1* germline mutation, have an increased oncogenic risk for different cancer localizations: up to 85% lifetime risk for BC, up to 60% for epithelial ovarian cancer (eOC). Elevated oncogenic risk exists

in *BRCA2* mutations carriers as well with up to 49% of lifetime risk for BC, and up to 18% for eOC [1, 8, 9, 20, 21].

There are conflicting data on the subcellular distribution of the protein product through which the *BRCA* genes perform its functions. It accumulates in the nucleus, but the movement of protein from the nucleus into the cytoplasm has also been found [8]. The complete loss of function of the *BRCA1* gene in mammary epithelial cells is considered to be an accelerator of proliferation and tumor progression. Altered gene activity leads to impaired function with abnormal expression and subcellular distribution of their respective proteins.

There are few publications, related to the use of the IHC method to determine the status of BRCA-related proteins. According to some of them, decreased or absent expression is observed only in tumor cells, but in normal – it is strong and monomorphic [8, 9, 19]. In our study, BRCA1 expression also showed homogeneous strong nuclear and weak cytoplasmic expression in epithelial cells of terminal duct lobular units in normal breast; in some of these cases, loss of expression in tumor cells was observed.

Breast cancer may be most frequently sporadic and rarely hereditary [22]. Only 5–10% of all BC are inherited and are due to germline mutations in highly penetrating sensitive genes, such as *BRCA1* and *BRCA2*, *PALB2*, T*P53*, *CDH1* and *PTEN*, leading to a cumulative risk of the development of this and other neoplasms. However, penetrance is incomplete and depends on various factors, such as the type and location of the mutation, the influence of population and exogenous factors. Only <5% of the familial BC have a mutation in the *BRCA1* and *BRCA2* genes, with the frequency and types of mutations varying by geographical location [18].

Most cases are sporadic and are not the result of a hereditary genetic predisposition. Some of them have characteristics (phenotype) of *BRCA1* and *BRCA2* germ-mutated tumors [1] and are associated with somatic mutations and/or epigenetic alterations that inactivate the *BRCA1* and *BRCA2* genes, the so-called "BRCAness" BC. Epigenetic mechanisms important for the regulation of gene expression may also be involved in hereditary cases, but are more common in sporadic cases [8, 9, 18, 20–23].

*BRCA1* mutated and BRCAness tumors are a heterogeneous group with various pathological and clinical data, molecularly associated with increased genomic instability. Predominant morphological features include invasive ductal (no special type – NST) histological type, tumors with a high proliferative index and low differentiation, i.e. with high histological degree (high grade/G3). Often manifest with pronounced necrosis and lymphocyte infiltrate (possibly more immunogenic), medullary characteristics, well demarcated from peripheral non-tumor tissue, negative hormonal receptor status for ER and PR, HER2-negative, without an *in situ* component [20, 21, 24–27].

Among the major molecular surrogate subtypes of BC, the TN subtype includes 15–20% of all BC cases. This subtype is most common in patients with *BRCA1* and *BRCA2* mutations or "BRCAness" BC, with 70% of germline *BRCA* mutated tumors being TN and 10–20% of TNBC having germline *BRCA1* and *BRCA2* mutations [1, 7, 8, 17, 23]. TNBC has aggressive clinical behavior and unfavorable morphological characteristics [1, 7, 8, 17, 23]. This reflects a poorer prognosis and necessitates the development of targeted therapy and the establishment of appropriate predictive markers, allowing the selection of patients in whom it would have a more favorable effect. 56% of TNBC have a basal-like phenotype in which the molecular and IHC profile shows expression of basal cell or myoepithelial markers (e.g., CK5/6, CK14, CK17, p-cadherin, EGFR, etc.). The majority of these tumors are non-special/ductal type [28]. But most special histological types of TNBC are basal subset [29]. 80% of basal-like carcinomas are TN, but TN and basal-like carcinomas are not synonymous. BLBC have the highest mutational load, including often having a *BRCA1* mutation and *vice versa*, most (about 80%) *BRCA1*-related carcinomas are basal-like [7, 8, 17, 23]. The predominant proportion of basal type of BC have aggressive clinical behavior [6, 28].

Existing similarities between *BRCA1* mutated, TNBC, and BLBC may be critical for clinical behavior, as well as prognostic and predictive value in patients with impaired function in the *BRCA1* and *BRCA2* genes [1, 23].

In our study there are also similar results regarding TN, basal-like BC, and these tumors with lost *BRCA1* IHC expression. The basal-like subtype was also found mainly in TNBC, compared to other surrogate molecular subtypes of BC. Furthermore basal-like BC predominates in the group of other special histological variants compared to NST and the lobular type of BC. In addition, we noticed that in the tumor cells of basal-like subtype, the negative expression for *BRCA1* is more common, compared to the non-basal category of the tumors, where IHC positivity is often preserved. The disadvantage of our study is that we do not know the *BRCA* genetic status of the studied patients. Thus, the likelihood that expression loss for *BRCA1* reflects genetic dysfunction in this gene is only an assumption.

Women with BRCA1-associated BLBC have been found to have a similar clinical course as compared to no mutation carriers [28, 30]. In our series there was a similar result, showing the unfavorable prognostic value of the combination of the basal-like subtype of BC and an absent IHC expression of the BRCA1 protein. Both were associated with <5-year survival of patients.

The immune system (IS) is important for the outcome of BC disease, but its relationship to tumor development and progression is complex and influenced by genetic, tumor-specific, and environmental factors. It is a dynamic process and depends on the inhibition and activation of signals forming a pro- or antitumor environment, reflected in a different amount and variety of TILs, with possible participation of inhibitory pathways (e.g. associated with PD-L1).

The modulation of the IR, e.g. through immune checkpoint inhibitors or some chemotherapeutics (e.g. anthracyclines),

facilitates the so-called "immunogenic cell death" and has a possible effect on highly mutated/genomically unstable tumors, e.g. BLBC [7, 26]. The optimization of predictive biomarkers for response to immunotherapy continues. Germinative mutations in the *BRCA1* and *BRCA2* genes associated with defective homologous DNA repair lead to pronounced carcinoma antigen presentation, with the formation of multiple carcinoma-specific antigens activating IS with pronounced IR. This makes the *BRCA1* and *BRCA2* mutated BC a subtype, in which immune modulation and immunotherapy would have a beneficial effect [7, 26]. TILs are thought to be a possible prognostic factor in *BRCA* mutated BC, and a high TILs count may be predicting factor for positive BRCA status [26]. Determination of additional immune factors, incl. TILs subtypes and the expression of checkpoint molecules may help to clarify the role of IR in basal-like and TNBC, incl. with impaired BRCA function.

In our study, a comparative analysis of the results for PD-L1 expression and cancer immune cell infiltrate according to BRCA1 expression showed no statistically significant differences ($p>0.05$). However we found that there is an activae tion of the immune response in the BLBC subtype, including TNBC, confirmed by the higher levels of tumor-infiltrating cytotoxic CD8 (+) T-lymphocytes and PD-L1-positive immune cells, infiltrating the tumor stroma. It is still unknown whether the mutation rate of breast tumor cells contributes to specific differences in the tumor infiltration of immune cells and PD-L1 expression [31]. We did not find data on the simultaneous study of PD-L1, lymphocyte subtypes, and BRCA status, using the IHC method.

Treatment in cases of BC is still a problem, especially in the TN subtype, in which there is no *HER2*-targeted or endocrine therapy. Patients with the same therapy have different responses due to the heterogeneous molecular and genomic nature of this neoplasm [1, 7, 8, 17, 23]. Despite advances in the study of tumor characteristics, there are a small number of approved prognostic and predictive markers for treatment choice in patients with TNBC. Ensuring the most effective therapy by finding new predictive markers for therapeutic response is of paramount importance in the implementation of personalized medicine in these cases [22, 23, 25].

It is essential to understand the importance of *BRCA1/BRCA2* genetic dysfunction in BC, and some molecular characteristics may affect sensitivity to chemotherapy and DNA-damaging agents in these patients. Cases with TN, *BRCA*-mutated BC have been suggested to be more sensitive to chemotherapy than high grade TNBC without the *BRCA1/BRCA2* mutation [1, 17, 22, 27]. According to some studies, *BRCA*-mutated BC, incl. the basal-like subtype, show higher sensitivity to DNA-damaging agents, for example platinum-containing (e.g. cisplatin) and poly (ADP ribose) polymerase (PARP) inhibitors. PARP inhibitors have an established effect in patients with metastatic HER2-negative BC with germline *BRCA1* and *BRCA2* mutations, but whether they are effective in those with acquired somatic *BRCA1* and *BRCA2* mutations or the BRCA-ness phenotype is not entirely clear. Some epigenetic mechanisms, mainly acquired *BRCA1* methylation, have been suggested to be a promising predictor for response to PARP inhibitor therapy in sporadic cases of BC [23]. Various mechanisms lead to primary resistance to platinum and PARP inhibitors, some of which are associated with inherited mutations in the *BRCA1* gene. During treatment, secondary mutations in the *BRCA* genes can lead to acquired resistance to therapy, and others to the recovery of their activity and the expression of the proteins encoded by them [20, 25].

Therefore, determining the status of *BRCA* allows the identification of some genetic and epigenetic disorders with probable prognostic and predictive therapeutic value in sporadic and familial cases of BC [20–22]. Finding test(s) that are safe, quick to implement and easily accessible to patients is essential.

There are currently some clear criteria for conducting genetic counseling and testing for *BRCA1/BRCA2* status in patients with BC [32–35]. It is recommended mainly in patients with some personal and family history (e.g. cancer diagnosed at age ≤45 years old; the presence of a neoplastic process in both breasts; diagnosed at age ≤60 years old with TNBC; the presence of the disease in at least two first-line relatives; a first- or second-line relative who has BC younger than 50 years old; male breast cancer and second female breast cancer, diagnosed at any age, regardless of familial history etc.). The establishment of morphological, immunohistochemical and molecular characteristics suggesting alterations in the *BRCA1* and *BRCA2* genes may assist in the selection of patients suitable for genetic testing. The pathologist should suggested genetic counseling in the histological response due to the possibility of carrying a *BRCA1/BRCA2* mutation [1, 21, 25].

When selecting for genetic analysis, not only familial but also sporadic cases of BC should be keep in mind; identification of some alterations in the *BRCA1* and *BRCA2* genes may allow more precise clinical and therapeutic behavior in these patients [20–22]. Clarification of *BRCA1/BRCA2* status and screening for specific mutations is no less prognostic for close relatives in the family of patients with BC, due to the possibility of detecting healthy individuals, but with a high risk of developing some neoplasms, including BC/ovarian cancer (OC) and others [1, 20].

There is a wide variety of molecular-genetic tests to determine the *BRCA* carrier, but they are expensive and time consuming to obtain a result due to the large size of the genes studied, the presence of hundreds of different mutations, including those without proven clinical significance, the lack of hot-spot regions with mutations to study. This requires a more precise selection of applicant families for mutation testing [1, 7].

Histopathological features, together with clinical data, can be used as a predictive factor for determining *BRCA1/BRCA2* status by mutation screening. Validation of IHC results

using molecular confirmation may allow IHC also to facilitate the selection of high-risk cases suitable for genetic analysis [8]. An IHC analysis, which determine the expression of BRCA-linked proteins that reflect impaired gene function, is a promising quick, low cost, and easy to implement test.

The established contradictory data regarding the prognostic role of BRCA status in hereditary or sporadic cases with BC require further studies to clarify it. Finding correlations between clinico-pathological (morphological and IHC) and molecular characteristics of BRCA tumors can give a clearer picture of their biological behavior. This may allow the development of a prognostic algorithm in patients with BC, which is important for more accurate determination of the clinical and therapeutic approach in them [1, 8, 18, 22, 36].

## Conclusions

Our results show that there is a difference in the expression of the BRCA1 protein in tumor cells in different surrogate molecular subtypes of BC; it is most significant in the basal-like subtypes, which is more often with the TN phenotype. Using immunohistochemistry, it is possible to detect a clinically relevant type of protein expression that may reflect altered *BRCA1* gene activity, allowing better selection of patients for subsequent molecular genetic analysis. More studies are needed to confirm the clinically meaningful applicability of IHC expression for BRCA in BC.

The phenotype of BLBC, with absent BRCA1 protein expression and higher rate of TILs, may identify a group of patients who may be subjected to genetic screening for the search of pathological mutations in *BRCA*. Further research and prospective validation are necessary to confirm our hypothesis.


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**Conflict of interest:** none declared



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# Avelumab use in Merkel cell carcinoma treatment

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Avelumab is a programmed death-ligand 1 (PD-L1) blocking human IgG1 lambda monoclonal antibody. It was the first immunotherapy to be approved for the treatment of MCC. In March 2017, the FDA granted accelerated approval to avelumab for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC) –irrespective of prior therapy. In July 2017, the European Medicines Agency (EMA) recommended the approval of avelumab as a monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC). Approvals were based on the efficacy and safety demonstrated in JAVELIN Merkel 200 (NCT02155647), a multi-center, open-label, single-arm, phase II clinical trial [1]. Part A of the study consisted of patients treated in the second line with metastatic, chemotherapy-refractory MCC. Part B consisted of systemic treatment-naive patients who received avelumab as a first-line treatment for metastatic or distally recurrent MCC. In the first line the ORR is 39.7%. Durable responses lasting at least 6 months were observed and the majority of responses are observed early with the median time to response of 6.1 week. PFS rate at 6 and 12 months are 41% and 31%, respectively. Median OS is 20.3 months. The OS rate at 1 year is 60%.

**Key words:** Merkel cell carcinoma, avelumab, immunotherapy, skin

## Introduction

The development of immune checkpoint inhibitors (ICIs) represents a revolutionary innovation in the field of oncology. It is rapidly evolving and offers an attractive therapeutic option for many cancers, including Merkel cell carcinoma (MCC). MCC is a rare, neuroendocrine, clinically aggressive, cutaneous malignancy with a high mortality rate and a dramatically increasing incidence rate, rising from 0.5 to 0.7 per 100,000 persons between 2000 and 2013 [2, 3]. In both Europe and the United States, approximately 2500 new cases of MCC are diagnosed each year and metastatic disease is diagnosed in 5–12% of patients [4, 5]. Population ageing in the 21$^{st}$ century is predicted to have a major impact on MCC incidence, which is estimated to reach 3,284 cases in 2025 [3, 6, 7].

Merkel cell carcinoma has a significantly higher prevalence in elderly people and tends to affect individuals later in life compared with melanoma. The median age at diagnosis is 75–79 years for both genders *versus* 65–69 years and 60–64 years for male and female melanoma patients, respectively [3]. Of note, the rate of most cancers tends to decline among individuals over the age of 85, however, the rate of MCC continues to rise. Important risk factors associated with this cancer type include light skin colour, male sex, immunosuppression, exposure to ultraviolet radiation, and Merkel cell polyomavirus (MCPyV) infection, which is present in approximately 80% of MCC tumors [8]. Its most significant characteristics are summarized in an acronym: AEIOU – asymptomatic/lack of tenderness, expanding rapidly,

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immunosuppression, older than age 50, and UV-exposed site on a person with fair skin [7, 9].

Historically, MCC was associated with very poor outcomes, especially for patients with metastatic disease. Traditional treatment options for MCC included surgery, radiation, chemotherapy, and treatment for metastatic or stage IV MCC was most often palliative. Before the dawn of immunotherapy in the treatment of MCC in 2016, there was no effective therapeutic option that offered a confirmed survival benefit for MCC patients with metastatic disease not amenable to surgery and/or radiotherapy. Despite its low incidence compared with melanoma, research on immune-checkpoint inhibitors in MCC continues to gain attention. Patients with this tumor type have been shown to be good candidates for immunotherapy due to high immunogenicity [6, 7, 10]. A study of 5823 prospectively enrolled MCC cases from the National Cancer Data Base (NCDB) reported that the relative survival at five years post diagnosis was:

- ~64% for patients presenting with local disease,
- ~39% for patients with regional nodal disease,
- ~18% for patients presenting with distant metastatic MCC [11, 12].

It has been estimated that mortality rates increased from 0.03 to 0.43 per 100,000 persons, from 1986 to 2011 in the US, based on data from the Surveillance, Epidemiology and End Results program [5]. Moreover, MCC is generally associated with less favourable prognoses, higher recurrence and mortality rates compared with melanoma [13].

In 2017, the U.S. Food and Drug Administration (FDA) granted accelerated approval to avelumab (BAVENCIO, EMD Serono, Inc.), an anti-PD-L1 blocking human IgG1 lambda monoclonal antibody, for first-line treatment of patients 12 years and older with metastatic MCC. Approval was based on data from an open-label, single-arm, multi-center clinical trial (JAVELIN Merkel 200) demonstrating a clinically meaningful and durable overall response rate (ORR). In 2018, the FDA granted accelerated approval to pembrolizumab (KEYTRUDA®, Merck & Co. Inc.) for adult and pediatric patients with recurrent locally advanced or metastatic MCC. Approval was based on data from a multi-center, non-randomized, open-label clinical trial (KEYNOTE-017). The major efficacy outcome measures were overall response rate (ORR) and response duration assessed by blinded independent central review per RECIST 1.1. [14].

## Avelumab – second-line treatment

Avelumab was first studied in second line treatment. The eligibility criteria for part A of the JAVELIN Merkel 200 study required that all enrolled patients were at least 18 years of age, had a good performance status (Eastern Cooperative Oncology Group 0–1 [ECOG 0–1]), life expectancy of >3 months, histologically confirmed mMCC with disease progression following at least one previous systemic therapy used in the metastatic setting, at least one unidimensional measurable lesion by RECIST v. 1.1 criteria (response evaluation criteria in solid tumors), and adequate hematological, renal, and hepatic function. Patients with autoimmune conditions were ineligible for enrollment. The participants received avelumab at a dose of 10 mg/kg of body weight intravenously once every 2 weeks until experiencing disease progression or unacceptable toxicity. 59% of patients were reported to have had one prior anti-cancer therapy for mMCC and 41% had two or more prior therapies. The median age was 72.5 years (range, 64.5–77.0). Tumors were assessed every 6 weeks and the primary end-point was confirmed objective response (OR; CR or PR) based on independent assessment and RECIST v. 1.1 criteria. Efficacy and safety populations included patients who received at least one dose of the study drug.

The study cohort included 88 patients with a median follow-up time of 10.4 months from the first received dose of avelumab treatment to the first analysis cut-off date in 2016 [1]. The ORR was found to be 31.8% (95% CI: 21.9–43.1%; n = 28), with CR in eight patients and PR in 20 patients. Stable disease (SD) was observed in nine patients. The responses were long-lasting and, at the time of analysis, were maintained in 23 patients. The duration of response (DOR) was at least 6 months in 92% of cases. In comparison, an observational study published in the same year, reported that the proportion of patients with chemotherapy-refractory mMCC who responded to chemotherapy in the second-line setting was 23%, with a 6-month DOR in 6–7% of cases [15].

