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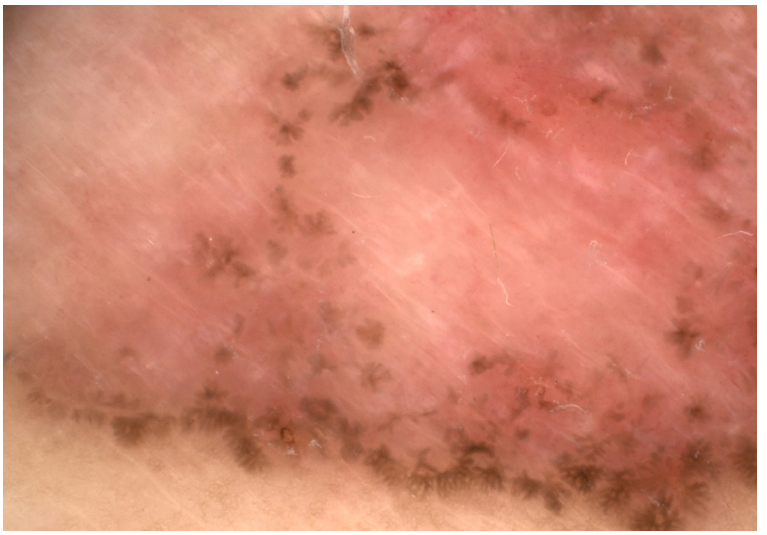

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Cover photo: A dermoscopic image in polarised light and 10-fold magnification demonstrates dermoscopic structures characteristic of basal cell carcinoma (BCC): on the edges there are brown and grey structures resembling leaves, with shiny crystalline bands in the middle. Thanks to the courtesy of prof. Grażyna Kamińska-Winciorek

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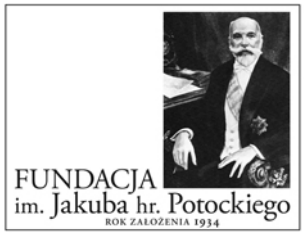

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Proposals for the modification of diagnostics and combination treatment of breast cancer during the COVID-19 pandemic

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Introduction

These recommendations focus on potential limitations in the availability of combined treatment for breast cancer due to the COVID-19 pandemic and indicate the options for therapy postponement and/or the correct selection of patients for modified treatment. They were prepared with the aim of preventing negative health consequences for patients due to treatment priorities, and to indicate admissible alternative procedures adapted to the epidemiological situation and the resources available to a given oncological clinic.

General rules of conduct during the COVID-19 pandemic

The team drafting these guidelines offers the following recommendations:

- In centres where it is possible, combined treatment of tumours should be consolidated and offered in a 'virus-free' space, i.e. at a place free of COVID-19.
- A decision on the treatment method and its modification related to the general epidemiological situation in the country because of the pandemic, its prospects, and the available resources (materials, drugs and staff) required for combined treatment, should be made each time by a council of specialists in many fields.
- A decision on the treatment method should be made together with the patient and take into account the patient's wishes, the potential advantages of anticancer treatment and its risks, including the risk related to SARS-CoV-2 infection during therapy, and its consequences (also with regard to the course of oncological treatment).
- The fundamental requirement that ensures treatment for cancer patients is the need to secure oncological clinics against SARS-CoV-2 infection by adequate *triage* of patients, the provision of personal protective equipment and its appropriate use by staff and patients, access to tests confirming the infection for patients and staff, and the monitoring of the epidemiological situation in a given clinic. It is recommended that, if possible, the medical staff works only at one clinic.
- Before the patient arrives at the oncological clinic, it is recommended that the patient be contacted on the phone in order to obtain the patient's epidemiological history with the emphasis on the symptoms and risk of infection, and inform the patient about the ways of reducing

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the risk of infection (including self-isolation, i.e. a regime close to quarantine lasting 7-14 days before admission to the hospital).

- Before admission to an oncological clinic, in particular if invasive procedures or treatment involving the risk of immunosuppression is planned, patients should be tested for the SARS-CoV-2 infection.
- It is necessary to ensure sufficient space so that it is possible to maintain the recommended distance between patients at oncological clinics (the current recommendation is 2 metres) where necessary and where there are more people (e.g. waiting rooms or the rooms where infusions are administered).
- During oncological diagnostics it is recommended patients be informed about the general rules reducing the risk of infection, emphasising the negative impact of possible SARS-CoV-2 infection on the possibilities and therapeutic effectiveness of anticancer therapy.
- **If SARS-CoV-2 infection has been confirmed or is suspected, the patient's oncological treatment should be postponed.**
- The risk of serious complications in COVID-19 is more than 3 times higher for oncological patients than for the general population.
- It is necessary to make every effort to maintain the continuity of oncological treatment during the pandemic because its duration cannot be defined, while excessive postponement of treatment, both radical and palliative, may reduce the chances for its success and cause the deterioration of the cancer patient's quality of life.

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Minimally invasive image diagnostics of breast diseases during the COVID-19 pandemic

As regards image diagnostics and breast lesion biopsies, the team drafting these guidelines offers the following recommendations:

- Do not postpone image diagnostics for patients with clinical symptoms of breast cancer.
- Do not postpone needle biopsies of lesions qualified as BIRADS 4 or 5.
- Consider image diagnostics according to schedule in young patients (up to 45 years of age) whose treatment ended no more than 4 years ago or in patients up to 55 years of age – in the case of malignancies with a high risk of early recurrence (i.e. TNBC and HER2+).
- Consider check-ups for the carriers of a *BRCA1/2* mutation under the age of 40 if the envisaged postponement of planned check-ups is more than 6 months.
- If the patient's lesions are qualified as BIRADS 3, consider observing following the protocol employed so far (i.e. 6–6–12 months) or the simplified protocol (i.e. 12–12 months) if the pandemic continues.
- Reschedule/postpone planned screening mammography examinations.

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Systemic treatment of breast cancer patients during COVID-19 pandemics

As regards the systemic treatment of breast cancer patients, the team drafting these guidelines offers the following recommendations:

- In particular for the patients **in radical treatment**, the therapy should be conducted if only it is possible, following the standards in force. The modification of treatment regimens (e.g. selecting oral instead of intravenous drugs or a regimen with longer breaks between cycles) aims to reduce the number of visits to the oncological clinic to a minimum, which is rational, but it may not result in offering sub-optimal therapy.
- The treatment offered at an outpatient clinic or at a day ward at the centre which is the closest to the patient's residence reduces the risk of infection.

The definition of systemic treatment urgency

To ensure the most optimal access to oncological care during the SARS-CoV-2 pandemic, cancer patients have been divided into two groups:

- **Group A** – patients who are not being treated at present, who have completed treatment, or whose disease is under full control, e.g. those who are receiving auxiliary hormone treatment.

- **Group B** – patients who are undergoing treatment because of an early or advanced tumour; patients in this group qualify for active anticancer treatment including surgery, radiotherapy and systemic treatment.