In this study the mPFS was 2.7 months (95% CI: 1.4–6.9), and the rate of PFS at 6 months was 40%. The PFS curve reached a plateau. The mOS was 11.3 months (95% CI: 7.5–14.0) and the OS rate at 6 months was 69%. In this analysis, five grade 3 treatment-related adverse events were reported in four (5%) patients: lymphopenia in two patients, aminotransferase increase in one patient, creatine phosphokinase increase in one patient, and blood cholesterol increase in one patient. There were no treatment-related grade 4 AEs or treatment-related deaths reported. PD-L1 expression (≥1% positive cells) was assessable in 74 patients and it was found to be present in 58 cases (78%). MCPyV status was assessed in 77 cases and 60% (n = 46) were positive. Better outcomes were reported in patients who received fewer prior lines of systemic therapy [1].

Updated analyses were published in 2018 and provided confirmation of continued durable responses and meaningful survival outcomes. The patient cohort had a median follow up for 29.2 months (24.8–38.1) [16]. The mOS was 12.6 months (95% CI: 7.5–17.1), and the OS rate at 2 years was 36%. The median treatment duration was 3.9 months (0.5–36.3). The confirmed ORR was 33.0% (95% CI: 23.3–43.8) and remained unchanged from analyses conducted at 12 and 18 months [17]. The median DOR was not reached (2.8–31.8). The PFS values were 29% after 12, 29% after 18, and 26% after 24 months of follow-up. Clinical activi-

ty was observed irrespectively of PD-L1 expression status and MCPyV status [16, 18]. The results of the next updated analysis were published in 2020, and provided further confirmation of avelumab efficacy in the group of previously pretreated patients [19]. Again, the ORR was 33.0% (95% CI: 23.3–43.8%). CR was observed in 10 patients (11.4%). In 17 of 29 patients who achieved a response to treatment (58.6%), the response was maintained. Four patients had a continuous response lasting at least 3 years. DOR was 40.5 months (median; 95% CI: 18.0 months – not estimable). PFS rate at 2 years and 3 years was 26% (95% CI: 17–36%) and 21% (95% CI: 12–32%), respectively. After ≥44 months of follow-up, OS was 12.6 months (median; 95% CI: 7.5–17.1 months). OS rates at 3 years and 3.5 years were 32% (95% CI: 23–42%), and 31% (95% CI: 22–41%) respectively.

In avelumab therapy, high tumor mutational burden and high expression of MHC I (major histocompatibility complex class I) were associated with trends in the improvement of OS and ORR. Long-term responses, i.e., responses for at least 3 years, were observed regardless of PD-L1 expression. Any grade AEs and grade ≥3 AEs were reported in 97.7% and 73.9%, respectively. Any grade TRAEs and TRAES G ≥3 occurred in 77.3% and 11.4% of participants, respectively. The most frequently reported TRAEs were fatigue, diarrhea, and nausea. Immune-related adverse events (irAE) were reported in 19 patients (21.6%). Four irAE were grade ≥3: increased transaminases, increased alanine aminotransferase, autoimmune disorder, and hypothyroidism. Eight patients (9.1%) discontinued therapy due to TRAEs. There were no deaths related to the study treatment [19].

The most recent analysis of this patient group was performed after >5 years of follow-up (median 65.1 months, range 60.8–74.1 months) and published in December 2021 [20]. The median OS remained unchaged at 12.6 months (95% confidence interval [CI] 7.5–17.1 months). The 5-year OS rate was reduced to 26% (95% CI: 17–36%). Only one patient (1.1%) continued to receive avelumab, and another patient (1.1%) had reinitiated treatment following previous discontinuation. Despite the fact that resposes to avelumab occurred regardless of PD-L1 status, interestingly, it was observed that patients with PD-L1+ tumors had longer OS and higher 5-year OS rate compared with patients with PD-L1 negative tumors. Consistent with the trends observed in previous analyses, the median OS was 12.9 months (95% CI: 8.7–29.6 months) *versus* 7.3 months (95% CI: 3.4–14.0 months) and the 5-year OS rate was 28% (95% CI: 17–40%) *versus* 19% (95% CI: 5–40%), respectively (HR 0.67; 95% CI: 0.36–1.25) [19]. Nonetheless, the OS of both subgroups greatly exceeded that recorded in retrospective analyses of second-line or subsequent chemotherapy in patients with mMCC, whose 1-year OS rate was 0%. This further supports the evidence that avelumab can offer a significant OS benefit irrespective of tumor PD-L1 status. During the course of the >5 year follow-up, death occurred in 71.6% of patients, however, there were no cases attributed to treatment-related adverse events. In conclusion, avelumab showed durable responses in the long-term OS study and manageable safety profile in patients who received prior systemic chemotherapy.

## Avelumab – first-line treatment

Subsequently avelumab was studied in first line. The enrollment criteria for patients who participated in part B of the JAVELIN Merkel 200 trial were the same as those in part A, however, the efficacy of avelumab was explored in a cohort of eligible patients with metastatic MCC who had not received prior systemic therapy for metastatic disease [21]. As previously mentioned, the therapy was approved in 2017 by the US FDA and the EMA as a first-line treatment for patients who were at least 12 years of age with metastatic MCC. The preliminary results of part B of the study using avelumab in chemotherapy-naive mMCC patients were published in 2017 [22]. At the analysis cut-off point, 29 of the 112 planned patients had been enrolled in the trial. The median age was 75.0 years (range 47–87). The drug was administered at a dose of 10 (mg/kg) as a 1-hour intravenous infusion once every 2 weeks until the patient experienced unacceptable toxicity, therapeutic failure or significant clinical decline [22].

After a follow-up period of at least 3 months, 16 of 29 patients were found to have an unconfirmed ORR of 68.8% (95% CI: 41.3–89.0) with CR in 18.8% and confirmed ORR 56.3% (95% CI: 29.9–80.2; 1 unconfirmed PR with discontinuation) [22]. All recorded responses were ongoing at the time of this analysis. The safety assessment revealed that 20 of 29 patients (69.0%) experienced a TRAE, including grade ≥3 TRAE in 5 patients (17.2%), which led to treatment discontinuation in all cases. They included two cases of infusion-related reactions, one case of aspartate aminotransferase increase, one case of alanine aminotransferase increase, one case of cholangitis, and one case of paraneoplastic syndrome [22]. There were no treatment related deaths at this time [21].

Subsequent analyses were published in 2018 and used novel statistical methods to extrapolate long-term patient survival data. For patients treated with avelumab in the first-line setting, the expected mean survival rate was calculated to be 49.9 months (6.3; 179.4), and 1 year and 5 year survival rates were 66% and 23%, respectively [23]. For patients treated with avelumab in the second-line or later setting, the expected mean survival rate was calculated to be 42.3 months (28.4; 77.4), and 1 year and 5 year survival rates were 51% and 19%, respectively. Based on this extrapolation, it was expected that the hazard of death was greater for chemotherapy-refractory patients than for treatment-naive patients.

At the next analysis cut-off point, 39 of 112 planned patients had been enrolled in the trial, with a median follow-up of 5.1 months (range, 0.3–11.3 months) [21]. Efficacy was assessed in 29 of 39 patients who had at least 3 months of follow-up. They were found to have a confirmed ORR of 62%

(95% CI: 42.3–79.3%), which consisted of 4 patients (13.8%) having CR and 14 patients (48.3%) having PR. At the time of analysis 14 of 18 responses (77.8%) were continuing. Additionally, 3 patients (10.3%) had stable disease. The majority of responses to treatment (89%) were recorded during the first assessment since treatment initiation, approximately at 6 weeks [21].

All enrolled participants were evaluable for safety and 28 of 39 (71.8%) experienced a TRAE, while TRAEs of grade 3 occurred in 8 patients (20.5%). There were no grade 4 TRAEs or treatment-related deaths reported. In patients who responded to aveumab treatment, the proportion of responses with a duration ≥3 months was 93% (95% CI: 61–99%), while the proportion of responses with a duration ≥6 months was 83% (95% CI: 49–96%), based on the Kaplan-Meier estimates [21].

For all the 116 patients in longer follow-up, the ORR was 39.7% (95% CI: 30.7–49.2%), of which 19 patients (16.4%) showed CR and 27 patients (23.3%) showed PR. Durable responses lasting at least 6 months were observed in 35 patients, resulting in a DRR of 30.2% (95% CI: 22.0–39.4%). Importantly, the majority of responses were observed early; 43 (93.5%) of 46 patients responded to treatment by 3 months and the median time to response was 6.1 weeks (range: 5–36). In PD-L1+ patients (n = 21) ORR was 61.9% (95% CI: 38.4–81.9%), and in the PD-L1- - participants (n = 87) the ORR was 33.3% (95% CI: 23.6–44.3%). Median DOR was 18.2 months (95% CI: 11.3 months – not estimable). The PFS rate at 6 months and at 12 months was 41% (95% CI: 32–50%) and 31% (95% CI: 23–40%), respectively. Median OS was 20.3 months (95% CI: 12.4 months – not evaluable). The OS rate at 1 year was 60% (95% CI: 50–68%), and in PD-L1+ and PD-L1 groups 1 year OS rates were 71% (95% CI: 47–86%) and 56% (95% CI: 45–66%), respectively [19].

The most recent efficacy and safety data analysis of this study was published in July 2021. A cohort of 116 patients treated with avelumab in the first-line setting had a median follow-up of 21.2 months (range: 14.9–36.6) [24]. The median duration of treatment was 24 weeks (range: 2.0–154.0). At this cut-off point, 26 patients (22.4%) continued to receive treatment. The most numerous reasons for treatment cessation were PD (n = 48; 41.4%) and AE (n = 23; 19.8%). Any grade TRAEs occurred in 94 patients (81.0%), which included grade ≥3 reported in 21 patients (18.1%). Any grade irAEs occurred in 35 patients (30.2%), which included grade ≥3 reported in

**Table I.** Major avelumab toxicities reported in JAVELIN Merkel 200 study

| Study | Grade 1 or 2 toxicity | Grade 3 or 4 toxicity |
|---|---|---|
| JAVELIN Merkel 200 treatment line 1 [24] | ALT increased* (n = 4; 3.5%)<br>AST increase (n = 1; 0.9%)<br>asthenia (n = 16; 13.8%)<br>chills (n = 12; 10.3%)<br>decreased appetite (n = 5; 4.3%)<br>fatigue (n = 23; 19.8%)<br>infusion-related reaction (n = 12; 10.4%)<br>lipase increase (n = 2; 1.7%)<br>maculopapular rash* (n = 6; 5.2%)<br>pruritus* (n = 14; 12%) | ALT increased* (n = 1; 0.9%)<br>amylase increase (n = 3; 2.6%)<br>AST increase (n = 1; 0.9%)<br>autoimmune nephritis* (n = 1; 0.9%)<br>autoimmune neuropathy* (n = 1; 0.9%)<br>cholangitis (n = 1; 0.9%)<br>colitis (n = 1; 0.9%)<br>decreased appetite (n = 1; 0.9%)<br>dehydration (n = 1; 0.9%)<br>dermatitis psoriasiform* (n = 1; 0.9%)<br>diabates mellitus* (n = 1; 0.9%)<br>fatigue (n = 1; 0.9%)<br>gait disturbance (n = 1; 0.9%)<br>infusion-related reaction (n = 1; 0.9%)<br>lipase increase (n = 4; 3.4%)<br>liver function test increase* (n = 1; 0.9%)<br>paraneoplastic encephalomyelitis (n = 1; 0.9%)<br>paraneoplastic syndrome (n = 1; 0.9%)<br>polyneuropathy in malignant disease (n = 1; 0.9%)<br>pruritus* (n = 1; 0.9%)<br>troponin increase (n = 1; 0.9%)<br>tumor lysis syndrome (n = 1; 0.9%) |
| JAVELIN Merkel 200 treatment line >1 [20] | asthenia (n = 7; 8%)<br>blood creatine phosphokinase increase (n = 1; 1%)<br>decreased appetite (n = 5; 6%)<br>diarrhoea (n = 8; 9%)<br>fatigue (n = 21; 24%)<br>hyperthyroidism* (n = 2; 2%)<br>hypothyroidism* (n = 3; 3%)<br>infusion-related reaction (n = 15; 17%)<br>maculopapular rash (n = 5; 6%)<br>nausea (n = 8; 9%)<br>pneumonitis* (n = 1; 1%)<br>rash (n = 6; 7%)<br>type I diabetes mellitus* (n = 1; 1%) | aminotransferase increase (n = 1)<br>blood cholesterol increase (n = 1; 1%)<br>blood creatine phosphokinase increase (n = 1; 1%)<br>lymphopenia (n = 2; 2%) |

* – TRAEs including immune-related adverse events (irAEs)

7 patients (6%), namely pruritus, increased ALT, autoimmune nephritis, autoimmune neuropathy, dermatitis psoriasiform, diabetes mellitus, and increased liver function tests. There were no treatment-related deaths reported in this cohort (tab. I).

For avelumab, first line treatment patients whose response rates were numerically higher had tumors that were PD-L1 positive, Merkel cell polyomavirus (MCPyV) negative, and with increased intratumoral CD8+ T-cell density. The study cohort was largely dominated by patients with PD-L1– tumors (75.0% *vs.* 18.1% with PD-L1+ tumors). Conversely, part A of the JAVELIN Merkel 200 trial, which examined the efficacy of avelumab in mMCC patients in the second-line setting, had a majority of participants with PD-L1+ tumors, specifically 78% of assessable patients had PD-L1+ tumors [1]. This was also true for the Keynote-027 trial, which examined the efficacy of pembrolizumab in mMCC patients in the first--line setting, including patients having PD-L1+ tumors [25]. Consistent with results from part A of this trial, patients with both PD- L1+ and PD-L1– tumors in the systemic treatment--naive cohort experienced responses to treatment, however, higher response rates were observed in those with PD- L1+ tumors. MHC class I expression did not correlate with response to treatment or patient OS [1].

Based on the findings reported from part A and B of the trial, it appears that response rates of mMCC patients treated with avelumab (anti-PD-L1) in the first-line setting may be higher than those with chemotherapy-refractory tumors treated in the second-line or later setting. The ORR of participants in part A (n = 88) of the JAVELIN Merkel 200 trial was 33.0% *versus* 39.7% in part B (n = 116) and the median OS was 12.6 months *versus* 20.3 months, respectively [20, 24]. This finding is also supported by results from the phase II Keynote-017 trial (n = 50) of first-line treatment with pembrolizumab (anti-PD-1) of patients with stage IIIB (n = 7) or stage IV (n = 43) MCC, where the ORR was 56% and median OS was not reached after a median follow-up of 14.9 months [25].

## Avelumab – expanded access program

The efficacy of avelumab in the real world was assessed in the expanded access program, which included mMCC patients with disease progression during or after chemotherapy and patients ineligible for chemotherapy or clinical trial participation. The efficacy and safety results were consistent with these from the JAVELIN Merkel 200 clinical trial. The enrolled population also included patients who had an ECOG PS 2 or 3, who had brain metastases stable after therapy, or were potentially immunocompromised. The median duration of avelumab treatment was 7.9 months (range, 1.0–41.7). 240 of 494 enrolled patients were evaluable for efficacy. The ORR was 46.7% in the evaluable patients, 22.9%, and 23.8% of participants achieved CR and PR. The safety data are limited. The most frequently reported AEs were an infusion-related reaction, fever, fatigue, rash, asthenia, abdominal pain, chills, and dyspnea. The relatively high number of infusion-related reactions resulted in the recommendation to use a premedication (paracetamol with antihistaminic) for at least the first four cycles of avelumab therapy [26]. In a European EAP 150 patients were treated and the objective response rate was 48.0%. In the responding patients, the median duration of treatment (DoT) was 7.4 months, with the longest duration of 41.7 months. Again the most common AEs were infusion--related reaction reported in 2.4% of cases and pyrexia in next 2.1% of patients. No new toxicities were observed in this study [27]. Moreover, in our real world study we enrolled 161 MCC patients who were treated with curative intent. Lymph node metastases at diagnosis were found in 26.9% of patients. Sentinel lymph node biopsy (SLNB) was performed in 36.5% of patients and was positive in 10.5%; 51.9% of our patients received perioperative treatment. After treatment, the relapse rate was 38.3%. With a median follow-up of 2.3 years, the median DFS was not reached, and the 1-year rate was 65%. The negative risk factors for shorter DFS were male gender, metastases in LN at diagnosis, no SLNB performed in patients without clinical nodal metastases, and no perioperative radiotherapy treatment. The estimated OS was 6.9 years with negative independent risk factors again male gender, age above 70, metastases in lymph nodes at diagnosis, and no SLNB in patients without clinical nodal metastases [10].

## Avelumab – adjuvant treatment

More avelumab studies are being conducted (tab. II). A multicenter, randomized, double-blinded, placebo-controlled, phase III trial of adjuvant avelumab (anti-PDL-1 antibody) in MCC patients with clinically detected lymph node metastases is currently ongoing. This is the ADAM trial: a multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab in Merkel cell carcinoma patients with clinically detected lymph node metastases (NCT03271372). It is expected to analyze 100 MCC patients. Enrolled patients must have clinically detected nodal MCC metastases before surgery with or without concurrent adjuvant radiotherapy. Avelumab is given every 15 days for the first 120 days (induction phase 1), and later on every 30 days for the next 120 days (induction phase 2), and finally every 120 days (maintenance phase) up to 2 years in total, or until disease progression, or unacceptable toxicity. Later on patients are followed up every 6 months for 3 years. The primary objective of the study is relapse-free survival (RFS), while secondary objectives are OS, distant metastases-free survival (DMFS), disease-specific survival (DSS), and toxicity analysis. This trial is investigator-sponsored study [28, 29]. The immunotherapy adjuvant trial in patients with stage I–III Merkel cell carcinoma (I-MAT) (NCT04291885) is still in the recruitment process. This is a phase II, prospective, randomised, placebo-controlled, multi-institutional trial for patients with stage I–III Merkel cell carcinoma. Patients receive either avelumab or a placebo for 6 months. RFS is the primary

**Table II.** Current avelumab clinical trials for Merkel cell carcinoma (April 2022)

| Clinical trial | Agent/interventions | Phase | Study population |
|---|---|---|---|
| NCT04261855 | avelumab external beam radiation therapy (EBRT)<br>lutetium-177 (177Lu)-DOTATATE | 1<br>2 | Merkel cell carcinoma |
| NCT03747484 | autologous MCPyV-specific HLA-A02-restricted TCR-transduced CD4+ and CD8+ T-cells FH-MCVA2TCR<br>avelumab<br>pembrolizumab<br>fludarabine cyclophosphamide | 1<br><br>2 | Merkel cell carcinoma |
| NCT04551885 | FT516<br>avelumab<br>cyclophosphamide<br>fludarabine drug: IL-2 | 1 | advanced solid tumors |
| NCT04792073 | avelumab<br>comprehensive ablative radiation therapy | 2 | Merkel cell carcinoma |
| NCT04393753 | domatinostat in combination with avelumab | 2 | Merkel cell carcinoma |
| NCT03853317 | avelumab<br>N-803<br>haNK™ | 2 | Merkel cell carcinoma |
| NCT03271372 | avelumab | 3 | Merkel cell carcinoma |

outcome. Overall survival rates at 12 and 24 months are the secondary endpoints.

## Conclusions

The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunosuppressive pathway is commonly upregulated in MCC and thus ICIs offer clinicians a promising approach to treat this cancer type. Data from non-randomized phase II clinical trials in patients with MCC have demonstrated high activity of PD-1/PD-L1 blockade and improved rates of durable response compared with cytotoxic therapy. On account of this, current guidelines recommend their use as the treatment of choice for patients with metastatic MCC [12]. Avelumab (Bavencio, EMD Serono, Inc.) is a programmed death-ligand 1 (PD-L1) blocking human IgG1 lambda monoclonal antibody. It was the first immunotherapy to be approved for the treatment of MCC. In March 2017, the FDA granted accelerated approval to avelumab for the treatment of adults and pediatric patients from 12 years and older with metastatic Merkel cell carcinoma (MCC) – irrespective of prior therapy. Building on this, in July 2017, the European Medicines Agency (EMA) recommended the approval of avelumab as a monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC). These approvals were a meaningful development for patients suffering from this particularly aggressive form of skin cancer. Approvals of avelumab by the FDA and the EMA were based on the efficacy and safety demonstrated in JAVELIN Merkel 200 (NCT02155647), a multi-center, open-label, single-arm, phase II clinical trial [1].

The study was split into two parts, A and B. Part A consisted of patients treated in the second line (n = 88), with metastatic, chemotherapy-refractory MCC, life expectancy of >3 months and a follow-up of at least 18 months. Part B consisted of systemic treatment-naive patients (n = 116), who received avelumab as first-line treatment for metastatic or distally recurrent MCC. Data obtained from part A of this study, first published in 2016, resulted in the approval of this drug for MCC therapy [1]. Subsequently, the FDA approved avelumab to be used in combination with axitinib (Inlyta) for the first-line treatment of patients with advanced renal cell carcinoma (RCC) in May 2019, as well as for maintenance treatment of patients with locally advanced metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-based chemotherapy. More avelumab studies are currently running (tab. II).

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# Short-course radiotherapy as part of total neoadjuvant therapy for locally advanced rectal cancer – a new standard?

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Selection of optimal perioperative treatment for rectal cancer remains a subject of controversy. Recently established new rationales for the use of short-course preoperative radiotherapy (SCRT – 25 Gy in 5 fractions), instead of standard long-course preoperative radio-chemotherapy (LCRT-CT), are presented and discussed in the present review. New data suggest that short-course radiotherapy combined with 6 cycles of CAPOX, or 9 of FOLFOX4, at present may be considered the best option for perioperative treatment of high-risk rectal cancer. However, there is a clear need to further optimize preoperative treatment using rapidly evolving markers of treatment response, including microsatellite instability and targetable or predictive tumour mutations.

**Key words:** rectal cancer, preoperative radiotherapy, total neoadjuvant treatment, chemotherapy, systemic treatment

## The rationale for short-course preoperative radiotherapy in rectal cancer

Despite extensive clinical research, that has included several randomized trials, the selection of the optimal perioperative treatment for rectal cancer remains a subject of controversy. While there is quite strong evidence to support the superiority of preoperative radiotherapy compared to postoperative treatment [1–4], several doubts remain over the selection of the optimal preoperative regimen. The origins of this debate are illustrated by the analysis of reduction in incidence of pelvic relapse rates as a function of total radiation dose and overall treatment time, determined based on the outcome of historical studies on preoperative radiotherapy for rectal cancer [5]. The results of the analysis indicate that short-course preoperative radiotherapy (25 Gy in 5.0 Gy per fraction) and long-course preoperative radiotherapy (50.4 Gy in 1.8 Gy per fraction) are, in general, iso-effective in terms of locoregional control, providing the adequate dose increment is delivered in long-course regimens to compensate for the extension in overall treatment time and reduction in the fraction size. The exact contribution of each of these factors (i.e. overall treatment time and fraction size) towards local effectiveness of preoperative therapy is, however, still not well established, although existing studies suggest that subclinical deposits of rectal cancer repopulate rapidly [5] and the fractionation sensitivity of rectal cancer clonogens is relatively high with $\alpha/\beta$ estimates of approximately 5.0 Gy [6]. Considering the iso-effectiveness of adequately selected

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short-course and long-course regiments in terms of tumour control, both schedules have keen opponents and supporters. Diverse arguments have been raised (tumour response rate, sphincter preservation rate, early and late tolerance) in favour of a preferred option. A third, somewhat less explored option, which will not be further debated in this article, is preoperative treatment of an intermediate duration (e.g. accelerated fractionation or moderate hypofractionation) which, according to some judgements, may be considered as a rationally supported compromise between long and short treatment [6–8].

To further improve the outcome of preoperative treatment, several attempts have been made to combine radiotherapy with chemotherapy, both in concurrent and sequential fashion. The rationale for such a combination is enhancement of the local effectiveness of treatment (usually mild chemotherapy regimens given concurrently to radiotherapy) and a reduction in the rate of distant metastases (mostly intense chemotherapy given sequentially to radiotherapy). One of the earliest prospective studies that explored the effectiveness and tolerance of long-course preoperative radiotherapy combined with chemotherapy (LCRT-CT), as compared to short-course radiotherapy alone (SCRT), was the Polish Colorectal Study Group Trial (Bujko et al. 2004, 2006) [9, 10]. In general, the outcome of this study showed no difference in long-term outcome between SCRT and LCRT-CT. Importantly, despite significant downsizing, chemoradiation did not result in an increased sphincter preservation rate in comparison with SCRT. Considering that the duration of SCRT is shorter compared to LCRT-CT, one could conclude that SCRT is a favourable option, also bearing in mind the labour intensity comparison of both therapeutic protocols.

Similar conclusions could be drawn based on results of the Trans-Tasman Radiation Oncology Group phase III Trial 01.04 (Ngan et al. 2012) [11]. No difference in long-term outcome between SCRT and LCRT-CT was recorded in this trial. Notably, both Polish and Trans-Tasman trial protocols required surgery to be performed shortly after the completion of radiotherapy. This raised some controversies, because delaying surgery after SCRT could potentially increase the response rate and improve the tolerance of treatment. On the other hand, delayed surgery could result in diminished local effectiveness, should repopulation during waiting time for surgery counterbalance the effect of radiotherapy. These concerns were resolved by the Stockholm III trial (Erlandsson 2017) [12], which showed a therapeutic advantage (improved tumour downstaging, and a lower postoperative complication rate) providing surgery was delayed for 4–8 weeks after SCRT, compared to surgery within 1 week after radiotherapy. Based on the outcome of the trials discussed, one could conclude that SCRT with delayed surgery is, at present, the best therapeutic option available for locally advanced rectal cancer, at least considering the evidence-based data from the prospective randomized trials. High incidence of distant metastases after optimal loco-regional therapy necessitates, however, a search for the most effective systemic therapy that can also be safely combined with radiotherapy.

## The rationale for preoperative chemotherapy

Several prospective randomized trials evaluated the role of adjuvant postoperative chemotherapy for patients with rectal cancer who underwent preoperative radiotherapy or radio-chemotherapy. In some of these trials, postoperative chemotherapy was given regardless of tumour response to preoperative radiotherapy/radio-chemotherapy, while in the other, chemotherapy was scheduled only for patients with upStage II–III disease. None of the trials demonstrated a statistically significant benefit of chemotherapy for OS or DFS. Two meta-analyses of these trials (Breugom 2015, Bujko 2015) [13, 14] confirmed that postoperative chemotherapy for rectal cancer did not significantly improve overall survival. Unsatisfactory clinical effectiveness of postoperative chemotherapy prompted attempts to deliver chemotherapy before surgery. The biological rationale for neoadjuvant systemic treatment is that subclinical cancer deposits would be eliminated before cytokines released at surgery and wound healing had triggered rapid repopulation of malignant clonogenes.

## Early trials of total neoadjuvant therapy (TNT-like treatment)

Based on the aforementioned results of the clinical trials, it was hypothesised that SCRT followed by preoperative chemotherapy and surgery may offer the best outcomes in high-risk rectal cancer. Such hypothesis was tested in a randomized trial performed by the Polish Colorectal Study Group (Bujko 2016, Ciseł 2019) [15, 16]. The trial compared 25 Gy in 5 fractions and three cycles of FOLFOX4, to LCRT-CT (50.5 Gy in 28 fractions) combined with 5-Fu/oxaliplatin-based chemotherapy. Eligibility included cT4 or fixed cT3 cases, only those with middle and low rectal cancer were included. These criteria indicated that only the patients with the highest risk of loco-regional relapses were included; the R0 resection rate was selected as the main trial end point. During the patients' accrual, new data emerged demonstrating no benefit of oxaliplatin addition to preoperative chemoradiation. For this reason, the protocol of the trial was amended to postpone the use of oxaliplatin. Postoperative chemotherapy in both groups was optional, meaning that part of the perioperative treatment was delivered after surgery. For this reason, from the present-day perspective, such therapy cannot be accounted for as total neoadjuvant (TNT) because a substantial part of the systemic treatment was delivered after surgery in some patients. Recent literature refer to such protocols as TNT-like treatment [17]. The long-term outcome of this trial did not demonstrate the superiority of SCRT plus chemotherapy over LCRT-CT, although acute toxicity of the SCRT group was lower than in the control arm.

STELLAR (Jin 2022) [18] is a trial of similar design, SCRT was, however, followed by four courses of CAPOX. Two additional cycles of CAPOX (intravenous oxaliplatin [130 mg/m$^2$, once a day] on day 1 and capecitabine [1000 mg/m$^2$, twice a day] from days 1 to 14) were given in the TNT group, while six cycles of CAPOX were prescribed in the CRT group after surgery. Considering that a significant portion of systemic therapy was delivered after surgery, the proposed schedule should be accounted for as another example of TNT-like therapy. There was no significant difference in metastasis-free survival or locoregional recurrence, but the TNT-like group had better 3-year overall survival than the CRT group. The prevalence of acute grade III–V toxicities during preoperative treatment was 26.5% in the TNT-like group, *versus* 12.6% in the CRT group ($p < 0.001$), meaning that an improvement in OS was achieved at the expense of an approximately twofold increase in toxicity. Another criticism to this treatment schedule is that the origin of survival improvement in the TNT-like arm is unclear, considering that the therapy did not significantly reduce the rate of distant metastases, compared to standard treatment.

## Recent trials on total neoadjuvant therapy

As opposed to Polish [15, 16] and STELLAR trials [18], the RAPIDO trial (van der Valk 2020, Bahadoer 2021) [19, 20] took advantage of exploring a more intense neoadjuvant chemotherapy protocol (6 cycles of CAPOX, or 9 of FOLFOX4) that was given after SCRT (25 Gy in 5 fractions) in the experimental arm. Only patients diagnosed with rectal cancer, less than 16 cm from the anal verge, with a high-risk features on MRI were included. While the protocol allowed for 9 cycles of FOLFOX, most of the patients recruited received 6 cycles of CAPOX (capecitabine 1000 mg/m$^2$ twice daily on day 1–14; and oxaliplatin 130 mg/m$^2$ *i.v.* on day 1). From the present point of view, intensification of preoperative systemic therapy, as proposed in experimental arm of the RAPIDO trial appears crucial, considering that distant metastases are the most common site cause of treatment failure, and postoperative chemotherapy did not significantly improve the outcome.In the control arm of RAPIDO trial LCRT-CT (50–50.4 Gy in 25–28 fractions) with concomitant capecitabine followed by surgery and optional postoperative chemotherapy (8 cycles CAPOX or 12 cycles FOLFOX4) was used. According to the protocol, the overall treatment duration was 22–24 weeks in TNT, compared to 44–48 weeks in the control arm. The compliance to chemotherapy was considerably better in the experimental arm: 84% of patients in the TNT arm received at least 75% of the prescribed chemotherapy, compared to 58% of those who received postoperative chemotherapy in the control arm [19]. Disease-free survival in STELLAR was significantly improved in the experimental group (23.7% *vs.* 30.4%; HR = 0.75), mostly due to a significant reduction in the rate of distant metastases. There was, however, no significant improvement in overall survival [20].

It is worthwhile mentioning that similar outcomes were presented in non-randomized studies, including matched-pair analysis of SCRT and FOLFOX chemotherapy, compared to LCRT-CT (Markovina 2017) [21]. The meta-analyses of total neoadjuvant therapy (TNT) *versus* standard neoadjuvant chemoradiotherapy for locally advanced rectal cancer (Liu 2021, Kasi 2020, Petrelli 2020) [17, 22, 23], including randomized and non-randomized studies, consistently showed an improved tumour response rate, disease-free survival and tendency for improved overall survival in TNT and TNT-like protocols, as compared to standard treatment.

One of the alternative approaches to TNT with SCRT may be TNT with intense induction preoperative chemotherapy followed by LCRT-CT and surgery. Such a treatment schedule was explored in PRODIGE 23 trial (Conroy 2021) [24]. The patients in the experimental arm received neoadjuvant chemotherapy with FOLFIRINOX (oxaliplatin 85 mg/m$^2$, irinotecan 180 mg/m$^2$, leucovorin 400 mg/m$^2$, and fluorouracil 2400 mg/m$^2$ intravenously every 14 days for 6 cycles), chemoradiotherapy (50 Gy during 5 weeks and 800 mg/m$^2$ concurrent oral capecitabine twice daily 5 days per week), total mesorectal excision, and adjuvant chemotherapy (3 months of modified FOLFOX6 [intravenous oxaliplatin 85 mg/m$^2$ and leucovorin 400 mg/m$^2$, followed by intravenous 400 mg/m$^2$ fluorouracil bolus and then a continuous infusion at a dose of 2400 mg/m$^2$ over 46 h every 14 days for six cycles] or capecitabine [1250 mg/m$^2$ orally twice daily on days 1–14 every 21 days]). This experimental therapy improved the disease-free survival (76% *vs.* 69%; HR = 0.69) and complete response rate, compared to the control arm. A criticisms that might be raised of this protocol is that a substantial part of chemotherapy was given postoperatively. For this reason, the novel therapeutic protocol proposed in the PRODIGE 23 trial can be accounted for as TNT-like, and not "true" TNT treatment. Another criticism refers to the duration of the therapy: it takes at least 31 weeks to complete PRODIGE 23 protocol, compared to 22–24 weeks of therapy offered in the RAPIDO trial. An attempt to compare the studies of TNT with SCRT and LCRT-CT was provided in the Liu meta-analysis [17]. While such effort has several limitations, the only difference found was a higher tumour response rate in SCRT *vs.* LCRT-CT trials. Considering the long duration of PRODIGE treatment and the lack of apparent difference in effectiveness compared to the RAPIDO protocol, bearing in mind that only 32% of the patients in the experimental arm of the PRODIGE 23 trial were aged of ≥65 years, the practical utility of the proposed protocol raises some controversies, at least according to our opinion.

## Total neoadjuvant therapy and the potential for organ preservation

One of the outcomes that were significantly improved in the TNT arm of the STELLAR trial, as compared to the control arm, were pathological complete tumour responses

(28% *vs.* 14%, OR = 2.37). Notably, an improved rate of CT offers the potential opportunity for organ preservation. This issue is of rising interest, and is further explored in the other trials, specifically dedicated to explore this subject.

An example of such research is a large phase II OPRA trial (Garcia-Aguilar 2020) [25] in which induction preoperative chemotherapy was followed by radio-chemotherapy (INCT-CRT) or radio-chemotherapy was followed by preoperative consolidation chemotherapy (CRT-CNCT). Chemotherapy in both groups consisted of 4 months of infusional fluorouracil-leucovorin-oxaliplatin or capecitabine-oxaliplatin and conventionally fractionated radiotherapy (5000 to 5600 cGy) combined with either continuous infusion fluorouracil or capecitabine during the radiation course. Based on tumour response, the patients were offered either a total mesorectal excision (TME) or active follow-up (watch-and-wait). The three-year DFS MFS and OS were the same in the INCT-CRT and CRT-CNCT groups. The proportion of patients who actually preserved the rectum (TME-free survival) was, however, higher in the consolidation preoperative chemotherapy arm (CRT-CNCT), compared to the induction preoperative chemotherapy (INCT-CRT); the respective proportions were 60% *vs.* 47%, the difference was statistically significant.

The higher organ preservation rate in patients treated with CRT-CNCT compared with INCT-CRT is consistent with results of the other phase II trial (CAO/ARO/AIO-12) which reported a higher rate of pathologic complete response in patients with rectal cancer treated with CRT followed by three cycles of FOLFOX and TME, compared with patients treated with three cycles of FOLFOX followed by CRT and TME [26]. It has been hypothesised that the different time interval from the end of radio-chemotherapy to the assessment of response in INCT-CRT *vs.* CRT-CNCT may be considered a potential factor contributing to the difference in organ preservation between the groups [25].

## Future directions

Modern-day clinical oncology has been enjoying, over the last years, rapid expansion of novel therapies and of molecular biomarkers that are of indispensable value in the selection of optimal systemic therapy. Therapy for colorectal cancer is among the beneficiaries of this progress [27]. The selection of treatment schedule in metastatic colorectal cancer is now routinely based on KRAS, NRAS and BRAF mutational status. Anti-EGFR antibodies (cetuximab, panitumumab), VEGF inhibitors (bevacizumab, aflibercept) and the VEGFR tyrosine kinase inhibitor (regorafenib) are among the targeted drugs used in therapy for metastatic disease. The encorafenib and cetuximab combination was recently introduced for therapy of BRAF V600E mutated colorectal cancer based on results of the phase III BEACON trial [28]. Novel therapeutic targets and biomarkers of practical clinical importance include a common KRAS mutation and sotorasib, a small molecule that specifically and irreversibly inhibits KRAS [29]. Other, less common, targetable mutations of therapeutic importance in metastatic colorectal cancer include *NTRK1/2/3*, *ROS1*, *ALK* and *HER2*.