The treatment selection process should take into account the factors related to the tumour (progression level and phenotype) and the patient (general condition and comorbidities) as well as the individual SARS-CoV-2 infection risk associated with the treatment offered and the need to visit the oncological clinic. This is especially important in the case of older patients (>60 years of age) with cardiovascular and respiratory diseases who smoke and require transport to the clinic (remote place of residence). If the risk of infection exceeds any potential benefits of standard therapy in this group, it seems justified to modify it, e.g. offer pre-surgical hormone therapy, even in the case of operative luminal tumours, shorten Trastuzumab therapy to 6 months or administer individual hormone treatment instead of hormone therapy combined with CDK 4/6 inhibitors (table I).

The rules for the systemic treatment of breast cancer patients during the COVID-19 pandemic according to the cancer phenotype and progression

As regards the treatment of patients according to the progression and phenotype of breast cancer, the team drafting these guidelines offers the following recommendations:

- Recommendations for patients with a local-regional stage of breast cancer without metastases can be found in table II a.
- Recommendations for patients with metastatic breast cancer can be found in table II b.

Treatment monitoring

As regards the monitoring of breast cancer patients' systemic treatment, the team drafting these recommendations emphasises the following:

- The number of tests performed should be reduced, in particular for clinically stable patients.
- Laboratory tests of patients who live far away from the oncological clinic should be performed locally.
- Complications may be monitored by phone or online contact.

Auxiliary treatment

As regards auxiliary treatment for breast cancer patients, the team drafting these recommendations emphasises the following:

- Because of the additional infection risk related to neutropenia as well as the potential difficulty with distinguishing the COVID-19 infection from other pathogens, patients on chemotherapy with a medium or high risk of neutropenic

Table I. The division of patients into groups according to the cancer treatment stage and recommended strategies

Patient group	Strategy	Means
Currently not under treatment	– Infection prevention – Postponing check-ups if there are no symptoms of an active disease – Phone or online consultations	– Education on the pandemic and infection prevention methods – Dissemination of information on protective measures
With a diagnosis of early stage cancer, radical treatment (preoperative, auxiliary, surgical)	– Infection prevention – Optimal treatment available at SARS-CoV-2-free hospitals – Treatment modification if needed with the lowest possible risk of its effectiveness	– All the above-mentioned measures – Severe restrictions of direct contact – Adequate use of personal protection equipment by staff – Monitoring of complications and potential infection symptoms – Clinical pathway secured against the SARS-CoV-2 infection – If oral medications are used, patients are prescribed drugs for 2–3 months of therapy – Treatment regimen modification if needed (extension of the break between cycles) – Phone or online consultations in the case of complications
With metastatic stage cancer	– Infection prevention – Optimal treatment available at SARS-CoV-2-free hospitals – Treatment modification if needed with the lowest possible risk of its reduction in effectiveness	– All the above-mentioned measures – Treatment postponement or a temporary break in treatment if no risk of unacceptable progression is involved – Treatment with the use of oral medications of the lowest myelotoxicity level if the clinical situation allows it – If oral medications are used, patients are prescribed drugs for 2–3 months of therapy – Postponement of the use of CDK4/6 inhibitors (this option remains available in the second line of treatment) in patients with luminal HER2-positive breast cancer if the clinical situation allows it – Optimum auxiliary treatment, routine use of growth factors in patients with the medium and high risk of neutropenic fever, reduced use of corticosteroids, oral instead of intravenous bisphosphonates, extension of the period between administration if it is justified – Rational monitoring of the therapy effectiveness, postponement of imaging tests in patients in a stable clinical condition

Table II a. Rules for the systemic treatment of patients with an early and locally advanced stage of the disease during the COVID-19 pandemic

Subtype (local progression, without M1)		Treatment	Remarks
Early tumour	Luminal HER2-negative	Surgery or preoperative HTH if surgery entails high risk	
	HER2-positive – non-luminal subtype or – triple-negative luminal subtype	Preoperative chemotherapy (±anti-HER2 treatment) or surgery	In HER2-positive patients on multi-drug chemotherapy (including anthracyclines or docetaxel with carboplatin), for the patient group with a low risk of recurrence, it is possible to discontinue Trastuzumab after 6 months of anti-HER2 treatment
Locally advanced tumour	Luminal HER2-negative	Preoperative chemotherapy or hormone therapy according to standards	
	HER2-positive – non-luminal subtype or – triple-negative luminal subtype	Preoperative chemotherapy (±anty-HER2 treatment)	

Table II b. Rules for the systemic treatment of patients with metastatic cancer during the COVID-19 pandemic

Subtype (metastatic, M1)	Treatment	Comments
Luminal HER2-negative	Individual hormone therapy or in combination with molecular drugs	It is recommended to use oral drugs (e.g. aromatase inhibitors or Tamoxiphen instead of Fulvestrant) and exercise caution when starting the CDK4/6 inhibitor therapy if it can be employed in the second line treatment
HER2-positive – non-luminal or – luminal	Chemotherapy or hormone therapy + anti-HER2 treatment	
'Triple-negative'	Oral chemotherapy if possible and/or of the lowest myelotoxicity	

fever should be administered granulocyte colony-stimulating factor.
- Exercise caution when administering corticosteroids.
- Due to the limited access to GPs/primary care, including laboratory tests performed locally, it seems justified to use empirical antibiotic therapy when such tests cannot be performed for patients with infection symptoms.
- In patients with stable bone metastases, it is possible to extend the breaks between the administration of parenteral drugs modifying bone metabolism (bisphosphonates and denosumab). It is also recommended that the possibilities of offering this therapy outside oncological clinics, e.g. in home hospices, be created.

The observation of patients after radical treatment

As regards the rules for the observation of breast cancer patients after radical treatment, the team drafting these recommendations emphasises the following:
- It is recommended that the number of visits during the observation period be reduced, but it is necessary to avoid exposing patients to the risk of the failure to detect recurrence that might potentially qualify for radical treatment.
- Optimum imaging tests (e.g. control MMG) should be performed depending on the disease recurrence risk. They should be postponed for low risk patients.
- It is recommended that consultations be carried out on the phone instead of check-ups; check-ups in person should be reserved for patients with concerning symptoms.

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Radiotherapy of breast cancer patients during the COVID-19 pandemic

Breast cancer patient categorisation for radiotherapy

As regards the rules for breast cancer patients' radiotherapy, the team drafting these recommendations proposes the following categorisation of patients according to the rules defined in table III.

Table IV presents the way of modifying treatment fractionation during the COVID-19 pandemic.

Moreover, the authors of these recommendations propose the following regimen modifications as regards radical surgical treatment:

- Each time, consider whether the extension of margins after breast-conserving therapy with a microscopically positive focal margin should be abandoned. Patients with microscopically positive focal margin may be qualified for

Table III. The method of breast cancer patient categorisation for radiotherapy during the COVID-19 pandemic

Category	Procedure	Clinical situation
A	The highest priority; it is necessary to begin radiotherapy up to 8 weeks after the completion of surgical or systemic treatment	– Inflammatory breast cancer – Massive metastases to ≥4 lymph nodes – Massive LVI – TNBC with N+ – ypN+ – Regional recurrence
B	It is necessary to begin radiotherapy up to 16 weeks after the completion of surgical or systemic treatment	– T4 (other than inflammatory breast cancer) – TNBC, N0 – ypT+ and ypN0 – LVI (NOS) – Invasive cancer in patients below 40 years of age – ER+ with 1–3 positive lymph nodes and other unfavourable prognostic factors (G3, LVI)
C	It is possible to postpone radiotherapy up to 20 weeks after the completion of surgical or systemic treatment	– Tumour T1, T2, N0 hormonosensitive – HER2-negative – Patients above 40 years of age – Patients on hormone therapy – Unfavourable prognostic factors (close margins, G3)
D	It is possible to abandon radiotherapy	– Patients above 65 years of age – Tumours up to 30 mm, N0 – ER+, HER2-negative, G1-2, margins ≥2 mm; please note – radiotherapy reduces the 5-year risk of local recurrence by 3% – DCIS, especially with ER+ – Patients on hormone therapy

Table IV. Modifications of fractionation method during the COVID-19 pandemic

Indications	Fractionation
APBI – Age >50 years old; tumour ≤2 cm T1, negative margin width min. 2 mm without LVI, ER+, BRCA negative, or – DCIS of low and medium differentiation level, detected using screening MMG, size ≤2 cm with negative margins ≥3 mm, located especially on the left side	– 5 fractions of 6 Gy each every 2nd day up to the total dose of 30 Gy – IMRT technique or: – According to FAST Forward: 5 fractions of 5.2 Gy each up to the total dose of 26 Gy within a week
WBI – **Resignation from BOOST**: patients T1-2N0 at the age of 50 or older with negative margins ≥2 mm, without unfavourable prognostic factors (G3, DCIS component) – **Resignation from the radiation of lymph nodes**: Post-menopausal patients T1, ER+, HER–, G1-2, SLND up to 2 lymph nodes affected (level I together with the place left after the incorrect resection of the sentinel node are affected)	– According to UK FAST: 5 fractions of 5.7 Gy each once a week up to the total dose of 28.5 Gy or: – According to FAST Forward: 5 fractions of 5.2 Gy each up to the total dose of 26 Gy within a week
WBI + BOOST ± RNI	SIB 15 fractions of 2.66 Gy per breast and 3.2 Gy per boost up to a total dose of 40 Gy per breast/ 48 Gy per boost
	SIB 16 fractions of 2.66 Gy per breast + 3 Gy per boost up to a total dose of 42.56 Gy per breast/ 48 Gy per boost
WBI + RNI	15 fractions of 2.66 Gy up to a total dose of 40 Gy
Patients after mastectomy with breast reconstruction	Options to consider: – 15 fractions of 2.66 Gy up to a total dose of 40 Gy – or 20 fractions of 2.25 Gy up to a total dose of 45 Gy

a boost of teletherapy (the dose and the technique depend on the current possibilities of the radiotherapy centre).

- The decision to abandon lymphadenectomy if metastases to sentinel lymph nodes are confirmed and replace it with radiotherapy should me made individually for each patient by a council of specialists in many disciplines. It is necessary to take into account the current possibilities of the surgical ward and the radiotherapy centre.

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Surgical treatment of breast cancer patients during the COVID-19 pandemic

As regards the rules for the surgical treatment of breast cancer patients, the team drafting these recommendations proposes the following categorisation of patients according to surgery urgency as defined in Table V.

Depending on the intensity and activity of the pandemic and the availability of equipment and staff, a decision may be made to postpone all surgeries except for emergency clinical situations only, such as the incision and draining of breast abscess, the securing of haemorrhage and/or haematoma, the revision of ischaemic lobes after mastectomy or breast-conserving surgeries, etc.

Recommendations for surgery qualification

The team drafting these recommendations proposes the following categorisation of surgery types according to the surgery urgency category as defined in table V.

- Patients diagnosed with malignant breast cancer (Category 1) should be operated on as planned. If the patient's oncological condition allows it and all the standards are maintained, single-stage mastectomy with breast reconstruction should be preferred to delayed reconstruction.
- Such surgeries as: incision and draining of breast access, removal of haematoma, revision of ischaemic breast lobes after mastectomy or breast-conserving surgeries (Category 1) should be performed as planned.

In selected clinical situations, combined therapy should begin with preoperative systemic treatment, both as a result of classical indications in the case of patients with locally advanced tumours, patients with HER2 positive or triple-negative breast cancer (chemotherapy and, optionally, immunotherapy) and patients with early, luminal HER2 negative breast cancer (hormone therapy). Detailed recommendations can be found in the chapter entitled *Rules for the systemic treatment of breast cancer patients during the COVID-19 pandemic according to the cancer phenotype and progression.*

- In the case of the absence of the radiological and pathological correlation and the need for the diagnostic resection of lesions with a high cancer risk (>10%), surgical treatment should not be postponed by more than a few weeks. At the same time, patients awaiting surgery should be selected on the basis of the following order (starting with the most urgent cases), taking into account their age and comorbidities: BIRADS 5, 4C, 4B (Category 2).

  In the case of B3 lesions with a high risk of cancer diagnosis (>10%), surgical treatment should be planned taking into account the potential risk of cancer confirmation, the patient's age, and comorbidities (Category 2–3). There is

Table V. Categories of breast cancer surgery urgency during the COVID-19 pandemic

Category 1	– New diagnosis of malignant cancer (unless preoperative systemic treatment is planned) – Incision and draining of breast abscess, removal of haematoma, revision of ischaemic lobes after mastectomy or breast-conserving surgery	Operate as planned, without delays
Category 2	– No radiological and pathological correlation and necessary diagnostic resection of lesions with a high risk of cancer (>10%)	Do not postpone by more than 6–12 weeks
Category 3	– B3 lesions with a risk of cancer diagnosis not exceeding 10% – Surgeries reducing the risk of breast cancer development – Postponed breast reconstruction surgeries – Benign breast cancer surgeries	Postpone until the COVID-19 epidemic ends in Poland or until the epidemiological situation stabilises and the oncological clinic is secured in terms of optimum staff and equipment

data indicating that B3 lesions (e.g. ADH and LN with ER expression) may be treated using tamoxifen or aromatase inhibitors. Also, DCIS with ER expression may be subjected to hormone therapy lasting 6 months. For this reason, the urgency of surgeries in such cases should be qualified as Category 3 and, while awaiting surgery, the patient should undergo local treatment preceded by hormone therapy (if possible, it is recommended to fix a clip marking the lesion).

- In the case of B3 lesions with the risk of cancer diagnosis not exceeding 10% (the analysis of the biopsy result combined with the radiological image), surgery may be abandoned/postponed until the COVID-19 epidemic ends in Poland (Category 3).
- Most experts recommend that radical surgery (extension of margins) after breast-conserving therapy should be abandoned in the case of a low risk of residual cancer.
- Most experts recommend that additional surgeries in the axilla (e.g. SLB after cancer diagnosis following the removal of B3 lesions or auxiliary lymphadenectomy after the biopsies of metastatic sentinel lymph nodes) should be abandoned in the case of a low risk of residual cancer.
- Surgeries reducing the risk of breast cancer should be abandoned/postponed until the COVID-19 epidemic ends in Poland (Category 3).
- Breast reconstruction surgeries should be abandoned/postponed until the COVID-19 epidemic ends in Poland (Category 3).
- Surgeries of benign breast tumours should be abandoned/postponed until the COVID-19 epidemic ends in Poland (Category 3).