Among the greatest breakthroughs in systemic therapy for colorectal cancer are findings restricted to the relatively small subset (1–6%) of patients who harbour microsatellite instability (MSI): a molecular disorder typical for hereditary syndromes (e.g. Lynch syndrome) related to this disease. MSI is associated with impairment of the functions of the mismatch repair (MMR) genes that are encoding the proteins responsible for DNA repair. Several studies have demonstrated clinical activity of immune checkpoint inhibitors in MSI/MMR-deficient tumours, including colorectal cancer.

Pembrolizumab (PD-1 inhibitor) monotherapy appears to be more effective and better tolerated than chemotherapy in metastatic colorectal cancer patients with MSI, based on the results of phase III Keynote-177 study [30]. Likewise, nivolumab plus low-dose ipilimumab demonstrated very promising clinical activity and good tolerance as a first-line treatment for patients with metastatic colorectal cancer who harbour MSI [31].

While clinical oncology has rapidly implemented most of these innovations in clinical practice, particularly in metastatic patients, radiation oncology for rectal cancer seems to considerably lag behind, at least until recently. The first clinical attempts to combine preoperative radio-chemotherapy with immune checkpoint inhibitors in MSI/MMR-deficient colorectal cancer have, however, already been published, suggesting the promising safety and efficacy of such a combination [32].

One of the most stimulating recent findings, particularly considering the topic of the present article, is the outcome of a prospective phase 2 study in which single-agent dostarlimab – an anti-PD-1 monoclonal antibody – was administered every 3 weeks for 6 months in patients with mismatch repair-deficient stage II or III rectal adenocarcinoma [33]. Patients who had a complete clinical response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery (watch-and-wait policy). At progression after dostarlimab, chemoradiotherapy was to be used. Surgery would be restricted to those who did not have a complete response to chemoradiotherapy or who locally progressed after achieving a complete response. A total of 12 patients completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients had a clinical complete response, with no evidence of a tumour on the MRI, PET/CT, endoscopy, digital rectal examination, or biopsy. While a longer follow-up is needed to assess the duration of response to dostarlimab, and a prospective phase III trial would be needed to maturely assess the safety and efficacy of the proposed treatment, the outcome of this study confirms that MMR deficient, locally advanced rectal cancer is highly sensitive to single-agent PD-1 blockade. Also, it is increasingly recognized that the above-mentioned studies well designate

the future directions and strategies of highly individualized, biomarker-driven, neoadjuvant strategies for locally advanced rectal cancer [34].

## Conclusions

Short-course radiotherapy combined with 6 cycles of CAPOX may be considered, at present, as one of the best option for perioperative treatment of high-risk rectal cancer. The use of clinical and molecular predictive markers may help, in the future, to optimize such treatment and help to identify subgroups of patients who may benefit from TNT with SCRT with respect to overall survival, as well as those who may need a different treatment schedule.


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# Treatment of metastatic uveal melanoma

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Uveal melanoma is a rare malignancy with a poor prognosis. The risk of metastatic disease (mainly to the liver) exceeds 50% and is often observed many years after the primary treatment. The methods of local surgical treatment of metastatic lesions in the liver provide some chance for long-term survival but are possible in a small percentage of patients. The therapies currently used as a standard for cutaneous melanoma are not as effective in ocular melanoma. The first drug that prolongs the survival of patients is tebentafusp, but its applicability depends on the presence of HLA-A*02:01 expression.

**Key words:** uveal melanoma, local treatment, immunotherapy

## Introduction

Uveal melanoma (UM) is the most common primary neoplasm of the eye in adult patients [1–2]. Nevertheless, its occurrence is rare, and there are an estimated 2–11 cases per 1 million per year, with geographical differences [1–5]. UM differs from cutaneous and mucosal (including conjunctiva) melanoma; thus, the diagnostic and therapeutic approach is different [6].

Less than 3% of UM is present at the metastatic stage at primary diagnosis, and modern local treatment modalities offer high disease control rates [7–9]. Unfortunately, up to 70% of patients eventually develop metastases and will need systemic treatment [10, 11]. The recent advancement in the systemic treatment of metastatic cutaneous melanoma did not change the landscape of UM treatment; with median survival reaching 3 to 30 months in different studies and the 5-year survival rate under 20%, the necessity for improvement is evident [11–13].

This review discusses the monitoring and risk factors for metastatic disease development and current treatment approaches for metastatic uveal melanoma.

## Follow-up for metastases and risk factors

After initial treatment, the patient requires follow-up, which should be considered for local recurrence and distant metastasis' monitoring. Local monitoring is typically performed during clinical visits of 3 to 6 months during the first two years and 6 to 12 months after that. This monitoring can be performed using ultrasound, magnetic resonance imaging (MRI), gonioscopy, and optical coherence tomography (OCT), depending on the resources and the primary treatment modality [14]. The rate of local recurrences is low, occurring in less than 10% [15–18]. It is also noteworthy to state that there is no evidence of increased risk for melanoma in the contralateral eye [5, 19], or for that matter, cutaneous melanoma, either [20].

Patients with uveal melanoma need many years of monitoring, and the risk of metastases steadily rises during a 20-year observation across stages I to III [11, 21]. In the COMS studies, the 2-, 5- and 10-year metastasis rates were 10%, 25%, and 34%, respectively, in the study population [22].

There is no commonly adopted observation schedule after local treatment for the disease's spread. The evidence for su-

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rvival benefit in early detected (asymptomatic) metastases is not strong [23]. The patient's consent to undergo repetitive radiation-related tests should be obtained. The most important prognostic factor for metastases development is tumor size (based on AJCC TNM) [21]. Also, genetic information from the primary tumor can be informative: some known chromosomal abnormalities and several gene mutations are risk-related, separately or together [8]. A gene expression profile was proposed by Onken et al. [24]. The detailed description of clinical and genetic prognostic factors is summarized in table I [25–29]. Surveillance for high-risk patients should be made every 3 to 6 months during the first five years, then every 6 to 12 months until ten years, and yearly after that, although no evidence from prospective studies supports this [14]. Prospective studies have typically adopted a complete physical examination, chest X-ray, abdominal (liver) ultrasound, and liver function tests (LFTs) every six months [18, 22, 30, 31]. Other modalities commonly used in cancer patient monitoring have also been proven beneficial, although computed tomography (CT) and positron emission tomography/computed tomography (PET-CT) bear the risk of repetitive exposure to radiation; on the other hand, liver MRI has high sensitivity in detecting liver metastases in the early stage [32, 33]. LFTs are being debated [33–35], in the COMS study, the alkaline phosphatase (ALP), considered the most useful, has a sensitivity of only 14.7% at the time of final testing before the metastatic disease was revealed with imaging studies [22].

Liver metastases are the primary and most expected place of uveal melanoma spread in up to 90% of cases [36]. The rates of other sites are much lower; for the lungs, bones, skin, and lymph nodes, it varies – around 20%, 16%, 11%, and 10%, respectively. The rate of brain metastases is considered very low, under 5%; thus, no routine brain monitoring is indicated during the follow-up [22, 37, 38].

## Metastatic disease characteristics and workup

At the time of diagnosis of metastatic disease, a biopsy is encouraged. This material will confirm the diagnosis and serve for molecular findings, which may navigate the treatment choices and is often mandatory for enrollment in clinical trials. Chest to pelvis CT or full-body PET-CT may assess the spread of the disease if only liver involvement is suspected. Blood work is also routinely done. Early detection of the human leukocyte antigen (HLA) A*02:01 allele can benefit future decision-making.

Different negative prognostic factors for survival in stage IV were identified: older age, male sex, and poor performance status [13, 30, 31]. Also, elevated ALP and lactate dehydrogenase (LDH) are believed to be negative prognostic factors [13, 30, 39, 40]. The symptomatic patients also have a poorer prognosis, either those with a shorter time to progression and more disease burden [13, 30, 31]. Careful consideration of these prognostic factors helps to select who will benefit from treatment and who should only be offered supportive care.

Many treatment approaches for UM can be divided into local, i.e., liver-oriented and systemic methods. `Therapy selection should be based on the involved sites and the number of metastases: a small disease burden may result in complete response and more prolonged survival [40, 41]. Local modalities have led to longer median overall survival in clinical studies. That said, until now, the only UM-oriented treatment with FDA and EMA approvals is for a bispecific antibody – tebentafusp, which has shown meaningful survival benefits in a recently published clinical trial [42–44].

## Local treatment

Local treatment should be offered to patients with isolated liver involvement of UM. There are different methods used in this setting. The clear numerical benefit of prolonged overall survival observed in many studies of isolated hepatic metastases treatment may be partly related to patient selection bias [45–47]. Nevertheless, meaningful disease-free survival is observed in some patients when a complete response is obtained. Thus, the median overall survival (OS) in many trials exceeded 20 months and reached 35 months in one [45–47].

Surgical resection of metastases should be offered to patients with 1–2 lesions which are possible for R0 resection.

**Table I.** Known genetic alteration in uveal melanoma cells and their postulated prognostic role for disease spread and survival [24–29]

| Genetic alteration | Clinical information |
|---|---|
| Onken et al. class 2 gene expression profile: the assay includes 12 discriminating genes and is prognostic regardless of chromosome 3 status | 5 to 20 times higher risk of metastatic disease for class 2 |
| chromosome 3 disomy, chromosome 6p gain | better prognosis |
| chromosome 3 monosomy, chromosome 8q gain | increased risk of metastatic disease, risk rises when both are present |
| loss of chromosome 8p, loss of 1p, loss of 16q and loss of 6q | increased risk of metastases |
| gain of chromosome 6q (with the presence of chromosome 3 monosomy and chromosome 8q gain) | decreased risk of metastases in the presence of unfavorable genetic alterations |
| *EIF1AX* mutations | low risk of metastases |
| *SF3B1* mutations | medium risk of metastases |
| *BAP1* mutations or loss of BAP expression | high risk of metastases |
| preferentially expressed antigen in melanoma (PRAME) expression | increased risk of metastases |

In other cases, surgical techniques and local procedures should be considered [47].

Perfusion techniques are used to administer a high dose of a cytotoxic agent through the hepatic artery; during open surgery – isolated hepatic perfusion (IHP) or less invasive procedures – percutaneous hepatic perfusion (PHP) and hepatic arterial infusion (HAI) [41,47]. These methods result in moderate response rates (40–60%), with low rates of morbidity (<10%), and can be repeated if indicated [41, 47].

The embolization approach combines the use of cytotoxic agents (hepatic chemoembolization), immunotherapy (immunoembolization), or radiation techniques (transarterial radiation with yttrium-90) with the induction of ischemia [41, 48]. Multiple retrospective and prospective studies confirmed a high disease control rate after radioembolization (under 50%), even when used after previous local treatment failure [49–51].

The ablative procedures are used in complex tumors; they have low rates of complications, the most common being radiofrequency ablation (RFA) and microwave ablation (MWA). The ablation procedures offer modest efficacy, with survival time exceeding 20 months in most retrospective reports [52, 53].

When a complete response is achieved, patients can be offered adjuvant treatment in clinical trials. In all other cases, the observation algorithm remains similar to the high-risk patients after the primary treatment (discussed above).

## Systemic treatment

Many treatment approaches were tested for metastatic UM, including cytotoxic agents, targeted therapies, and immunotherapy. Small phase II and some phase III studies often delivered conflicting results. Thus, patients with advanced UM should be offered participation in clinical trials whenever possible.

Different cytotoxic agents can be used in monotherapy and combinations, most commonly dacarbazine (DTIC), paclitaxel, temozolomide, fotemustine, bendamustine, treosulfan, vincristine, arsenic trioxide, and lenalidomide [14]. Combination therapies often contain the platinum compound. Objective responses for monotherapy are rarely observed; the highest objective response rate (ORR) of 20% was demonstrated in a minor study of cisplatin/dacarbazine/vinblastine combination, with a median progression-free survival (PFS) of 5.5 months and OS of 13.0 months [54]. This need to be interpreted with caution because no other trial of cytotoxic agents, even in combinations, has failed to reach over 6% ORR [55–58]. Based on meta-analyses, chemotherapy results in ORR of around 4% with poor PFS of 2.6 months and median OS of 9 to 11 months [13, 59, 60]. In an interesting EORTC 10821 study, patients with isolated liver metastases were randomized to obtain local HAI or systemic treatment with fotemustine. The median OS was not different between the treatment arms (14.6 months *vs.* 13.8 months), and it seemed that the main factor for survival benefit was the disease burden and not the treatment itself [61].

Molecular alterations in UM cells are distinct from cutaneous melanoma, most notably KIT overexpression and GNAQ and GNA11 mutations resulting in MAP kinase activation [6, 62–64]. Many single-arm trials were conducted using targeted therapies, including imatinib (for KIT) [65–67], trametinib [68], and selumetinib (MEK inhibitors, the latter is not registered for use by FDA nor EMA) [69, 70], and many others. No meaningful benefit was demonstrated, and it is widely accepted that targeted therapies did not significantly improve survival over chemotherapy. The combination of chemotherapy and targeted agents also failed to achieve any PFS or OS prolongation [70–72].

Immunotherapy remains the best out of all poor options for metastatic UM. Although unlike cutaneous melanoma, no significant benefit was seen with single-agent anti-CTLA-4 antibodies ipilimumab and tremelimumab [73, 74], nor with single-agent anti-PD-1 antibodies nivolumab and pembrolizumab (ORR under 10%) [75–77]; some more hope was seen with the nivolumab/ipilimumab combination. Lately, breakthrough results of the phase III study of tebentafusp have been published [44].

As for the nivolumab/ipilimumab combination, one phase II study reported a median OS of 19.1 and median PFS of 5.5 months [78], which is numerically high compared to all past studies. Also, ORR was relatively high – 18%. These results were not repeated in the second nivolumab/ipilimumab trial, and further investigation is needed [79].

Tebentafusp, previously known as IMCgp100, was tested in a phase III randomized trial. Patients with HLA-A*02:01 expressing T-cells (about 45% of the screened population) were randomized 2:1 to receive tebentafusp or investigator choice treatment (monotherapy with pembrolizumab, ipilimumab, or DTIC). The study demonstrated a significant survival benefit at one year: 73% *vs.* 59%, which translated into a hazard ratio (HR) for death of 0.51 (95% CI: 0.37–0.71, $p < 0.001$). Median OS was prolonged from 16.0 months in the control arm to 21.7 months in the tebentafusp arm, despite a cross-over being allowed. It is also noteworthy that 43% of tebentafusp patients continued the treatment post-progression. A moderate benefit was also seen in median PFS prolongation from 2.9 to 3.3. Nevertheless, the ORR was relatively low, only 9% in the investigated arm. The toxicity profile was manageable, with no treatment-related deaths and only 2% of events that led to treatment discontinuation in the tebentafusp arm. Cytokine release syndrome, related to tebentafusp infusion, is prevalent during the first few cycles (occurs in more than 30% of patients); the injection needs to be monitored in the hospital [42–44].

## Conclusions

Local therapies should be considered the best option when suitable for metastatic UM, despite the efficacy not being confirmed in randomized trials. The recent approval of te-

bentafusp has impacted the treatment landscape of UM, but the requirement of HLA-A*02 positivity will limit its use. This orphan disease still has an inferior prognosis at the metastatic stage, and the need for new compounds is high.

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# Post-treatment follow-up in common solid malignancies: expert panel recommendations

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Post-treatment follow-up is an essential component of comprehensive cancer care. Determining optimal follow-up schedules is crucial on clinical, organisational and economic grounds. Owing to the scarcity of prospective clinical follow-up trials, most recommendations are based on retrospective studies and expert opinions. In 2014, the first post-treatment follow-up recommendations in the most common solid malignancies was published by Polish oncology and family medicine experts. In this article, we present an update of this document that takes into account the current literature and the quality of the available scientific evidence.

**Key words:** cancer, post-treatment follow-up, recommendations

## Introduction

Post-treatment follow-up is an essential part of comprehensive care for cancer patients. Its aim is to detect cancer relapse or secondary tumours, to allow early initiation of potentially effective retreatment, detection and treatment of late complications, psychological and social support, and assessment of late treatment outcomes. Other essential aspects of follow-up include physical and mental rehabilitation and reestablishment of the patient's social and familial roles. The most important objective of follow-up after palliative treatment is to provide

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the best possible quality of life. Follow-up after cancer therapy should be a reasonable compromise between the expectations of patients and their families and the actual value and cost of particular procedures.

Increasing public expectations, frequently combined with entitled attitudes, drive doctors to perform many unnecessary diagnostic procedures. Besides, the lack of unequivocal and widely accepted follow-up standards creates a gap in medical knowledge and exposes physicians to accusations of failure to maintain due diligence. In Poland, there have been no general or uniformly structured recommendations for cancer follow-up. This made it difficult for clinicians to conduct their daily practice, caused much arbitrariness and prohibited the development of clear financing rules.

Defining optimal follow-up schedules is not easy, as high-level evidence from prospective clinical trials for most malignancies is lacking. Even if such trials have been performed, the rapid progress of diagnostics and treatment does not allow the simple implementation of their results in contemporary clinical practice.

In 2014, the Polish Cancer Society developed national guidelines on post-treatment follow-up in the most common malignancies [1]. After eight years, it is necessary to update this document. The current version additionally describes the quality of the scientific evidence and the strength of particular recommendations (tab. I–II) [2].

**Table I.** Quality of scientific evidences

| Grade | Evidence quality |
|---|---|
| I | evidence from at least one large controlled randomised clinical trial (RCT) of high methodological quality (low risk of bias) or a meta-analysis of well-designed RCTs without significant heterogeneity |
| II | small RCTs or large RCTs at risk of bias (lower methodological quality), meta-analyses of such studies or RCTs with significant heterogeneity |
| III | prospective cohort studies |
| IV | retrospective cohort studies or case-control studies |
| V | studies without a control group, case reports or expert opinions |

**Table II.** Strength of recommendations

| Grade | Recommendation strength |
|---|---|
| 1 | recommendation based on high-quality evidence about which the expert team has reached unanimity or a high level of agreement |
| 2A | recommendation based on lower-quality evidence about which the expert team has reached unanimity or a high level of agreement |
| 2B | recommendation based on lower-quality evidence about which the expert team has reached a moderate level of agreement |
| 3 | recommendation based on any evidence about which the expert team has not reached agreement |

## Head and neck cancer

The risks of failure to cure or recurrence in early-stage and advanced head and neck cancer (HNC) are 20%–30% and 60%–70%, respectively [3]. Additionally, patients with HNC carry an increased risk (3%–5% per year) of developing a second independent cancer of the chest or upper gastrointestinal tract [4].

The leading cause of HNC is active exposure to tobacco smoke. The continuation of smoking after a cancer diagnosis significantly worsens treatment outcomes and increases the risk of secondary tobacco-dependent malignancies [5]. Hence, smoking addiction should be recorded at each follow-up visit, and continuing smokers, irrespective of the malignancy, should be provided with evidence-based cessation support [6].

After treatment, patients require close observation because early detection of relapse or progression increases the chance of effective salvage treatment. In patients with locoregional recurrence or radiotherapy-induced second head and neck cancer, the treatment of choice is salvage surgery or, less frequently, reirradiation. However, curative retreatment is possible in only about 20% of patients; others are managed with systemic palliative or symptomatic therapies [7].

An important aspect of follow-up after curative HNC treatment is the monitoring of late sequelae of disease and its treatment, potentially causing functional disorders and quality of life deterioration [8]. The first visit 2–3 months after the completion of treatment is crucial to assess its results. The frequency of subsequent follow-up visits and the type of diagnostics should consider the clinical situation (tab. III). Traditionally, a five-year active post-treatment follow-up has been practiced. However, although the risk of primary cancer progression after three years is relatively low, a proportion of HNC patients will develop a second primary cancer of the respiratory or upper gastrointestinal tract. Hence, the follow-up should extend beyond five years [9]. It should include detailed physical examination, upper respiratory tract endoscopy and evaluation of the patient's general condition. Assessment of treatment outcome usually necessitates computed tomography (CT) or, preferably, magnetic resonance imaging (MRI) of the head and neck 2–3 months after treatment completion. Thereafter, these studies are reasonable only for patients with symptoms or abnormalities in physical examinations.

Follow-up visits usually include an annual chest X-ray (CXR) or chest CT, although their usefulness in asymptomatic patients has not been proven [10]. Continued tobacco smokers, apart from cessation support, should undergo annual chest CT. Other imaging is reasonable only in case of symptoms or suspicion of cancer recurrence. In metastatic disease, curative treatment is rarely possible, and most patients are managed with palliative or symptomatic treatment. Detection of a second independent malignancy, e.g. lung cancer, requires the implementation of a new therapy, taking into consideration the tumour stage and general condition of the patient. There is no clinical use of tumour markers in HNC [11]. It is also unreasonable to regularly perform labora-

**Table III.** Recommended follow-up schedules for head and neck cancers (IV, 2B/3)

| Treatment intent | Examinations | Frequency | Comments |
|---|---|---|---|
| curative | interview and physical examination with upper respiratory tract endoscopy | every 1–2 months for the first 6 months, every 2–3 months for the next 6 months, every 4 months in the 2nd year, every 6 months in years 3–5, then annually | necessary histopathological verification of all lesions suspected of tumour recurrence or progression TSH[a] every 6–12 months in patients irradiated in the thyroid area |
| | head and neck CT or MRI | 2–3 months after treatment completion, then only in patients with symptoms or physical signs | cessation support and chest CT annually in smoking patients |
| | CXR | annually | |
| | neck USG with fine needle biopsy of suspicious nodes | in patients with signs of lymph node recurrence | |
| palliative treatment | interview and physical exam | 1–2 months after treatment completion, then depending on the occurrence and severity of symptoms | observation and treatment by a palliative care team |
| | laboratory tests and imaging | as per individual indications | mainly to explain the causes of persistent complaints (especially pain) |

[a] – TSH (*thyroid-stimulating hormone*) – thyrotropic hormone; USG – ultrasonography; CXR – chest X-ray

tory tests, except for thyroid function assessments in patients who underwent neck irradiation [9].

The consequences of radical surgery, apart from permanent, sometimes unavoidable complications, usually appear already in the postoperative period and decrease over time. However, late radiotherapy sequelae are difficult to reverse and may increase. Assessment of radiation reactions should particularly include a consideration of the patient's treatment history and evaluation of the irradiated area. The cumulative doses of cytotoxic drugs used concomitantly with radiotherapy are generally low; therefore, the risk of late toxicity after chemotherapy is relatively small.

The most important aim of follow-up in patients receiving palliative treatment is to maintain the best possible quality of life. To this end, patients' complaints should be carefully assessed and, if necessary, promptly managed. Imaging is used in particular situations – for example, to determine the cause of symptoms.

In HNC, there have been no high-quality prospective cohort studies or randomised controlled trials; therefore, follow-up schedules generally reflect the practices of individual centres and expert opinions. Since this group of malignancies is heterogeneous, their management should consider the individual patient's situation [10, 11].

## Central nervous system malignancies

The largest group of primary central nervous system (CNS) malignancies are gliomas. In the new WHO classification published in 2021, an important role in determining individual types and grades of gliomas was attributed to molecular aberrations, such as isocitrate dehydrogenase mutations (favourable prognosis), 1p/19q co-deletions (favourable prognosis) or CDKN2A/B deletions (unfavourable prognosis) [12]. Grade 2 gliomas include astrocytomas, oligodendrogliomas and mixed gliomas; the Grade 3 group consists of astrocytomas or anaplastic oligodendromas, and Grade 4 includes glioblastoma.

Follow-up schemes for patients with gliomas after curative treatment depend on the WHO grade (tab. IV). There is no evidence that regular follow-up improves prognosis in this group [13]. Generally accepted follow-up in malignant brain tumours includes regular visits in the treating centre, with assessment of neurological status and repeated MRI (V, 2B) [14]. Early diagnosis of limited recurrence or tumour progression allows in some patients secondary resection or radiotherapy. The frequency of imaging examinations depends on the histological tumour type, grade, molecular features and prognosis [15]. Notably, Grade 2 and 3 gliomas with favourable prognosis may undergo histological transformation and may progress even several years after primary treatment.

Early imaging of glioblastoma after neurosurgery and chemoradiotherapy may cause difficulties due to 'pseudo-progression', i.e., radiological post-treatment changes simulating cancer progression. Pseudo-progression usually occurs within a few months after treatment. Useful techniques for differentiating between pseudo-progression and genuine progression include diffusion and perfusion imaging, MRI spectroscopy [16] and positron emission tomography with computed tomography (PET-CT) using labelled tyrosine, choline, thymidine or methionine [16].

The second most common CNS malignancies are meningiomas. They are often detected incidentally and in asymptomatic patients, the preferred option is observation with periodical contrast-enhanced MRI. The post-treatment follow-up for a meningioma is long lasting and tailored to individual

**Table IV.** Recommended follow-up schedules for brain malignancies

| Malignancy | Examinations | Frequency | Comments |
|---|---|---|---|
| grade 2 and 3 gliomas | interview and physical examination | every 3–6 months for 5 years, then every 6–12 months | glucocorticoids should be discontinued in a dose-reduced manner as soon as possible after treatment |
| | laboratory tests | according to clinical indications (e.g. monitoring of chemotherapy toxicity or anti-epileptic drugs) | |
| | | MRI every 3–6 months for 5 years, then every 6–12 months | |
| grade 4 gliomas | interview and physical examination | every 3–4 months for 2–3 years, then less frequently | |
| | laboratory tests | according to clinical indications (e.g. monitoring of chemotherapy toxicity, glucocorticosteroids or anti-epileptic drugs) | |
| | | MRI every 2–6 weeks after completion of radiotherapy, then every 3–4 months for 2–3 years, and then less frequently | |
| meningiomas | interview and physical examination | at 6 and 12 months post-treatment, every 6–12 months for 5 years and then every 2–3 years | follow up intensity considering recurrence risk |
| | laboratory tests | as clinically indicated | |
| | imaging | MRI scheme as detailed above | |

patient's situation. In patients after surgery, the primary goal is to detect early tumour recurrence or progression. Within five years, this occurs rarely in patients after Simpson 0 surgery (total tumour resection with a margin of 2–3 cm) and in up to 80%–100% of patients after the Simpson 5 surgery (tumour biopsy). Early detection of the recurrence or progression of an unresected or irradiated tumour in many patients allows for salvage treatment. After definitive radiotherapy, an important goal of follow-up is to detect new neurological symptoms, which can be either treatment complications or tumour relapses. The mainstay of follow-up is contrast-enhanced MRI performed 3–6 months after treatment completion, every 6–12 months for five years and then every 2–3 years (V, 2B). However, there is no evidence that follow-up imaging alters therapeutic decisions in asymptomatic patients [17]. The intensity of follow-up should be adjusted to the risk of progression, age and comorbidities [18]. Because meningioma recurrences may occur even beyond ten years, the duration of observation is difficult to determine.

Similar recommendations apply to patients with less common and benign CNS malignancies. Therefore, post-treatment follow-up for CNS malignancies should be conducted in the treating centre that has access to the documentation, including the radiotherapy plan. The frequency of follow-up visits should consider the patient's situation, initial treatment outcome, tumour location and histology.

## Thoracic malignancies

Follow-up in patients with primary thoracic malignancies (lung cancer, carcinoids, pleural mesothelioma and thymic malignancies) aims to detect recurrence and manage treatment-related complications [19]. Its most important aspect is tobacco prevention and the provision of cessation support [5, 20]. Follow-up in lung cancer patients should also include a search for secondary smoking-related tumours [20].

Due to the scarcity of controlled clinical trials, recommendations for primary thoracic malignancies are based on relatively weak scientific evidence. Follow-up schedules depend on the aim of primary treatment. In patients treated with curative intent, observation should be based on structured schedules, whereas in patients treated palliatively, the type and frequency of follow-up examinations depend on the individual clinical situation; in both cases, there is no reason to actively search for asymptomatic extrathoracic disease [19, 21].

### *Non-small cell lung cancer*

Most non-small cell lung cancer (NSCLC) recurrences after complete pulmonary resection with or without adjuvant chemotherapy or radiotherapy occur within the first two years, which justifies more intensive follow-up during this period [20, 22] (tab. V). A standard component of follow-up after curative surgery is contrast-enhanced chest CT (II, A). CT allows detection of recurrence or secondary thoracic malignancy earlier than CRX, but its impact on survival is questionable [19, 21, 23–26]. Performing CT more often than every six months does not improve treatment outcomes [27]. After two years, depending on the recurrence risk, follow-up with low-dose, non-contrast-enhanced CT may be considered. There is no evidence based reason to perform PET-CT as a part of follow-up after curative treatment. Follow-up schedules after definitive chemoradiotherapy follow the same principles and are the extrapolation of schedules used in surgically treated patients (IV, 2A).

**Table V.** Recommended follow-up schedules for thoracic malignancies

| Malignancy and treatment intent | Examinations | Frequency | Comments |
|---|---|---|---|
| **NSCLC** | | | |
| curative intent | interview and physical examination (considering symptoms suggesting cancer recurrence and treatment complications) | every 3 months for the first 2 years, then every 6 months or as clinically indicated | follow-up based on electronically reported symptoms may be more effective; no reason to search for asymptomatic extrathoracic disease; increased CT frequency in cases with residual disease |
| | contrast-enhanced chest CT | every 6 months for the first 2 years, then annually[a] | |
| palliative intent | based on the individual clinical situation | | follow-up based on electronically reported symptoms may be more effective |
| **SCLC** | | | |
| stage I–III | as in NSCLC after curative treatment | | |
| stage IV | as in advanced NSCLC | | |
| **carcinoids** | as in lung cancer, depending on the treatment intent | | |
| **pleural mesothelioma** | as in lung cancer, depending on treatment intent | | |
| **thymic malignancies** | | | |
| stage I–II, curative treatment | interview and physical examination | every 3 months | |
| | chest CT | after 3 months, then annually | |
| stage III–IV | chest CT | every 6 months for 2 years, then annually | |

NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; [a] – after two years, consider further follow-up with low-dose CT

The follow-up of NSCLC patients after palliative treatment depends on the individual clinical situation. The type and frequency of check-ups should mainly consider possible treatment options. Most important are interviews and physical examinations performed every three months and, in patients who respond to treatment, imaging (mainly CRX and, in doubtful situations, CT) (III, 2A). A randomised controlled trial showed that follow-up based on symptoms reported electronically by patients allows for earlier detection of tumour progression, provides more treatment possibilities and prolongs overall survival compared to the traditional system [28].

Longer survival of NSCLC patients associated with the widespread use of molecular targeted therapies and immunotherapy justifies a more active observation of selected patients. Monitoring of specific complications is also essential (e.g. early and late toxicity of immune checkpoint inhibitors).

### *Small cell lung cancer*

Follow-up in stage I–III small cell lung cancer (SCLC) patients is similar to that recommended for NSCLC after curative treatment (tab. V). However, these recommendations are based only on the results of observational studies (III, B). The follow-up benefits may apply particularly to patients with a complete response after chemoradiotherapy, fit and without persistent complications, who might benefit from salvage treatments [29].

Follow-up in stage IV SCLC is similar to that in advanced NSCLC (III, B). In patients who did not receive elective brain irradiation as part of their primary treatment, brain MRI may be considered every three months in the first year and then every six months [30] (I, 2A).

### *Carcinoids*

Follow-up of patients with respiratory carcinoids is similar to that in lung cancer (IV, 2A), depending on the histological type (typical or atypical carcinoids) and treatment intent (curative or palliative) [31].

### *Pleural mesothelioma*

Depending on the treatment intent (curative or palliative), follow-up of patients with pleural mesothelioma includes an interview, physical examination and chest CT (IV, 2A) [32].

### *Thymic malignancies*

Follow-up in stage I and II thymomas undergoing curative treatment includes an interview, physical examination (every three months) and chest CT (after three months and then annually). For more advanced thymomas, imaging should be performed every six months for two years and then annually (IV, B) [33].

## Gastrointestinal malignancies

Follow-up after curative treatment of gastrointestinal (GI) malignancies generally lasts for five years (tab. VI). However, follow-up schedules are based on recommendations of scientific societies, expert opinions and clinical practice, and not on randomised clinical trials. Therefore, the quality of scientific evidence and the strength of the recommendations for all items listed in table VI should be set at V, 2A at best. Notably, no improved prognosis associated with regular follow-up has been demonstrated at any GI malignancy. This indicates the need for individualisation of follow-up procedures that accounts for the risk of recurrence, organisational conditions and patient expectations.

The management of patients with colorectal cancer (CRC) needs more extensive discussion, mainly due to results of randomised trials and the established role of surgery in metastatic disease. CRC is characterised by a high incidence of relapses potentially eligible for curative treatment (limited hepatic spread and local recurrences). This suggests that regular follow-up (in particular, imaging) of patients after curative treatment may translate into earlier detection of relapse, increasing the use of salvage surgery and improving prognosis.

The results of consecutive meta-analyses of randomised controlled trials published in the Cochrane database, which evaluated the value of intensive regular observation compared to so-called minimal observation in CRC patients after local curative treatment, led to surprising conclusions. Reviews published in 2002 and 2007 indicated that regular follow-up and additional check-ups were associated with lower overall mortality but did not significantly impact cancer-related mortality. This was attributed, among other causes, to the positive impact of intensive follow-up on more effective general health awareness, more frequent detection and treatment of late adverse symptoms and more effective detection and treatment of comorbidities, including secondary malignancies. The prolongation of overall survival has historically provided strong argument in favour of intensive surveillance in CRC patients. However, the heterogeneity of the studies included in the meta-analysis did not allow for defining the optimal pattern and duration of follow-up. However, since 2016, updates to this publication, including additional studies, have not confirmed the benefit of intensive follow-up. The latest Cochrane meta-analysis of 16 clinical trials, including 15 (with over 12,500 patients) with an analysis of overall survival, was published in 2019 [34]. As in previous publications, patients undergoing more intensive follow-up were subjected almost twice more often to salvage surgery and interval relapses (i.e. those diagnosed due to symptoms between scheduled follow-up visits) occurred almost twice less frequently. Nevertheless, the hazard ratio (HR) of death in patients undergoing more intensive follow-up was 0.91 (95% CI: 0.80–1.04) compared to minimal follow-up, which proves with the highest degree of scientific credibility that it does not significantly reduce overall mortality. As before, there was also no reduction in CRC-related mortality (HR 0.93, 95% CI: 0.81–1.07). None of the evaluated interventions: more frequent follow-up, carcinoembryonic antigen (CEA) monitoring and imaging had any effect on overall survival compared to their absence. Despite such strong evidence, the latest recommendations of scientific societies have not changed significantly.

Some light on the type of follow-up that has an impact on the frequency of surgery at relapse may be shed by the results of a prospective randomised study FACS (follow-up after colorectal surgery) published in 2014 [35]. This study included 1,202 CRC patients who had undergone curative treatment, and compared four follow-up strategies:

1. monitoring of serum CEA every three months for two years and then every six months for three years,
2. performing CT of the abdomen, pelvis and chest every six months for two years and then annually for three years,
3. CEA monitoring and CT imaging combined,
4. minimal observation, during which tests were performed only in the case of symptoms.

In groups 1 and 4, a single CT scan of the abdomen, pelvis and chest between 12$^{th}$ and 18$^{th}$ month of follow-up was possible at the physician's request as expressed at the study outset. In all patients, colonoscopy was performed at one year and repeated after five years; in patients from groups 2 and 3, colonoscopy was also performed after two years. After almost five years, the incidence of salvage surgery for relapses was higher in groups 1–3 compared to group 4 (6.7%, 8% and 6.7% *vs.* 2.3%, respectively); however, there was no significant difference in mortality. The results of this study contradict the recommendations for intensive surveillance and, in particular, for combining regular imaging with CEA monitoring. Most likely, a single CT scan between 12$^{th}$ and 18$^{th}$ month combined with CEA monitoring every three months for two years and then every six months for three years can well replace multiple CT imaging.

However, the results of the FACS study have been ignored, and the European Society for Medical Oncology, United States National Comprehensive Cancer Network and American Society of Clinical Oncology all recommend performing both regular CEA and imaging in CRC patients, which is reflected in the current document (tab. VI) [36–40].