Remarks related to surgical treatment

It needs to be emphasised that:

- The qualification of patients for mastectomy instead of breast-conserving therapy is not recommended because of better quality of life and long-term results (survival) following breast-conserving therapy as compared with mastectomy.
- Single-stage mastectomy with direct-to-implant breast reconstruction (DTI) are optimal procedures in the case of mastectomies performed due to malignant breast tumours (Category 1). Reconstructions with the patient's own tissue should be postponed, but in the situations when they are performed the revision/revascularisation of an ischaemic lobe using the patient's own tissue should be performed as an emergency procedure.

Planned admissions to breast cancer surgeries

The authors of this document propose that the admission procedure to a surgical ward for breast cancer patients during the COVID-19 pandemic include the following elements:

- It is recommended to determine the potential risk of SARS-CoV-2 infection in patients about 48 hours before the surgery (which includes obtaining the history of B and C symptoms – table VI – and the possibilities of potential contact with persons infected with SARS-CoV-2 from patients on the phone or in person).
- It is recommended that patients undergo self-isolation (self-isolation criteria are identical to the quarantine criteria) for 7–14 days before admission to a surgical ward.
- It is recommended that:
  - Patients express consent to self-isolation at the moment they are enrolled in the list of patients qualified for surgery as well as to the RT-PCR test before their admission to the hospital.
  - Patients sign a declaration that they are aware of the risk of SARS-CoV-2 infection despite the precautions and care exercised by the hospital with regard to prophylaxis and the protection measures used,
  - Only patients with no symptoms suggestive of SARS-CoV-2 infection or other upper respiratory tract infection who have a negative result on the PCR test for SARS-CoV-2 infection and who have undergone self-isolation for 7-14 days may be admitted to surgeries.

Please note!

In the case of each patient with the symptoms of cancer who has a positive result on the COVID-19 test, it needs to be determined when the patient may qualify for oncological treatment. Patients with positive results in emergency and urgent situations (e.g. abscess, haematoma, lobe necrosis) must be operated on in a hospital dedicated to the treatment of patients with SARS-CoV-2 infection.

Admissions to urgent breast and lymph node surgeries

It is recommended to divide surgeries that require immediate intervention in the following way:

- **EMERGENCY** surgeries, e.g. severe haemorrhage, revascularisation using a lobe of the patient's own tissue.
- **URGENT** surgeries, e.g. haematoma, abscess, revision of an ischaemic lobe after mastectomy/breast-conserving therapy.

Testing before the admission of an emergency patient to a surgical ward involves obtaining the patient's epidemiological history and, if preoperative RT-PCR is impossible, a chest CT scan (the majority of patients with indications for emergency surgery have a higher temperature and often non-specific pain; they should be checked for type B or C of symptoms – table IV).

The chest CT scan and RT-PCR recommendations do not apply to the patients with haemorrhage that occurred during hospitalisation at a given centre before which RT-PCR was performed. This recommendation applies to patients with severe haemorrhage admitted to hospital from home or other centres, only if it can be performed considering the patient's clinical condition.

Table VI. Categories and definitions of SARS-CoV-2 infection symptoms

Category of symptoms	Definition
Symptoms B (*mild symptoms suggestive of COVID-19*)	– temperature of 37–37.9°C or possible fever symptoms such as interchangeable shivering and sweating – shivering – muscle pain – sore throat – diarrhoea – loss of sense of smell and taste or change of taste – non-specific pain – upper respiratory tract infection
Symptoms C (SARS)	– cough – dyspnoea – fever of 38°C and higher

Conflict of interest: none declared

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Guidelines and recommendations

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Guidelines from the Polish Surgical Society and Polish Society of Oncological Surgery Concerning Quality Assurance for Centres Performing Cytoreductive Procedures and HIPEC Procedures in the Treatment of Primary and Secondary Peritoneal Tumours

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Surgical treatment of patients with peritoneal metastases in combination with Hyperthermic intraperitoneal Chemotherapy (HIPEC) and systemic treatments is applied with increasing frequency and, with correct patient qualification, allows for obtaining 5-year survival at a level of 32–52%. The conditions necessary for positive results of such treatment include the high experience of a given centre, its appropriate infrastructure, and appropriate patient qualification for the procedure. As a result of the debate connected with the need to evaluate treatment quality and results, at the request of the Peritoneal

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Cancer Section of the Polish Society of Oncological Surgery, the conditions for quality assurance were worked out and a Quality Assurance Commission was set up for the centres performing cytoreductive procedures and HIPEC procedures in the treatment of primary and secondary peritoneal tumours.

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Key words: quality assurance, cytoreduction, HIPEC, treatment quality, peritoneal cancers

Introduction

Surgical treatment of patients with peritoneal metastases, in combination with Hyperthermic IntraPEritoneal Chemotherapy (HIPEC), and systemic therapies is currently applied with increasing frequency. The results of numerous studies have shown that with appropriate patient qualification, 5-year survival may reach a level of 32–52% [1–3]. Good treatment results depend on the local cancer stage within the peritoneal cavity and the possibility of performing a radical cytoreduction of the peritoneal metastases.

CytoReductive Surgery (CRS) is very extensive, time-consuming and requires a great deal of experience in such procedures on the part of the surgeon. Experience is the outcome of the number of cytoreductive procedures performed by a given surgeon and also of their skills in large surgeries within the abdominal cavity [3, 4]. Gaining experience through an increasing number of procedures, called the "learning curve", is evaluated differently depending on the following factors: the experience of a given centre, the experience of the surgeon, the qualification for the procedure, and the type of tumour. The experience of a centre in the pre-surgical and post-surgical treatment and management of the patient after extensive surgical interventions is equally important [4].

All these issues affect the quality of the procedures, the rate of postoperative complications and the resulting mortality, and, which is of extreme significance, the length of overall survival (OS) and the length of recurrence-free survival (RFS).

In Poland, between 2009 and April 2020, 1056 CRS/HIPEC procedures were performed in 7 centres, and in 5 of them there were more than 150 procedures/centre conducted. Since May 2019, CRS/HIPEC procedures have been reimbursed by the National Health Fund, at a level covering the basic costs of the surgery, which allows such procedures to be performed more frequently in the centres of oncological surgery, general surgery, oncological gynaecology and paediatric surgery.

As a result of the debate connected with the need to evaluate treatment quality and results, at the request of the Peritoneal Cancer Section of the Polish Society of Surgical Oncology (PTChO), a joint Quality Assurance Commission was set up, consisting of the members of the Polish Surgical Society (TChP) and PTChO, whose task will be to evaluate the centres performing cytoreductive surgeries regarding all the above factors affecting the treatment results in patients with peritoneal metastases. To this end, a register of CRS/HIPEC procedures was also created, and, following the examples of German [5] or French [7] centres, the case of each patient treated with the CRS/HIPEC will be reported in this register, which is one of the obligatory conditions for quality assurance.

Indications for cytoreductive surgeries and HIPEC

Cytoreductive surgery (CRS) and Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) are generally recognised methods of the treatment of peritoneal metastases (PM) of such tumours as: appendiceal malignancy tumours, peritoneal mesothelioma, pseudomyxoma peritonei, and also, in some selected cases – peritoneal metastases of colorectal cancer, gastric cancer and ovarian cancer.

In the case of pseudomyxoma peritonei, peritoneal mesothelioma, primary peritoneal cancer (PPC) and peritoneal metastases of appendiceal malignancy tumours, cytoreductive surgery in connection with HIPEC are the treatment of choice. In the presence of peritoneal metastases of colorectal cancer, the CRS/HIPEC procedures are performed in selected cases, in whom the Sugarbaker Peritoneal Cancer Index (PCI), is not higher than 20 score with concomitant lack of distant metastases, with the exception of metachronous liver metastases (up to 3 resectable lesions) and lung metastases (one single resectable lung metastasis). In the case of peritoneal metastases of gastric cancer, cytoreductive procedures are performed only in a few selected patients in whom the disease stage of peritoneal metastases does not exceed 6–8 score in the PCI classification.

In patients with ovarian cancer, the CRS/HIPEC procedures are recommended in those with IIIc stage, after neoadjuvant chemotherapy in whom there was a positive response to systemic treatment.

In the case of patients with other types of cancer in whom peritoneal metastases occurred and in patients with resectable peritoneal metastases (or metastases in other locations) in whom all the possibilities of systemic treatment have already been used the CRS/HIPEC procedures can be performed if there is an absence of organ metastases, good general condition of the patient, and expected improvement in the condition after surgery. The decision concerning the possibility and necessity of such treatment is taken by a therapeutic team consisting of a surgeon, a clinical oncologist, a radiologist, and a pathologist. Cytoreductive surgeries and HIPEC procedures should not make up a treatment as such, but rather comprise a part of integrated multispecialist therapy, comprising neoadjuvant and adjuvant systemic treatment, surgeries, ablations,

targeted therapies, immunological systemic treatment and others, worked out in an individual treatment scheme for each patient. In a patient in whom it is possible to carry out treatment allowing for a macroscopic resection of a tumour, each combined/adjuvant treatment should be performed with the intention of a complete cure.

An integral therapeutic action which affects the treatment results is the improvement of the nutritional status and respiratory efficiency before the onset of therapy and also evaluation of comorbidities, made as early as possible. The biological condition of the patient should influence the decision about the surgery qualification, term and scope.

CRS/HIPEC procedures are burdened with a high rate of complications (reaching even 40%) resulting mostly from the extensive character of the surgery. Perioperative mortality is about 1–4%. Generally, the frequency rate and degree of complications connected mostly with CRS/HIPEC procedures are comparable with major surgeries such as pancreatic head resection (pancreatoduodenectomy). Therefore, the qualification for the procedure, preoperative preparation, early postoperative care, and patient management after the procedure all mean certain expectations from the medical team, comprising: experience in major surgeries, comprehensive professional preparation, allowing for surgery in all areas of the abdominal cavity and experience in multi-organ surgery. The scope of cytoreduction of the tumour tissue sometimes requires extensive organ resections, extensive peritoneal resection and long surgical procedures connected with patient hypothermia during the surgery or the use of a glucose solution as a perfusion fluid (with the administration of oxaliplatin), which might lead to osmolarity disorders, posing a danger to the central nervous system, among other things. That is why CRS/HIPEC procedures must be performed in centres which, thanks to an appropriate infrastructure and the experience of the surgeons and the entire therapeutic team, guarantee the best possible and safest therapeutic process.

Conditions allowing for good treatment results and the limitation of post-operative complications. Learning curve for CRS/HIPEC procedures

A condition for the success of CRS/HIPEC procedures is the possibility of achieving a complete (CC-0) or nearly complete (CC-1) cytoreduction and the limitation of post-operative complications.

Bhatt et al. [7] analysed the treatment results of 384 patients with primary and secondary peritoneal tumours, treated by 8 surgeons: five of them had 10–15 years' experience in oncological surgery, two – 5 to 10 years and one – more than 15 years; 6/8 had a specialisation in general and oncological surgery, whilst 2/8 in surgery of the GI tract.

PCI score ranged from 3 to 36, with 18 average. CC-0 was performed in 86.7% patients, and CC-1 in 4.2%, whereas in all others – CC-2/3. In 114/384 additionally EPIC (Early Postoperative Intraperitoneal Chemotherapy) was performed with the use of 5FU in 29% and Paclitaxel in 71% patients. 3–5 Clavien-Dindo grade 3-5 complications were observed in 27.3% patients. The 30-day perioperative mortality was 7.3%, and here the most frequent cause of mortality was neutropenia-related sepsis. The complications were as follows: neutropenia – 13%; anastomotic leakage – 7.8%, obstruction – 7.6%, pulmonary complications – 4.7%, sepsis – 4.4%. Revision surgery was required in 21/30 patients. In the conclusions of the study, the authors observe that the experience of the surgeons performing the CRS/HIPEC procedures is necessary for any improvement in the therapy results.

Andreasson et al. [8] evaluated the treatment results of 128 patients with pseudomyxoma peritonei (PMP) selected out of a general number of 307 CRS/HIPEC procedures in the treatment of peritoneal metastases. The group was divided into two parts: I – patients within the learning curve – 73 patients, II – patients after the learning curve. The R0/R1 radicality in group I and in group II was 48% *vs.* 80% ($p = 0.0002$) respectively. Intraoperative bleeding in group I and in group II amounted to 2000 ml *vs.* 800 ml ($p < 0.0001$) respectively, whilst the length of stay in group I was 18 days, and in group II – 16 days ($p = 0.016$). The 4-year survival was definitely longer in group II, in comparison with group I – 80% *vs.* 63% ($p = 0.02$). The recurrence free survival (RFS) in group I and group II was: 64% and 80%; the difference was clear in spite of the lack of statistical significance. Survival was conditioned by basic factors, such as: PCI and histopathological result (MCP-L *vs.* MCP-H). The stabilisation of the treatment results in PMP was observed after 220+/–10 procedures, which is a larger number than generally accepted for other types of peritoneal cancers. This is the outcome of a higher PMP stage in PCI score in the patients qualified for surgery than in the case of, for example, colorectal cancers – the scope of the surgical procedure is larger, which is connected with an increased rate of post-operative complications.

The learning curve should not only consist in the improvement in surgical skills (although they are of key importance for cytoreductive procedures and multi-organ resections), but also in the ability to correctly qualify patients for CRS/HIPEC procedures. The authors believe that an optimum level of CRS stability for a given centre is obtained after 200 procedures of this type.