## Breast cancer

The main aims of post-treatment follow-up in breast cancer include early detection of local and regional recurrence and secondary cancers, managing late complications (e.g. related to

**Table VI.** Recommended follow-up schedules for gastrointestinal malignancies (V, 2A)

| Cancer | Examinations | Frequency | Comments |
|---|---|---|---|
| oesophageal cancer | interview and physical examination | every 3–6 months for 2 years, then annually | patients eligible for curative treatment of local recurrence (e.g. after chemoradiotherapy) may benefit from regular endoscopy and imaging; in other patients, the follow-up should primarily be focused on treatment complications and nutritional status |
| | laboratory tests, imaging and endoscopy | as indicated clinically | |
| gastric cancer | interview and physical examination, blood counts | every 3–6 months for 2 years, then annually | assessment should evaluate treatment consequences, including nutritional status; vitamin $B_{12}$ deficiencies should be supplemented |
| | other laboratory tests, imaging and endoscopy | as indicated clinically | |
| pancreatic cancer | interview and physical examination | every 3–6 months for 2 years, then annually | mainly for diagnosis and consequences of curative treatment (e.g. diabetes, pancreatic enzyme deficiency) |
| | laboratory tests and imaging | as indicated clinically | |
| liver cancer | interview and physical examination, liver function tests, CT or MRI of the abdomen | every 3–6 months for 2 years, then every 6–12 months | regular imaging is reasonable, as it frequently allows for salvage local treatment of recurrent disease. Hepatic function should be assessed in all patients. Patients who underwent liver transplant due to immunosuppressive therapy should be observed in transplantation centres |
| cholangiocarcinoma | interview and physical examination | every 3–6 months for 2 years, then every 6–12 months | ESMO[a] recommends regular laboratory tests and imaging |
| | laboratory tests (including CA 19.9 in patients with baseline elevated concentration) and imaging | as indicated clinically | |
| colon cancer | interview and physical examination | every 3–6 months for 3 years, then every 6–12 months for 2 years | possible modifications considering the risk of relapse. Controversies are presented in the text |
| | laboratory tests, imaging and colonoscopy | serum CEA[b] every 3–6 months for 3 years, then every 6–12 months for 2 years; CT of the abdomen, pelvis and chest every 6–12 months for 3 years, then annually for 2 years; colonoscopy[c] at 1 year, then every 3–5 years; other imaging (including PET-CT) – as clinically indicated | |
| rectal cancer | interview and physical examination | every 3–6 months for 3 years, then every 6–12 months for 2 years | possible modifications considering the risk of relapse. Controversies are presented in the text. The value of intensive follow-up is even more controversial than in colon cancer, as local recurrence is more frequently accompanied by clinical symptoms; in patients undergoing endoscopic surgery or managed without surgery after complete clinical remission following induction chemoradiotherapy, close endoscopic and imaging supervision is carried out in specialised centres |
| | laboratory tests, imaging and colonoscopy | serum CEA[b] every 3–6 months for 3 years, then every 6–12 months for 2 years; CT scan of the abdomen, pelvis (or MRI of the pelvis) and chest every 6–12 months for 3 years, then annually for 2 years; colonoscopy[c] at 3–5 years; other examinations (including PET-CT) – as clinically indicated | |
| anal cancer | interview and physical examination | first assessment 2 months after chemoradiotherapy completion, then every 3 months for 3 years and every 6 months for the next 2 years (always including *per rectum* examination); in women, annual cytological examination of cervical swab | finding a residual tumour on the first follow-up visit does not allow for a diagnosis of treatment failure |
| | laboratory tests and imaging | as indicated clinically | |

[a] – European Society for Medical Oncology; [b] – *carcinoembryonic antigen;* [c] – if a full colonoscopy was not performed prior to curative treatment, it should be performed within a few months after the surgery to detect possible synchronous tumours

early menopause or osteoporosis), psychological and social counselling (including recommendations of physical activity and maintenance of proper body weight), and the assessment of late treatment results. The active search for asymptomatic distant metastases is less important because detecting them through more intensive follow-up does not significantly impact on overall survival and quality of life (I, 1) [41–44].

The effectiveness of follow-up performed by oncology specialists and trained primary care physicians is comparable (I, 1) [41, 42, 45, 46]. Breast cancer relapses may occur even after many years, but their risk gradually decreases, whereas other ageing-associated health problems arise. Hence, after the period of greatest risk recurrence, the preferred option is a more comprehensive follow-up provided by a primary care physician [41, 42, 45].

Follow-up schemes for stage I–III ductal in situ and invasive breast cancer are presented in Tab. VII [47]. Follow-up visits are recommended every 3–4 months for the first two years, every 6–8 months between third and fifth year and then annually (II, 2A). This scheme has been developed empirically, as no prospective studies have defined the optimal frequency of follow-up in the entire breast cancer population and particular subgroups [41–44, 46, 48].

The most important elements in relapse detection are interview and physical examination [47]. The follow-up should also include the assessment of the patient's mental condition and the presence of endocrine symptoms (hot flushes, dyspareunia, vaginal dryness or sexual disorders). The only recommended imaging is annual mammography (MMG) (II, 2A), which, regardless of the patient's age, has been demonstrated to reduce breast cancer mortality [41–44, 48, 49]. In patients treated with breast-conserving approaches, the first MMG should be performed six months after the completion of postoperative radiotherapy. There is no indication for routine breast ultrasonography (USG) or MRI; both are reasonable only if MMG imaging proves difficult [50, 51]. MMG is of limited value and is not recommended in patients who have undergone breast reconstruction using endoprostheses. In these patients, a physical examination supplemented by MRI is more accurate in diagnosing recurrence in the subcutaneous tissue or chest muscles [52].

Laboratory tests (blood count or biochemistry), serum tumour markers (CA15-3, CA27.29 or CEA) or imaging other than MMG (e.g. USG, CXR, CT, MRI, PET or bone scintigraphy), do not impact survival and are not recommended in asymptomatic patients (I, 2A) [41–44]. Patients with preserved uterus who receive adjuvant tamoxifen have an increased risk of endometrial cancer, which justifies an annual gynaecological examination (I, 1) [41–43, 53]. The frequency of these examinations can be reduced in patients after hysterectomy and ovariectomy. There is no evidence justifying routine intravaginal USG [41–43].

Postmenopausal patients (following natural and pharmacologically or surgically induced menopause), particularly those receiving aromatase inhibitors, have an increased risk of osteoporosis [41, 42, 54, 55]. A higher risk of skeletal events also applies to patients over 65 years, with osteoporosis or a family history of osteoporosis, with a body mass index <18 kg $m^2$, with a history of smoking, alcohol abuse or low physical activity [56]. Therefore, regular densitometric evaluation of bone density and supplementation with calcium and vitamin D3 (I, 1) are recommended in these groups.

Patients with HER2-positive breast cancer after adjuvant trastuzumab treatment who have no symptoms of drug-related cardiotoxicity do not necessitate regular echography or electrocardiography (I, 1) [41–43].

In patients with a family history of cancer, genetic testing for hereditary *BRCA* mutations should be considered if not performed earlier. Patients should be encouraged to exercise (for at least four hours a week), avoid alcohol and smoking (II, 2A), and follow an appropriate diet to maintain a body mass index in the range of 20–25 (II, 2A) [57, 58].

Pregnancy after breast cancer treatment does not increase the risk of recurrence. The safe interval between treatment completion and pregnancy has not been established. Pregnancy is contraindicated during adjuvant endocrine treatment. Pregnancy should be prevented using mechanical measures (condoms or intrauterine devices), as there are scarce data on the safety of hormonal contraception in breast cancer survivors. Hormonal replacement therapy (HRT) containing oestrogen and progesterone increases the risk of tumour recurrence and is contraindicated (I, 1) [59]. The safety of oestrogen-only HRT requires further research [60]. In patients with dyspareunia or other vaginal menopausal symptoms, oestrogens applied in the form of creams or vaginal tablets may be considered, but the impact of such treatment on the risk of recurrence is unclear [61–64].

There are no standard follow-up schedules for disseminated breast cancer. It is reasonable to adjust them to cancer location, symptoms and general patient condition.

## Gynaecological malignancies

Data from prospective studies assessing the impact of follow-up on the survival of patients with gynaecological malignancies are scarce, and recommendations are based mainly on literature reviews and expert opinions [65–68]. In this group, a necessary component of post-treatment follow-up is gynaecological examination. In Poland, this examination is not routinely performed by general practitioners (GP), therefore, follow-up is carried out mainly by gynaecologists or oncologists. The follow-up of patients who underwent radiotherapy should involve a radiation oncologist, due to the possibility of late radiation reactions and increased risk of secondary malignancies. Follow-up of less common gynaecological ma-

**Table VII.** Follow-up of breast cancer patients after curative treatment, as recommended by the Polish Society of Clinical Oncology [47]

| Examinations | Frequency | Quality, strength |
|---|---|---|
| self-examination | monthly | III, 1 |
| physical examination | every 3–4 months for 2 years[a], every 6–8 months at years 3–5, then annually | III, 1 |
| mammography[b] | annually; in patients who have undergone breast-conserving treatment, first examination after 6 months | I, 1 |
| gynaecological examination | annually in women with preserved uteruses treated with tamoxifen[c] | III, 2B |
| laboratory tests and imaging | only as clinically indicated | V, 3 |
| densitometry[d] | every 12–24 months | III, 2B |
| body mass | recommended maintenance of body mass index in the range of 20–25 | III, 2A |

[a] – in ductal *in situ* cancer, follow-up every 6 months for the first 2 years, then annually; [b] – MRI to be considered in carriers of *BRCA* mutations; [c] – no indications for intra-vaginal USG and endometrial biopsy in patients without genital symptoms; [d] – applies to patients at high risk of osteoporosis associated with aromatase inhibitor treatment or ovarian suppression

lignancies (uterine sarcomas, nonepithelial ovarian tumours, trophoblastic disease) should be carried out in specialised centres, and for patients managed with organ-sparing surgery, in the centre that provided the treatment.

The gynaecological examination should include a visual assessment of the perineum and vulva, a speculum assessment of the vagina and cervix, a two-handed vaginal examination, a rectal examination and an assessment of peripheral lymph nodes (tab. VIII). Transvaginal ultrasound, often performed in Poland, is not a part of international follow-up recommendations [65–67, 69–71], and the Society of Gynaecologic Oncologists even discourages its use [65].

Recurrences of gynaecological malignancies are most often detected by clinical symptoms or physical examinations. Therefore, it is essential to educate patients about recurrence symptoms and to explain the unreasonableness of imaging and laboratory tests in the absence of symptoms.

For low-risk gynaecological cancers, the British Gynaecological Cancer Society recommends on-telephone nurse follow-up supplemented by in-person patient visits in the event of symptoms (so-called 'patient-initiated follow-up') [72].

### *Endometrial cancer*

Recurrences may affect 2%–15% of stage I endometrial cancer patients and up to 50% of patients with higher stages or unfavourable histologies [65]. Approximately 70%–100% of recurrences occur within the first three years [65, 71, 73]. In about half of patients, recurrence is accompanied by clinical symptoms, whereas in asymptomatic patients, physical examination detects 35%–70% of recurrences [65]. More than 80% of recurrences are accompanied by clinical symptoms or abnormalities in physical examination [65]. A prospective study comparing less and more intensive follow-up, even in patients with increased recurrence risk, did not demonstrate increased survival with more intensive follow-up, including additional examinations [74]. Cytology, CXR and CA125 monitoring, as well as intravaginal USG are not recommended in asymptomatic patients [65]. Imaging, such as CT, MRI or PET-CT, is used to verify possible recurrence and to select treatment in recurring patients [65, 71].

### *Cervical cancer*

Approximately 75% of cervical cancer recurrences occur within the first 2–3 years after treatment completion [75]. Typical symptoms of recurrence include abdominal or pelvic pain, vaginal bleeding or pain, lymphatic leg oedema, urinary symptoms, cough and weight loss. Only 26%–36% of relapses are detected at follow-up visits. Physical examination, including vaginal and rectal examination, allows the detection of asymptomatic recurrences in 29%–75% of cases [76]. Cytology may mainly detect new vaginal lesions and should be performed annually (tab. VIII). Cytology abnormalities always necessitate colposcopy and biopsy, however, only 0%–17% of relapses are diagnosed with this method [75, 76]. Cytology is less useful after radiotherapy [75].

An annual CXR is not recommended [65, 67, 69, 75] and, like other imaging methods (CT, MR and PET-CT), is indicated only in patients with symptoms or physical signs [77]. The value of transvaginal USG is questionable. Measurement of squamous cell carcinoma antigens is not recommended. Since almost 40% of patients come for unplanned follow-up visits due to worrying symptoms, they should be educated about recurrence symptoms [75]. In patients who have undergone a trachelectomy (a uterus-saving procedure) follow-up should be performed at the traeting institution.

### *Vulvar cancer*

Recurrence usually occurs within the first two years after treatment, more often in patients with lymph node metastases. Beyond 24 months after treatment completion, the risk of re-

**Table VIII.** Recommended follow-up schedules in cervical and endometrial cancer (IV, 2B), vulvar cancer (V, 2B), vaginal cancer (V, 2B) and ovarian, fallopian tube and primary peritoneal cancer (IV, 2B)

| Cancer | Examinations[a] | Frequency |
|---|---|---|
| **endometrial cancer** | | |
| FIGO[b] stage IA G1/G2 (endometrioid type) | interview and physical examination with gynaecological and *per rectum* examination; optionally, transvaginal USG | every 6 months in the first year, every 6–12 months in the 2nd year, then annually |
| FIGO[b] stages IA G3, IB–II (endometrioid type) | as above | every 3 months in the first year, every 6 months until 5 years, then annually |
| FIGO[b] stages III–IV and all stages for non-endometrial cancers | as above | every 3 months for 2 years, every 6 months until 5 years, then annually |
| **cervical cancer** | | |
| low recurrence risk: IA, patients treated with surgery alone | interview and physical examination, gynaecological and *per rectum* examination | every 6 months for 2 years, annually until 5 years, then standard care, as in the general population |
| | cytology | annually |
| | imaging | only if clinically indicated |
| increased risk of recurrence: patients treated with postoperative adjuvant treatment or undergoing radio(chemo)therapy | interview and physical examination with gynaecological and *per rectum* examination | every 3 months for 2 years, annually until 5 years, then standard care, as in the general population |
| | imaging | only if clinically indicated |
| **vaginal and vulvar cancer** | | |
| FIGO[b] stages I–IV | interview and physical examination, gynaecological and *per rectum* examination; in patients with vulvar cancer, particularly careful macroscopic assessment of the vulva, perineum and groin (optionally vulvoscopy) | every 3 months for 2 years, every 6 months until 5 years, then annually |
| **ovarian, fallopian tube and primary peritoneal cancer** | | |
| FiGO[b] stage I–IV | interview and physical examination with gynaecological and *per rectum* examination, transvaginal USG | every 3 months for 2 years, every 3–6 months in the 3rd year, every 6 months until 5 years, and then annually |
| | CA125 | upon discussion with the patient, together with examination |
| | imaging | only if clinically indicated |
| | recommended genetic consultation | at the time of initiation of follow-up or onset of a new malignancy in the family |
| **borderline malignancy ovarian tumours** | | |
| FiGO[b] stage I–IV | as in ovarian cancer | every 6 months until 5 years, then annually |
| FIGO[b] stage I with reproductive organ preservation (after adnexectomy or ovariectomy) | consider also hysterectomy and contralateral adnexectomy | after the end of reproduction |
| **ovarian germ-cell tumours** | | |
| I. dysgerminoma | as in ovarian cancer | every 3 months for 2 years, then annually |
| II. non-dysgerminoma | | |
| 1. yolk sac tumour | physical examination, AFP[c], HCG[d], LDH[e] | every 3 months for 2 years |
| 2. immature/malignant teratoma | imaging | only if clinically indicated and with increased marker levels, more often for the first 2 years in cases with normal marker levels during initial treatment |
| 3. germ-cell carcinoma | | |
| 4. non-gestational choriocarcinoma | | |
| III. mixed germ-cell tumours | | |

→

**Table VIII cont.** Recommended follow-up schedules in cervical and endometrial cancer (IV, 2B), vulvar cancer (V, 2B), vaginal cancer (V, 2B) and ovarian, fallopian tube and primary peritoneal cancer (IV, 2B)

| Cancer | Examinations[a] | Frequency |
|---|---|---|
| **sex cord tumours** | | |
| I. granular and stromal tumours | as in ovarian cancer | every 3 months for 2 years, then every 6 months |
| 1. folliculoma | imaging | only if clinically indicated |
| 2. thecoma-fibroma | | |
| II. Sertoli cell and stromal tumours | | |
| 1. Sertoli cell tumour | | |
| 2. Leydig cell tumour | | |
| III. sex cord and stromal tumours with annular tubules | | |

[a] – imaging at all stages only when clinically indicated; [b] – FIGO (International Federation of Gynaecology and Obstetrics); [c] – AFP (alpha-fetoprotein); [d] – HCG (human chorionic gonadotropin, chorionic gonadotrophin); [e] – LDH (lactate dehydrogenase)

currence is not related to lymph node involvement but persists for many years (recurrence after five years occurs in 35% of patients) [78]. Late recurrence occurs locally in more than 90% of patients [79]. Due to the role of human papillomavirus in vulvar cancer, the diagnostics should also include cervical, vaginal and anal cancers, which have the same aetiology. Additional imaging has no proven value and is not recommended (tab. VIII). The value of transvaginal USG is questionable. Relapse or suspected symptoms necessitate imaging and treatment similar to that in cervical cancer [65].

### *Vaginal cancer*

Vaginal cancer is relatively rare, and data on post-treatment follow-up are scarce. There is no proven benefit of routine cytology or imaging (including transvaginal USG) in asymptomatic women (tab. VIII) [65].

### *Ovarian, fallopian tube and primary peritoneal cancer*

Approximately 75% of patients with ovarian cancer relapse after primary treatment. In stages IIB-IV, the median time to recurrence is approximately 22 months [65]. In around 37% of patients, the first sign of recurrence is an elevation of CA125, which precedes the clinical symptoms by, on average, five months. In 15% of patients, the recurrence is first manifested by clinical symptoms, while in 4%, it is accompanied by an increased CA125 [65, 80]. A large, randomised study demonstrated that the initiation of chemotherapy based only on an increased CA125 does not prolong survival [81]. Therefore, it is advisable to discuss the need for regular marker measurement with the patient. Similarly, routine post-treatment serum HE4 measurement is not recommended [82].

Imaging examinations (CT, MRI or PET-CT) are used for the verification of suspected recurrence and for selection for salvage surgery [83]. There are no indications for routine use of these examinations in asymptomatic patients.

In borderline malignant ovarian tumours, the risk of relapse is about 8%, and about 30% of relapses are malignant [84]. Relapses often occur many years after primary treatment: 70% after five years and 30% after ten years [65]. The risk of relapse is greater after organ-sparing treatment [84, 85]. In this group, periodic transvaginal USG may allow for the early diagnosis of relapse in the preserved ovary and for salvage surgery [86, 87]. Imaging examinations (CT, MRI or PET-CT) are used only to verify suspected relapse.

### *Non-epithelial ovarian malignancies and sex cord tumours*

A large proportion of patients with non-epithelial ovarian malignancies are managed with the preservation of the uterus and contralateral ovary. Recommendations in this group are based only on expert opinions [65, 68]. Long-term observation is necessary because half of the relapses occur more than five years after treatment completion, of which about half are in the pelvis. In patients with sex cord tumours, relapse may occur even 20 years after primary treatment [88]. Some patients may benefit from second-line chemotherapy [89].