The publication of Chang et al. [9] compared the therapy results of patients with peritoneal tumours treated in a centre collaborating with a more experienced mentoring centre. In the study material, 24 patients had PMP with average PCI score of 20.3 (6–39), whilst in 26 patients the metastases of other cancers were found in the peritoneum (mostly of colorectal cancer) with average PCI 8.7 (2–21). CC-0 was performed in 80.8% patients with peritoneal metastases of colorectal cancer, whilst in patients in PMP, the CC-0 rate was 75%. The average

length of stay at the ICU (Intensive Care Unit) was 5 days, whilst the average length of hospital stay – 14 days. In the post-operative period, no III/IV grade complications or deaths were observed. In 32% cases there were I/II grade complications. 29 patients needed blood transfusions, and in PMP patients the quantity of transfused blood units was larger than in patients with colorectal cancer. The CRS/HIPEC interventions made up a complex of various procedures: diagnostic, qualifying, preparatory, surgical, oncological and anaesthesiologic. All of these translated into the final treatment results. According to the authors, in order to get optimum stable therapy results, which also includes the limitation of complications and perioperative mortality, it is recommended that 90–180 procedures within the "learning curve" should be performed in a centre which performs CRS/HIPEC procedures. The evaluation of the authors' own results showed the number of procedures within the learning curve may be lower, provided that a centre is supervised by an "authorising" centre which has adequate experience in CRS/HIPEC procedures.

Publications concerning the analysis of the experience of a surgeon and a centre performing CRS/HIPEC procedures quote the work of Voron et al. [10] extensively. These authors list the following risk factors for perioperative complications: a patient history of earlier procedures within the abdominal cavity, age above 60 years, the stage of the lesions within the peritoneal cavity above 12 score in the PCI scale and comprising more than 6 regions. In the analysis of the results obtained in their own material, Voron proposes the following recommendations for new centres introducing CRS/HIPEC procedures: the avoidance of risk factors, the limitation of cytoreductive surgeries to only the metastases of colorectal cancer, appendix and ovaries and excluding these procedures in patients with a peritoneal myxoma or mesothelioma. The supervision by surgeons fully trained in CRS/HIPEC is recommended. According to the authors, it is necessary that the surgeon's experience in such procedures should not be fewer than 40 CRS procedures, which is the condition for performing >70% procedures with complete macroscopic radicality (CC-0), and 140 for complete and satisfactory results with regards to the reduction of complications, radicality of surgical interventions, and obtaining the best therapy results.

In the study of Polanco et al. [11], the analysis concerned the results of treatment with the method in 370 patients with the following types of cancer: appendiceal malignancies (282), peritoneal mesothelioma (60) and gastric cancer (24), in whom peritoneal metastases were diagnosed. The CC-0 radicality was obtained in general in 84.2% patients, the 60-day complication rate was 30%, whereas perioperative mortality – 1.9%. The evaluation of the stage of the lesions with the PCI score showed that the higher the PCI score, the larger the rate of non-radical surgeries. Causes of serious perioperative complications was a high tumour grade, a diagnosis of *mesothelioma peritonei*, and peritoneal metastases of gastric cancer. The authors observed that in order to minimise the risk of non-radical surgery and to reduce serious perioperative complications, as many as 180 CRS/HIPEC procedures must be performed in a given centre. For the improvement of oncological treatment, the learning curve is – according to these authors – 90 procedures. With this number of procedures performed, the rate of 2-year survival in patients increases. The authors emphasise the necessity of performing these procedures in high-volume hospitals as this allows these surgeries to be carried out in accordance with generally adopted safety criteria.

One of the earlier papers discussing the necessity of gaining experience for the improvement in the surgical treatment results in patients with peritoneal metastases comes from a Dutch centre [12]. In this study, the treatment results of 323 patients with peritoneal metastases of colorectal cancer (184 patients) and peritoneal myxoma (139 patients) in three subsequent 3-year periods were analysed. CC-0 was, in these subsequent periods: 35.6%, 48.8% and 65.1%. The difference between specific periods was statistically significant ($p = 0.012$). The rate of postoperative complications decreased from 71.2% to 34.1% ($p < 0.001$). A tendency in hospital stay reduction was observed, decreasing from 24 to 17 days in comparison between the II and III periods, a feature that was not seen between periods I and II. The 2-year survival rate increased from 59.7% in period I, through 61.9% in period II, to 71.7% in period III. The authors showed a continual improvement in the treatment results, evaluated with regards to the possibility of CC-0 resections, was seen after 130 procedures.

The opinions concerning the necessary (and beneficial) supervision of a more experienced centre over a centre which is at the stage of introducing cytoreductive surgeries, were presented in the study by Kusamura et al. [13]. The collaboration with regards to mentoring assistance allows for shortening the learning curve for the CRS/HIPEC procedures and for the reduction of the initial number of adverse factors connected with the procedure, such as: inappropriate patient qualification or the qualification of patients with too high a stage of peritoneal metastases in relation to the professional experience, which results in incomplete cytoreduction, the occurrence of serious perioperative complications and a high rate of perioperative mortality. This opinion was presented after the analysis of the authors' own materials from an Italian centre which was one of the most experienced in the treatment of peritoneal metastases [14]. This study evaluated the treatment results of 420 patients with peritoneal cancers undergoing CRS/HIPEC surgeries. The rate of incomplete cytoreductions, serious postoperative complications and perioperative mortality were analysed. The factors affecting the lack of complete cytoreduction in a multi-variant analysis were: worse general condition of the patients ($p = 0.01$), PCI > 20 score ($p = 0.001$), previous systemic chemotherapy ($p = 0.011$), tumour histological type ($p = 0.027$) and the experience gained by a centre – all these factors were evaluated with regards to the results of the subsequent 50-per-

son patient groups (p = 0.042). The factors connected with serious perioperative complications in a multivariant analysis were: older age (>52 year of age *vs.* <52 year of age, p = 0.009), decreased level of albumins < 3.5g/dL (0.019), PCI > 20 score (p = 0.002) and the timespan of the procedure >600 minutes *vs.* <600 minutes (p = 0.025). The occurrence of complications was not affected by the experience measured by the number of CRS/HIPEC procedures, which can be explained by the maximum level of complication reduction after the performance of 140 procedures. The authors note that such a number of CRS/HIPEC procedures allows for obtaining optimum results both with regards to the possibility of complete cytoreduction and the limitation of serious postoperative complications.

Huang et al. [15] presented the results of a study comprising a group of 800 patients treated with CRS/HIPEC procedures for primary and secondary peritoneal cancers. The study subjects were divided into 8 groups, each comprising 100 patients. The analysis showed an improvement in the treatment results evaluated with 5-year survival between group I (the first 100 patients) and group IV (patients 301–400). For the metastases of colorectal cancer, the survival was: 15% and 31% respectively, for PMP – 64% *vs.* 94%, and for peritoneal mesothelioma – 40% *vs.* 53%. An improvement in the results was also seen with regards to a decrease in postoperative complications, decrease in the amount of blood transfused and decrease in the length of hospital stay. The authors observe that the improvement in the treatment results was obtained after 200 CRS/HIPEC procedures. Also, the treatment of patients with a high stage of peritoneal metastases was reduced from PCI < 20 score to PCI < 15 score.

The problem of the effect of the learning curve on the treatment results of the patients with peritoneal metastases was also the subject of the study carried out by Kuijpers et al. [16]. The analysis concerned the results of 372 patients with peritoneal metastases treated with CRS/HIPEC in a centre with experience in performing cytoreductive surgeries and in a new centre introducing such procedures. Mentoring supervision by a more experienced centre had a positive effect on the initial rate of complete cytoreductions in the new centre, amounting to 86% in comparison with 66% in the mentoring centre for the first 100 procedures (p < 0.001). This supervision resulted also in a limitation of serious postoperative complications in comparison with a pioneer centre. The authors observe that mentoring supervision allows for shortening the learning curve, early improvement in the quality of cytoreductive procedures and the limitation of perioperative complications.

Expert opinions from the centres with the largest experience in cytoreductive and HIPEC procedures

The analysis of publications discussing the conditions which should be met by a surgeon performing CRS/HIPEC procedures pointed to large discrepancies in indications concerning the surgeon's experience in performing such procedures for optimal treatment results and for the reduction of the rate of perioperative complications. The required experienced is defined as the number of procedures performed ranging between 40 and 90, and often depends on the number of procedures in a given centre. The experience of a centre, in turn, should not be below 90 procedures (up to 200), before a centre is considered to meet the required conditions. Taking into consideration the influence of the collaboration between less experienced and more experienced centres on the decrease of the number of independently performed cytoreductive procedures ("from the start") by a given surgeon and also on the experience of the entire centre, the learning curve is not homogenous and depends on many factors.

In order to obtain credible expert opinions in the above respect, we have asked, in an email, for the opinion of some distinguished European experts in treatment of patients with peritoneal tumours with CRS/HIPEC procedures; the experts were:

1. Professor Beate Rau, Chirurgische Klinik Campus Charite Mitte, Berlin, Germany;
2. Professor Marcello Deraco, Director of the Peritoneal Surface Malignancies Unit Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Co-Director of ESPSO European School for Peritoneal Surface Oncology;
3. Professor Olivier Glehen, Service de chirurgie digestive et endicrinienne, Centre Hospitalier Lyon, France;
4. Professor Vic Verwaal, Aarhus University Hospital, Denmark.

In the opinion of the international experts presented in table I, at least 100 to 150 procedures with the CRS/HIPEC method are required to be performed in a centre for obtaining an optimum quality of cytoreductive procedures. Three experts drew attention to the need for performing such procedures in high-volume centres. The experience of the entire team is necessary, which translates into a minimum number of 25 or 20–30 procedures per year. Two experts pointed to the need to create a training programme in CRS/HIPEC procedures for surgeons, whilst all of them suggested the collaboration with mentoring centres as an element that is necessary for the best results in the new centres. One of the experts observed that a database is necessary for continuous improvement in the treatment results. Such databases exist in German, French and Dutch centres.

The proposal for the quality assurance recommendations of the Polish Surgical Society and Polish Society of Oncological Surgery concerning the necessary criteria for meeting the conditions for a Reference Centre

On the basis of the published data analysis, the experts' own experience and the consultations with the experts from foreign centres, a team of surgeons associated in the Peritoneal Tumour Section of the Polish Society of Oncological Surgery worked

Table I. European Experts' Opinion Concerning the Treatment of the Patients with Peritoneal Cancers with CRS/HIPEC Procedures

Data source (expert)	Learning curve of a centre	High-volume centre	The experience of a surgical team	Training programme	Collaboration with a mentoring centre	Database
Prof. B. Rau		Yes	Yes		Yes	Yes
Prof. M. Deraco	150 procedures	Yes	25 procedures/year		Yes	
Prof. O. Glehen			20–30 procedures/year	Yes	Yes	
Prof. V. Verwaal	100 procedures	Yes		Yes	Yes	

Table II. The quality assurance conditions defined by the Polish Surgical Society and the Polish Society of Oncological Surgery for centres performing cytoreduction and HIPEC procedures in the treatment of primary and secondary peritoneal tumours

No.	Quality assurance conditions
1.	A hospital performing a full profile of procedures in the peritoneal cavity
2.	Intensive postoperative high dependency unit providing specialist care after CRS/HIPEC procedures
3.	Hospital infrastructure allowing for the preparation, administration and disposal of cytostatic drugs
4.	Team experienced in the management of patients after chemotherapy
5.	The experience of the surgical team performing CRS/HIPEC procedures in extensive oncological surgeries in the abdominal cavity
6.	Surgical team dedicated to CRS/HIPEC procedures
7.	Surgeon's experience > 50 procedures CRS CC-0/1 (reference centre) or < 0 procedures CRS CC-0/1 (the centre with contracted co-operation for the evaluation of the CRS/HIPEC procedures with a reference-mentoring centre)
8.	Annual rate of CRS/HIPEC surgeries – at least 20–25 procedures
9.	Obligatory registration of all CRS/HIPEC surgeries in the CRS/HIPEC procedures register
10.	Obligatory participation in an annual analysis of the CRS/HIPEC procedures on the basis of the register data

out a model of the conditions necessary for awarding the status of reference centre (i.e. one that authorises the procedure) for an institution. The results are presented below in table II.

In the period of creation of specialist centres for the treatment of peritoneal tumours (i.e. combining surgical procedures with intraoperative chemotherapy) it is important to appoint the Procedure Leader i.e. a surgeon specialising in general surgery and/or oncological surgery. Such a person must have professional experience in the treatment of peritoneal cavity tumours with a full scope of surgeries performed within the abdominal cavity. Moreover, the results of surgical treatment in cytoreductive and HIPEC procedures will be regularly (annually) evaluated, which is supposed to guarantee appropriate quality for a given procedure, which is a key element for the treatment results in cancer. It is also required to a have a certificate in training in the use of HIPEC equipment.

The execution of the quality assurance process in CRS/HIPEC centres by the Polish Surgical Society and Polish Society of Oncological Surgery

In order to work out the principles of Quality Assurance, the Peritoneal Cancer Section of the Polish Society of Oncological Surgery submitted a request to the Management of the Polish Surgical Society and Polish Society of Oncological Surgery to analyse the proposals presented concerning the conditions for the centres and therapeutic teams which must be fulfilled for the best possible treatment of patients with peritoneal cancers. These proposals were presented and discussed twice at meetings with surgeons performing CRS/HIPEC procedures and possessing broad experience in extensive surgeries within the abdominal cavity. Additionally, each of the individuals interested in the debate had the opportunity to present their standpoint and conclusions from the discussion in an email. Then, after obtaining a positive opinion from the National Consultant for General Surgery and National Consultant for Oncological Surgery, an application was sent to the Managements of the Polish Surgical Society and Polish Society of Oncological Surgery for the creation of a joint Commission whose task would be to verify whether the quality assurance conditions in the centres which would like to be audited were met. Representatives experienced in CRS/HIPEC procedures or in extensive surgeries within the abdominal cavity, two for the Polish Surgical Society and two for the Polish Society of Oncological Surgery, were nominated.