## Genitourinary malignancies

### *Prostate cancer*

Routine follow-up after curative prostate cancer treatment should include an interview, prostate-specific antigen (PSA) measurement and, if necessary, rectal examination (tab. IX). The interview should consider psychological aspects and symptoms suggestive of relapse or late treatment complications. Follow-up visits should be performed every three months for the first year, every six months for another two years and then annually. There is no reason to perform imaging

**Table IX.** Recommended follow-up in patients with genitourinary malignancies after curative treatment

| Cancer | Examinations | Frequency |
|---|---|---|
| **prostate cancer** | | |
| | interview, PSA measurement[a] | 3 months after treatment completion, every 6 months for 3 years, then annually |
| | *per rectum* examination[b] | as above |
| **renal cancer** | | |
| low risk of recurrence[c] | USG and X-ray | at the 6$^{th}$ month and 2 years |
| | CT (chest, abdomen) | at the first and 3$^{rd}$ year, then every 2 years; the patient should be informed about the approximately 10% recurrence risk |
| medium and high risk of recurrence[c] | CT (chest, abdomen) | every 6 months in the first year, annually for 2 years, then every 2 years[d] |
| **bladder cancer** | | |
| I. non-invasive carcinoma | | |
| 1. low risk of recurrence | cystoscopy | at the 3$^{rd}$ and 9$^{th}$ month, then annually |
| 2. high risk of recurrence | cystoscopy | every 3 months for 2 years, then every 6 months for 3 years |
| | urine cytology | every 3 months for 2 years, then every 6 months for 3 years |
| | CT of the abdomen and pelvis, CXR | annual assessment of the upper urinary tract |
| | random biopsies of the bladder wall | in cases of positive cytology and normal cystoscopy |
| II. invasive carcinoma | | |
| 1. radical cystectomy | urine cytology | every 3–6 months for 2 years[d], then every 6–12 months[d] |
| | CT of the abdomen and pelvis, CXR | every 3–6 months for 2 years, then every 6–12 months |
| 2. bladder preservation therapy | cystoscopy | every 3–4 months for 3 years, then every 6–12 months |
| | urine cytology | every 3–4 months for 3 years, then every 6–12 months |
| | CT of the abdomen and pelvis, CXR | every 3–6 months for 2 years, then every 6–12 months |
| | random biopsies of the bladder wall | every 3–6 months for 2 years |
| **urothelial carcinoma of the upper urinary tract** | | |
| I. after nephroureterectomy | | |
| 1. low risk | cystoscopy | after 3 and 9 months, then annually |
| | CT of the abdomen and pelvis, CXR | every 6 months for 2 years, then annually |
| 2. high risk | cystoscopy | every 3 months for 2 years, every 6 months for 3 years, then annually |
| | urine cytology | every 3 months for 2 years, every 6 months for 3 years, then annually |
| | CT of the abdomen and pelvis, CXR | every 6 months for 2 years, then annually |
| II. after organ sparing surgery | | |
| 1. low risk | cystoscopy | at the 3$^{rd}$ and 6$^{th}$ month, then annually |
| | ureteroscopy | 3 months after the procedure |
| | CT of the abdomen and pelvis, CXR | every 6 months for 2 years, then annually |
| 2. high risk | cystoscopy | at the 3$^{rd}$ and 6$^{th}$ month, then annually for 5 years |

→

**Table IX cont.** Recommended follow-up in patients with genitourinary malignancies after curative treatment

| Cancer | Examinations | Frequency |
|---|---|---|
| | ureteroscopy | 3 and 6 months after the procedure |
| | urine cytology | at the 3rd and 6th month, then annually for 5 years |
| | urine sediment cytology (*in situ*) | after 3 and 6 months |
| **testicular malignancies**[e] [103] | | |
| | physical examination, AFP[f], B-HCG[g] and LDH[h], CXR | every 3 months for the first 2 years, every 6 months for the next 3 years, then annually |
| | CT scan of the abdomen and pelvis | every 6 months for the first 2 years, then as indicated |
| | chest CT | as indicated |
| | head CT | as indicated |
| **penile cancer** [104] | | |
| | physical examination | every 3 months for the first 2 years, then as indicated |
| | CT or MRI of the pelvis[i] | every 3 months for the first 2 years, then as indicated |

[a] – PSA (prostate-specific antigen); [b] – particularly reasonable in patients with undifferentiated or non-glandular cancers (e.g. sarcomas) that do not secrete PSA; [c] – based on nomograms based on T, N and M stages, symptoms at diagnosis, tumour grade and diameter [98–101]; [d] – only if clinically indicated and upon an individual risk assessment; [e] – guidelines of the European Association of Urology (according to the ESMO guidelines, each patient with testicular cancer in the second and fifth year of follow-up should undergo biochemical serum measurements (urea, creatinine, triglycerides, glucose, luteinising hormone, follicle-stimulating hormone, testosterone and cholesterol fractions) to evaluate late adverse effects; [f] – alpha-fetoprotein; [g] – beta-gonadotrophin; [h] – lactate dehydrogenase; [i] – only in patients with initial inguinal lymph node metastases

in patients without symptoms or biochemical failure. A single increase in PSA level should be verified by other examinations before instituting further diagnostics. The definition of biochemical failure is still debatable. If the lowest PSA level after radical prostatectomy does not exceed 0.01 ng/ml, the risk of clinical relapse is about 4% [90]. Among those with a PSA level above 0.05 ng/ml, about 2/3 will survive five years without biochemical failure [91]. In 2006, the Radiation Therapy Oncology Group and the American Society for Radiation Oncology defined biochemical failure after radiotherapy as an increase in PSA level by 2 ng/ml above the nadir [92]. PSA level after successful surgery should become indeterminable within six weeks [93]. Persistent, detectable PSA indicates active disease (micrometastases or residual disease in the pelvis). A rapid increase in PSA level is more indicative of dissemination, whereas local relapse is characterised by a late and slowly increasing PSA [94]. Unlike radical prostatectomy, radiotherapy leads to a much slighter decrease in PSA, and the nadir can be reached even after three years. A PSA decrease below 0.05 ng/ml is associated with a good prognosis [95]. The PSA doubling time (PSADT) depends on the relapse location; a PSADT lasting years or many months suggests local relapse, whereas a short PSADT (a few weeks or months) may indicate disease dissemination [96].

Rectal examination is particularly reasonable in patients with undifferentiated cancers or non-epithelial prostate tumours (e.g. sarcomas) [97]. In such cases, there is no PSA increase during progression, and rectal examination may be the only method for asymptomatic recurrence detection.

Endoscopic diagnostics should be considered in irradiated patients who have symptoms within the lower gastrointestinal tract to identify their cause (post-radiation enteropathy, chronic inflammatory processes or bowel malignancy).

### *Renal cancer*

There is no evidence that any follow-up strategy may improve renal cell carcinoma (RCC) outcomes in patients who have undergone radical surgery. The follow-up of RCC patients after curative treatment should consider recurrence risk determined by validated nomograms based on T, N and M stages, symptoms at diagnosis and tumour grade (tab. IX) [98–101]. Notably, the most common site of RCC metastases are the lungs, and the chest should be checked along with abdominal examinations.

### *Bladder cancer*

The risk of recurrence after radical cystectomy depends strictly on the pathological tumour stage, ranging from 5% in pT1 G3 to almost 100% in pN2. The risk of recurrence is greatest during the first two years, with a slight but continuous decrease thereafter. All patients undergoing transurethral electroresection of non-invasive bladder cancer (TURbt) and patients with invasive cancer managed with transurethral resection of the bladder tumour followed by concurrent chemotherapy and radiation should undergo cystoscopy after three months (tab. IX). In pT1 G2/G3 tumours, repeated electroresection of the involved sites should be performed after three months; more than one third of these patients will be diagnosed with

residual disease. For low-risk tumours (solitary tumour, pTa G1, diameter <3 cm), without recurrence within three months from the first TURbt, follow-up cystoscopy can be deferred until the ninth month and then performed annually. In high-risk patients, cystoscopy should be performed every three months during the first two years, every four months in the third year, every six months in fourth and fifth year and then annually. Determining the standard follow-up for intermediate-risk cancer is difficult due to the high variability of prognostic factors. At recurrence, periodic cystoscopy should be re-introduced. In patients with a single pTa G1 tumour who have not relapsed within five years, further cystoscopy may be waived. In other patients, an annual examination is advisable for ten years, and in patients with a high risk of relapse - throughout their lifetime. Follow-up, including USG of the kidney and bowel pouch and monitoring of creatinine and electrolytes, is carried out every three months during the first two years and then every six months up to a total of five years. Patients undergoing radiotherapy with bladder preservation require follow-up cystoscopy every three months for the first two years and then every six months [102].

### *Testicular malignancies*

There is no generally accepted follow-up for testicular cancer. The primary aim of follow-up (lasting for 5–10 years, is the early detection of relapse and treatment complications. Routine examinations include periodic measurement of serum tumour markers (AFP, βHCG and LDH) and CT of the abdomen and pelvis. Recently, CT tends to be replaced with MRI, which allows lower exposure to radiography contrast and avoids ionising radiation [103].

### *Penile cancer*

The five-year survival is approximately 85% in localised penile cancer, 60% in patients with lymph node metastases or regional invasion and 11% in metastatic disease. Some reports have demonstrated a better prognosis in HPV-associated penile cancers, but these findings warrant confirmation. Table IX presents the European Association of Urology guidelines for follow-up after curative treatment of penile cancer [104].

## Skin melanomas

To date, no universal, evidence-based follow-up schedules for skin melanoma have been developed. The frequency, type and duration of follow-up should consider the individual risk of recurrence based on the initial tumour stage (II, 2A).

The risk of recurrence is highest in the first three years after treatment; therefore, follow-up should be more intensive during this period (tab. X). However, melanoma recurrence can occur even ten years after the primary treatment [105–112], and its early detection may allow for effective salvage surgery [113–117]. Approximately 20%–28% of first melanoma recurrences are local or in-transit, more than 25% involve regional lymph nodes (with decreasing frequency after the implementation of sentinel lymph node biopsy) and 15%–50% are distant metastases.

Follow-up is based on the assessment of scar after the primary lesion excision and lymphadenectomy. Particularly important is the observation of regional lymphatic drainage (potential seeding for in-transit relapse). In addition to physical examination, USG is recommended for the evaluation of regional lymph nodes. The specificity of CXR for lung metastasis detection is only about 50% and this examination is of little use in patients with stages I–II and no clinical symptoms [118]. Since patients themselves can detect about 60% of locoregional recurrences, they should be encouraged to practice lifelong self-control of primary lesions and regional lymph nodes (III, 2A) [111]. Beyond five years, the risk of recurrence is below 5% [111, 117]. In early melanoma suffices less intensive follow-up (II, 2A) [119, 120-122].

Follow-up imaging (e.g. CT) is not reasonable in asymptomatic stage IA–IIA patients; however, can be considered for the first 2–3 years after surgery or systemic adjuvant treatment in stage IIB–IIIC patients (IV, 2B) [109, 110, 118]. This recommendation, among others, results from increasing treatment efficacy of disseminated melanomas [123]. In stage IIIC/D patients, the risk of brain metastases in the first 13 months after local treatment is approximately 5%, which may justify a follow-up including brain MRI [124]. In turn, in patients with clinical symptoms suggesting distant metastases (liver enzyme abnormalities, bone pain, neurological symptoms, cough or weakness), there is a need for detailed imaging, including CT, MRI, PET-CT and bone scintigraphy [115, 124, 125]. Routine follow up does not include monitoring of serum tumour markers.

Regardless of the initial stage, examinations should include the entire skin (and not only the area of the primary disease). As the risk of developing a second independent melanoma or other skin malignancy exceeds 10%, dermoscopy should be performed every 6–12 months [126–130]. Patients with atypical nevus syndrome should be assessed with repeated photography of the entire skin or regular videodermatoscopy. Patients must follow the principles of skin photoprotection and should be informed that their relatives have a higher risk of developing melanoma. However, there are no indications for genetic testing. Further information for patients, among other sources, is available on the websites of scientific societies, (e.g. www.akademiaczerniaka.pl).

## Soft tissue sarcomas

The aim of post-treatment follow-up for soft tissue sarcomas (STS) is the early detection of local or distant relapse, assuming that earlier treatment initiation may increase its efficacy. Follow-up strategies are based on three principles: uncomplicated but effective methods, accuracy and cost--effectiveness [131, 132]. Several proposals for STS follow-up have been developed, but they are based on scarce evidence and vary widely [131, 133–138].

**Table X.** Recommended follow-up in skin melanomas

| Cancer | Examinations | Frequency |
|---|---|---|
| early melanoma after excision of the primary lesion without lymph node metastases (stages IA–IIA) | interview and physical examination, including a thorough assessment of the entire skin, the primary tumour area and regional lymph nodes;<br>USG of regional lymph nodes in stages ≥pt1b when a sentinel node biopsy was not performed;<br>no indications for routine laboratory testing;<br>CXR (optionally);<br>contrast CT of the chest and abdomen, pelvis; neck CT or PET-CT, brain MRI and other imaging in all cases with clinical symptoms;<br>patient education on risk factors and self-examination of the skin and lymph nodes | every 6–12 months for the first 5 years, examinations can be conducted if clinically indicated (follow-up can be performed outside of the specialist centre) |
| locally advanced melanoma after excision of the primary lesion without lymph node metastases (stages IIB–IIC) | CXR, optional abdominal USG;<br>USG of regional lymph nodes if sentinel node biopsy was not performed in stages ≥pt1b;<br>consider contrast-enhanced CT of the chest, abdomen, pelvis; neck CT or PET-CT, brain MRI and other imaging every 6–12 months for the first 2 years and every 6–12 months for the next 3 years (obligatory in all cases with clinical symptoms);<br>no indications for routine imaging after 3–5 years;<br>no indications for routine laboratory testing; patient education on risk factors and self-examination of the skin and lymph nodes | every 3–6 months for the first 2–3 years, then every 6–12 months up to 5 years and examination after 5 years if clinically indicated |
| after excision of regional lymph node metastases or local recurrence/ satellite focus/in-transit focus (stages IIIA–IIID) or positive sentinel lymph node biopsy without lymphadenectomy | interview and physical examination, including a thorough assessment of the entire skin, primary tumour area and regional lymph nodes;<br>optional CXR;<br>USG of lymphatic drainage every 4–6 months in cases of positive sentinel lymph node biopsy without lymphadenectomy;<br>consider contrast-enhanced CT of the chest, abdomen, pelvis or neck along with PET-CT, brain MRI and other imaging every 3–12 months for the first 2 years, then every 6–12 months for the next 3 years, particularly in stage IIIC/IIID (obligatory in all cases with clinical symptoms);<br>no indications for routine imaging after 3–5 years;<br>no indications for routine laboratory testing;<br>patient education on risk factors and self-examination of the skin and lymph nodes | every 3–4 months fo the first 2 years, every 3–6 months for the next 3 years and examination after 5 years if clinically indicated |
| after treatment of metastatic disease (stage IV) | assessment of metastatic lesions; serum LDH;<br>contrast-enhanced CT of the chest, abdomen and pelvis;<br>neck CT or PET-CT, brain MRI or other imaging, depending on the metastasis location | individual follow-up schedules |

The estimated relapse rate in primary STS (depending on histological grade, primary tumour size, histology, location and local treatment accuracy) ranges between 40% and 60% [131, 135, 136, 139]. About 80% of relapses, particularly in high-grade STS, occur within three years after the primary treatment. The locations of relapses depend mainly on the primary tumour site. In patients with limb STS (the most common location), the first relapse most often develops in the lungs. With appropriate combined-modality treatment of the primary lesion, local recurrences are less common. In rare STS subtypes of the limbs and trunk (e.g. rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma or synovial sarcoma), more common are lymph node metastases, and in myxoid liposarcoma, metastases to the abdominal cavity and soft tissues. In turn, in STS of the retroperitoneal space (most often liposarcoma) or viscera (mainly gastrointestinal stromal tumours, GIST), most common are local or intraperitoneal relapses, followed by liver metastases.

In high-grade STS, about half of patients will die due to dissemination. The combined-modality salvage treatment in some patients may allow for long-term survival. Complete excision of lung metastases allows for significantly better results than non-surgical methods [137, 139, 140]. This justifies earlier detection of resectable (often quantifiable) lung metastases (III, 2A). Regular CXR allow detection of asymptomatic lung metastases in more than half of cases [131, 139, 141]. It is estimated that complete resection of exclusive lung metastases allows for 30%–40% long-term survival [140, 142, 143], but this applies only to clinically asymptomatic, quantifiable lung metastases [144, 145]. CXR allow the detection of more than 60% of asymptomatic lung metastases. After five years, CXR should be performed annually. There is no need for routine chest CT. However, CT is indicated in detected or suspected changes in CXR to assess their number and location, and evaluation of the pleura, mediastinum, and hilar and mediastinal lymph nodes. American College of Radiology recommends periodic chest CT only in high risk STS and after metastasis excision (II, 2A). On the other hand, the only randomised trial evaluating follow-up schedules in STS showed no advantage of CT over CXR [146].

Follow-up examinations to detect local STS recurrence should primarily include a careful physical examination, possibly with USG of the scar for easily accessible lesions, e.g. located in the limbs or trunk skin [147–149] (III, 2B). Patients should

also be informed about local recurrence symptoms because self-examination of the resection scar often allows the detection of interval recurrences. Some experts additionally recommend USG or MRI of the primary tumour area in high-grade limb STS, but the usefulness of MRI is controversial [150, 151] (III, 2B). Effective method in differentiating between tumour relapse and post-surgical changes is signal enhancement in T2-weighted contrast MRI. However, routine MRI is not reasonable considering its low cost-effectiveness.

Useful imaging in retroperitoneal or inguinal STS is spiral contrast-enhanced CT or MRI [134, 135] (III, 2A). Retroperitoneal or intraperitoneal STS recurrence is more common and more difficult to detect with physical examination than limb or skin recurrence. There is no evidence that earlier detection of retroperitoneal STS recurrence improves overall survival (III, 2B).

So far, no standard STS follow-up have been developed [134–137, 152–154]. Usually, it includes visits every 3–4 months for the first 2–3 years, every six months for the next two years and then annually. The recurrence risk depends on the tumour grade and size, completeness of the combined-modality treatment and time from treatment completion [134, 135, 137, 139] (III, 2A). For low-grade STS and those under 5 cm, the recurrence risk after curative treatment is very low. If the postsurgical scar can be assessed easily by a physical examination, there is no need for imaging other than a CXR every 6–12 months for the first three years and then annually (III, 2A). However, high-grade STS, which carries a significantly higher risk of pulmonary metastases and local recurrence, necessitates a regular CXR [139] (III, 2A). Assessment of regional lymph nodes is reasonable only for selected subtypes of STS (e.g. clear cell sarcoma and epithelioid sarcoma),

**Table XI.** Recommended follow-up in patients with soft-tissue sarcomas (excluding GIST)

| Clinical situation | Examinations | Frequency |
|---|---|---|
| after curative treatment for stage IA-IB STS (G1) | interview and physical examination<br>CXR every 6–12 months;<br>chest CT only in cases of suspected changes in the X-ray;<br>six months after the surgery, consider local assessment with MRI, CT or USG;<br>for retroperitoneal and intraperitoneal sarcomas, regular follow-up every six months for the first 2–3 years, then annually, with contrast CT of the abdomen and pelvis (in other locations, imaging only with clinical suspicion of recurrence);<br>patient education on self-examination | every 3–6 months for the first 2–3 years, then annually (over 10 years only in patients who underwent perioperative radiotherapy) |
| after curative treatment for stage II–III STS (G2/G3 or after resection of metastases to regional lymph nodes) | interview and physical examination, with particular attention to the area of the scar after the primary tumour resection and lymphadenectomy: check X-ray or CT;<br>consider local post-resection MRI, CT or USG 3–6 months after the surgery, then not more frequently than annually;<br>for retroperitoneal and intraperitoneal STS: contrast-enhanced CT of the abdomen and pelvis every 6 months for the first 2–3 years, then annually;<br>patient education on self-examination | every 3–4 months for the first 2–3 years, then every 6 months up to 5 years, and then annually |
| after treatment for stage IV | imaging depends on the location of measurable metastatic foci | individual schedules |

**Table XII.** Recommended follow-up in patients with gastrointestinal stromal tumours (GIST)

| Clinical situation | Examinations | Frequency |
|---|---|---|
| after curative treatment for very low- and low-risk GIST (stage I) | no absolute indications for regular follow-up; consider USG or CT of the abdomen and pelvis; the patient should be informed about the small risk of late recurrence | annually |
| after curative treatment for intermediate-risk GIST (stage II) | contrast-enhanced CT of the abdomen and pelvis;<br>other imaging depending on the primary tumour location (e.g. pelvic MRI for rectal GIST, chest CT for oesophageal GIST) | every 3–6 months for the first 2–3 years, then every 6–12 months until 5 years and annually after 5 years |
| after curative treatment for high-risk GIST (stage III) | interview and physical examination, contrast-enhanced CT of the abdomen and pelvis;<br>other examinations depending on the primary tumour location (e.g. pelvic MRI for rectal GIST, chest CT for oesophageal GIST) | every 3–4 months for the first 2–3 years, every 6 months until 5 years, and annually beyond 5 years after surgery or adjuvant imatinib |
| after treatment for stage IV | imaging depending on the location of measurable metastatic foci, typically CT or MRI of the abdomen and pelvis | individualised schedules |

and abdominal examination is only recommended for myxoid liposarcoma. Laboratory tests are useless for detecting STS recurrences [152] (III, 1). For tumours that are difficult to assess in a physical examination, e.g. those located retroperitoneally or intraperitoneally (such as GIST), regular double-contrast CT should be performed. The value of PET-CT is uncertain. Notably, patients should be informed that recurrence or radiotherapy-induced secondary malignancy may develop even after ten years [154, 155].

In low-grade GIST, follow-up visits may be performed annually [154, 156]. Patients with high- and medium-grade GIST who received no adjuvant treatment should be subjected to strict observation, with contrast CT of the abdomen and pelvis performed every 3–4 months for the first 2–3 years (when the recurrence risk is highest), every six months up to five years and then annually [153, 154, 155, 156] (II, 2A). This regimen also applies to patients following adjuvant imatinib.

## Bone sarcomas

The aim of post-treatment follow-up for bone sarcomas is the early detection of local or distant relapse, assuming that earlier treatment initiation may increase its efficacy [157–161]. In bone sarcomas, 70% of relapses occur in the lungs (in Ewing's sarcoma, relatively common are also bone metastases) [158–161]. Since most relapses occur within the first 2–3 years, during this time, follow-up visits every 3–4 months are reasonable, especially in higher-grade tumours. The follow-up should include an X-ray of the chest and the region of the operated bone (IV, 2A). Patients should also be informed about the need to observe the operated area, as they may detect some local recurrences themselves. Afterwards, follow-up visits may take place every 6–12 months (IV, 2A). A serious consequence of intensive combined-modality treatment (chemotherapy, radiotherapy and surgery) are secondary malignancies, which in small-cell sarcomas occur in 7%–10% of patients [162, 163]. Other important late sequelae of combined-modality treatment justifying long-term observation include heart failure, infertility and endoprosthesis complications [164–166] (V, 2A).

There is no standard follow-up based on randomised controlled clinical trials for bone sarcomas in adults. Routine follow-up visits are usually repeated every 3–4 months for the first 2–3 years, every six months for the next two years and then annually. The recurrence risk depends on the primary tumour grade and size, primary treatment radicalness and time from its completion. For low-grade sarcomas and those below 5 cm, the recurrence risk after curative treatment is very low. In such cases, X-ray imaging performed every 6–12 months for the first three years and then annually. In high-grade sarcomas, characterised by a significantly higher risk of pulmonary metastases and local recurrence, careful physical examination should be supplemented with CRX and imaging of the primary tumour area.

Primary bone malignancies in children and adolescents necessitate more intensive follow-up: every six weeks in the first and second years, every three months in the third year, every six months in the fourth year and then annually (IV, 2A).

## The role of primary care physicians in cancer follow-up

Post-treatment follow-up of patients with solid malignancies carried out by primary care physicians is important for detecting cancer relapse or secondary malignancy and preventing post-treatment complications [167]. In a GP's office, the patient also expects psychological support and assistance in organising care and everyday life [167]. In turn, patients whose treatment failed or was abandoned expect assistance in ensuring the highest possible quality of life.

**Table XIII.** Recommended follow-up in patients with bone sarcomas

| Clinical situation | Examinations | Frequency |
|---|---|---|
| after curative treatment of stage IA-IB sarcoma (G1/G2) | interview and physical examination every 6 months for the first 2–3 years, then annually;<br>CXR every 6–12 months;<br>chest CT only in cases of suspected changes in the X-ray | every 6 months for the first 2–3 years, then annually |
| | X-ray, MRI or CT of the primary tumour site | every 6 months for the first 2–3 years, then annually |
| | patient education on self-examination | |
| after curative treatment of stage II–III sarcoma (G3) | interview and physical examination, with a focus on the primary tumour site and regional lymph nodes; CXR or CT;<br>radiographic, MRI or CT site evaluation after resection;<br>in patients with Ewing's sarcoma, optional bone scintigraphy or PET-CT;<br>patient education on self-examination | every 3–4 months for the first 2–3 years, then every 6 months until the 5$^{th}$ year, and then annually |
| after treatment of distant metastases (stage IV) | imaging depending on the location of measurable metastatic lesions | individualised schedules |

A significant proportion of cancer patients receive inadequate post-treatment surveillance, including both insufficient and excessive supervision [168]. As high-quality, evidence-based data are missing, it is difficult to define generally the optimal moment for transferring patients from specialist care to a GP [169, 170]. Due to the small number of oncology specialists compared to the number of primary care physicians, it is increasingly important to define the latters' role in providing cancer care [171, 172]. The number of patients seeking post-treatment follow-up performed by GPs rather than oncologists gradually increases [173]. At the same time, during intensive cancer treatment, many patients lose contact with their GPs and do not know when or how to restore it [174].

It is difficult to standardise coordination rules for post-treatment cancer care, especially in the absence of data on cancer-related risks and the time elapsed from treatment. The authors of *Defining Survivorship Trajectories Across Patients with Solid Tumours. An Evidence-Based Approach*, published in 2018, attempted to estimate the high-risk period after treatment completion for each cancer based on the risk of death and the time since treatment completion [175]. During this period, care should be provided by an oncologist, or a multidisciplinary team including an oncologist, and may thereafter be continued by a GP.

The time of increased death risk varies for particular malignancies: e.g. is short (around one year) for localised prostate cancer; may be long (6–7 years) for lung cancer and very long (more than ten years) for some gastrointestinal cancers. The leading causes of death in cancer patients are the failure of primary cancer treatment (on average, over half of patients) and secondary cancer, but common cause is also cardiovascular disease [176]. Patients with increased risk of cardiac death could benefit more from the care provided by a GP than from an oncologist. The selection of the optimal model for post-treatment care should also consider the patients' quality of life, their quality of care and the incidence of other diseases [169].

Monitoring of patients' compliance with periodic follow-up recommendations should include the following steps [177]:

- supervision of oncology follow-up attendance,
- supervision of performing periodic follow-up examinations (e.g. MRI, CT or USG),
- referring patients to palliative medicine clinics, palliative home care teams or pain treatment clinics,
- risk assessment and monitoring for tumour recurrence,
- risk assessment and monitoring for secondary cancer,
- educating patients about above risks,
- assessment of treatment complications and their prevention, diagnosis and treatment.

Specific indications concerning the GP's roles in selected solid malignancies are presented in table XIV.

There are differences between the recommendations of oncology and family medicine specialists [178]. The former pay more attention to cancer control and its consequences, and the latter to the prevention of lifestyle-related diseases. Of particular importance is building the professional experience and competencies of primary care physicians. Considering nearly 200,000 new malignancies per year diagnosed in Poland and the total number of primary care physicians (including those performing this role as an additional job), a primary care physician may diagnose, on average, only 3–4 cancer patients a year [179]. At the same time, a primary care physician manages more patients after cancer treatment. Monitoring of these patients for post-treatment complications and secondary cancers remains insufficient [180].

GPs' involvement in the care of patients after treatment for solid malignancies should additionally include the following:

- monitoring compliance with specialist recommendations, including medication use, especially steroids or antiepileptic agents,
- monitoring indications for rehabilitation after cancer treatment, particularly anti-oedema therapy and general rehabilitation,
- monitoring and supervision of the patient's family, regarding an increased cancer risk (determined by genetic and environmental factors, e.g. passive smoking),
- providing medical devices to patients as needed,
- referring patients to support groups and patient organisations,
- encouraging preventive vaccination against pneumococcus, meningococcus, seasonal flu and SARS-CoV-2.

This particularly applies to high-risk groups, e.g. patients who underwent chemotherapy and radiotherapy.

There is a need for coordination of post-treatment patient care, given the specific characteristics of particular patient groups and the potential of the primary care and specialist care systems. Such a mixed-care model (so-called coordinated or combined-modality care) is most effective in terms of survival and quality of life [178, 181].

Particular attention should be paid to systemic limitations restricting GPs from making referrals for certain examinations, such as CT or cancer markers. Primary care physicians can effectively perform such monitoring, provided that patient groups are properly selected and systemic support is provided [169, 182]. Without diagnostic capacity, primary care physicians cannot effectively supplement specialist oncological care, including post-treatment follow-up.

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**Table XIV.** Specific indications for GPs' roles in the post-treatment follow-up of selected solid malignancies

| Cancer | GPs' roles | Evidence quality | Recommendation strength |
|---|---|---|---|
| head and neck cancer | evaluation of compliance with the specialist's follow-up recommendations, with special consideration of other respiratory or gastrointestinal malignancies | II | 2A |
| | encouraging the patient to quit smoking | | |
| CNS malignancies | evaluation of compliance with MRI follow-up scheme (as indicated by the specialist) | II | 2A |
| non-small cell lung cancer | evaluation of compliance with chest CT follow-up scheme (as indicated by the specialist) | II | 2A |
| | encouraging the patient to quit smoking | III | 2B |
| oesophageal and gastric cancer | risk assessment for treatment complications, including alimentation disorders and deficiencies, e.g. $B_{12}$ | IV | 2B |
| pancreatic or ampullary cancer | diagnosis and management of treatment sequalae (including diabetes and pancreatic enzyme disorders) | II | 2A |
| colorectal cancer | interview and physical examination every 3–6 months for 3 years and every 6–12 months for the next 2 years | II | 2A |
| breast cancer | observation for local recurrence; assessment of risk and monitoring for early menopause and bone mineral density disorders | II | 2A |
| | in patients with preserved uterus treated with tamoxifen, annual gynaecological examination | II | 2A |
| | encouraging patients to maintain a BMI in the range of 20–25, physical activity and a proper diet | II | 2A |
| prostate cancer | interview and physical examination, PSA monitoring, initially every 3 months, then every 6 months until 3 years and then annually | II | 2A |
| melanoma | educating patients in self-examination of the skin and lymph nodes of the treated area | II | 2A |

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# Deeply located Merkel cell carcinoma

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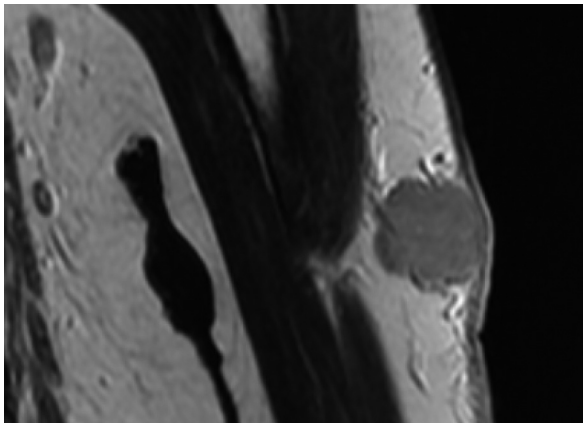

**Figure 1.** Polycyclic tumor in the adipose tissue lying at the level of the deltoid muscle attachment

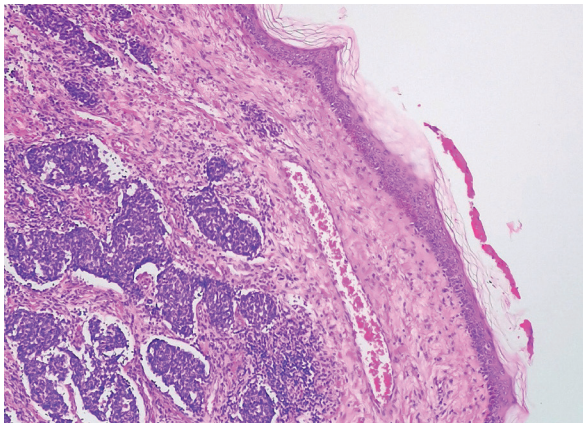

**Figure 2.** MCC infiltration. Tumor outbreaks in the dermal and subcutaneous tissue on the left arm (courtesy of Dariusz Pabis, MD)

Merkel cell carcinoma (MCC) is 40 times less frequent compared to melanoma and typically develops superficially on the head and neck skin in elderly patients. However there are infrequent cases located initially not superficially (i.e. not directly on the surface of the skin) [1]. In 89-years old female with a soft tissue tumor on her left arm not related to the skin, on palpation located subcutaneously, on MRI there was polycyclic 3 cm large tumor in the adipose tissue lying at the level of the deltoid muscle attachment with heterogenous contrast enhancement and edema of the adjacent adipose tissue (fig.1) In the axilla no enlarged lymph nodes were seen. The patient underwent core-needle biopsy guided by USG showing neuroendocrine carcinoma, probably MCC. Patient underwent a wide local excision for MCC with sentinel node biopsy. Histopathology revealed MCC pT2N0R0 with angioinvasion (LVI1) and epidermal ulceration (fig. 2). There were no sentinel nodes metastases. MCC typically presents as a rapidly growing, erythematous lesion in the dermal layer of the skin. MCC are grouped into growth patterns: nodular and infiltrative. Nodular type is characterized by relatively well – circumscribed – composed of one or two nodules. Infiltrative type is defined as ill-circumscribed tumor, cells infiltrate through dermal layer or deeper into soft tissue. MCC rarely occurs only in the subcutaneous tissues [2].

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# Stereotactic body radiation therapy for treatment of oligometastatic EGFR-mutated non-small cell lung cancer

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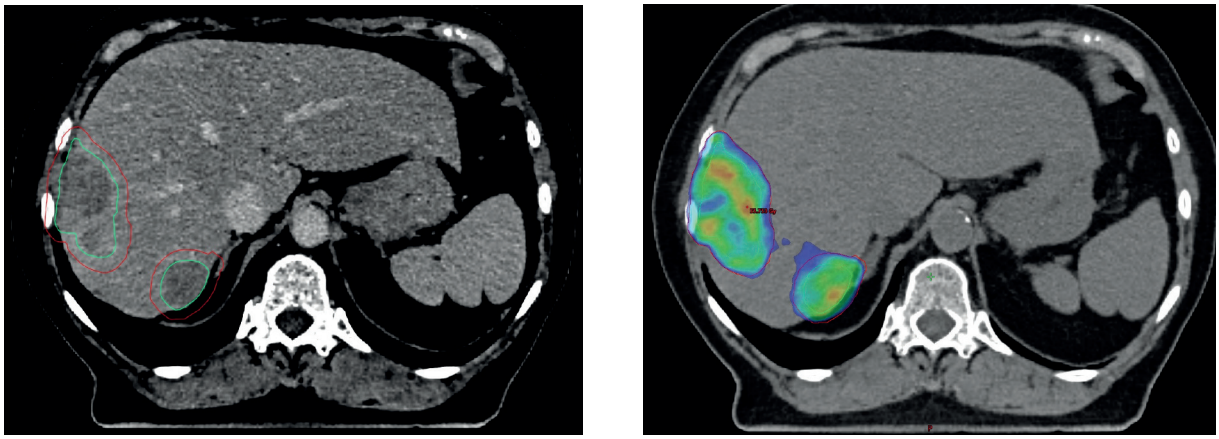

**Figure 1. A:** CT showing delineation of the lesion in the liver; green – gross tumor volume; red – planning target volume; **B:** SBRT with 50 Gy in 5 fractions

A 74-year old female was treated (from 2010) for a disseminated EGFR-mutated lung adenocarcinoma with chemotherapy (cisplatin + pemetrexed) then docetaxel, erlotinib and paclitaxel. Finally, because of *T790M* mutation detected in the tumour, she started osimertinib. In October 2019, solitary metastases in the liver were observed. According to ESMO guidelines [1], local therapy and continuation of tyrosine kinase inhibitors (TKI) was an option, therefore she was referred for SBRT to liver metastases with 50 Gy in 5 fractions (fig. 1). After 3 months, stabilization of the disease was noted in control CT. She remains free of progression with good performance (ECOG 1), and continues osimertinib treatment (progression-free survival after SBRT: 32 months). This case shows the importance of local ablative treatment with oligometastatic lung cancer. Oligoprogression is defined as a limit on the number and locations where progressive disease appears [2]. Hypothetically, when PD is observed in oligoprogressive state, local treatment could eradicate resistant clones of the tumor cells before they seed into other organs. Such management could enable continuation of the same TKI, as it is active in all other affected areas. Local treatment in oligoprogressive NSCLC is one of the options leading to clinical benefit for the patients as shown in this case.

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