The centres which obtain a positive opinion from the Quality Assurance Commission will be entered into the register of CRS/HIPEC procedures and will be regularly verified with respect to the results of the treatment of patients with peritoneal cancers. The centres with less experience (an absence of or fewer CRS/HIPEC procedures than the number required for Quality Assurance) are obliged to select a reference centre which meets all the Quality Assurance requirements and to co-operate with them. This is compliant with the opinions of international experts and with the published data. Every year, the Quality Assurance Commission will analyse the quality of cytoreductive procedures with regards to patient qualification

and the quality of surgical procedures on the basis of the data from the CRS/HIPEC procedures register. Each patient who is treated with CRS/HIPEC procedures will have to be reported to this Register. This is one of the conditions for positive Quality Assurance from the Polish Surgical Society and two from the Polish Society of Oncological Surgery for a given centre.

This article was prepared by the Peritoneal Cancer Section of the Polish Society of Oncological Surgery, which actively collaborates with the Polish Surgical Society. This publication will be jointly published in *Polski Przegląd Chirurgiczny* [Polish Journal of Surgery] and *Nowotwory. Journal of Oncology*.

Abbreviations

CC-0 – complete cytoreduction procedure
CC-1 – nearly complete cytoreductive procedure
CRS – cytoreductive procedures
EPIC – early postoperative intraperitoneal chemotherapy
HIPEC – Hyperthermic intraperitoneal Chemotherapy
ICU – Intensive Care Unit
OS – overall survival
PCI – peritoneal cancer index
PM – peritoneal metastases
PMP – pseudomyxoma peritonei
PTChO – Peritoneal Cancer Section of the Polish Society of Oncological Surgery
RFS – recurrence free survival
TChP – Polish Surgical Society

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The prognostic significance of HLA-A2 expression on somatic cells in patients with left-sided colon and rectal cancers

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Introduction. Current knowledge about colorectal cancer (CRC) identifies tumor immunogenicity as one of the more important issues. In cancers, a prerequisite for immune system activation is the presentation of tumor associated antigen (TAA) epitopes to immunocompetent cells. HLA-A2 is one of the antigens in the context of which TAAs are present, but data on the possible impact of HLA-A2 antigen expression on the survival of patients with colorectal cancer are scarce and sometimes contradictory. The aim of this study was to analyse the relationship between HLA-A2 expression in patients with left-sided colorectal cancer in various stages of disease and their long-term survival, and to answer the question of whether a lack of HLA-A2 expression is actually a negative prognostic factor.

Material and methods. A prospective analysis of 58 patients with left-sided colorectal cancer was carried out. Expression of HLA-A2 was determined by patient blood lymphocyte staining, and analysed using flow cytometry.

Results. In the study group, patients with HLA-A2 expression lived statistically longer than HLA-A2 negative patients ($p = 0.027$). There was no significant difference in overall survival between the HLA-A2+ and HLA-A2- groups with stage II and III left-sided CRC. However, the Cox proportional hazard model showed that a lack of HLA-A2 expression was a negative prognostic factor in the group of radically operated patients without distant metastases.

Conclusions. HLA-A2 status may affect the clinical course of patients with left-sided colon and rectal cancer, although left-sided tumors are less immunogenic than right-sided ones. HLA-A2-positive patients with left-sided colorectal cancer lived statistically longer than those who were HLA-A2-negative ($p = 0.027$). Lack of HLA-A2 expression was a negative prognostic factor in the group of radically operated patients.

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Key words: HLA, HLA-A2, left-sided colon cancer, overall survival, prognostic biomarker

Introduction

The appropriate immune response to tumor cells is dependent on their ability to be recognized by immunocompetent cells. Tumor associated antigens (TAA), or their epitopes, are presented by antigen presenting cells (APCs) in the context of human leukocyte antigen (HLA) expression. Some TAA-derived

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epitopes require a specific HLA, or other antigens, for presentation. HLA class I antigens are integral membrane glycoproteins that are inherited and expressed at varying levels on the surface of virtually all somatic cells [1]. It is known that HLA-A2 (MHC class I) is common among Caucasians (approximately 45% of the Caucasian population) [2] and that some antigens characteristic for colorectal cancer (CRC) are presented in its context. These include CSNK1A1, GAS7, HAUS3, SRPX, WDR46, ERBB2, AKAP13, and MUC1 antigens.

A large proportion of cancer vaccine research has been limited to the HLA-A2-positive population, and HLA-A2-negative patients have been used as a control group in targeted immunotherapy studies [3]. However, some findings show that HLA status itself can influence the clinical course of the disease, as the natural immune response may differ between patients with or without this antigen expression.

Many studies have described HLA expression in patients with cancers of the head and neck [4], breast [5], ovary [6, 7, 8], prostate [8], primary laryngeal squamous cell cancers [9], non-small cell lung cancer [10], melanoma [1], as well as on tumor cells.

Data on the possible impact of HLA-A2 antigen expression on the survival of patients with colorectal cancer are limited and sometimes contradictory. Most data covers a mixed population of right and left-sided colon and rectal cancer patients. Since we know that MHC class I expression is often absent in micro-satellite instability (MSI) tumors [11, 12], which are clinically characterized as having a favorable prognosis and are more frequently observed in right-sided colon tumors [13, 14], the results obtained from a mixed population of all colon and rectal cancer patients might not be representative [15].

According to UICC cancer statistics published in 2018, colorectal cancer is the 3rd cancer in terms of incidence and second in cancer-related mortality in the world. Despite progress in prevention and therapy, there is still space for new therapies and translational research in colorectal cancer. In recent years, several trials on immunotherapy using checkpoint inhibitors in colorectal cancer have produced promising results [16]. However, more than 50–80% of cancer patients fail to respond to checkpoint inhibitor therapy [17]. Therefore, the investigation of predictive and prognostic factors in various subgroups of colorectal cancer patients is justified.

Colorectal cancer is not a homogenous disease in terms of primary tumor location, and there is evidence that right-sided and left-sided cancers may have different biologies and prognoses [18–21]. CRC immunogenicity, understood as the ability to induce an immune response, also differs between the right and left sides of the colon. There are two different types of colorectal cancer – those which are highly immunogenic (with multiple DNA mutations, chromosomal stability (CS), microsatellite instability (MSI) phenotype and the presence of multiple tumor-infiltrating lymphocytes (TILs), prevalent in the right colon) and those with low immunogenicity (with a limited number of DNA mutations, a microsatellite stable (MSS) and chromosomally instable (CIN) phenotype located in the left side of the colon and rectum) [22]. This heterogeneity should be used to stratify patients in order to provide them with the most optimal, current, and novel immune-based therapeutic strategies available in clinical practice [21].

In this study, we concentrated on tumors located in the left colon and rectum – a more homogenous sub-group of CRC. Locally advanced malignancies were the main area of interest.

The aim of this study was to answer the question of whether HLA-A2 expression is an important prognostic factor in left-sided CRC, which may present with decreased immunogenicity compared to right-sided CRC.

Material and methods

The study group consisted of 58 colorectal cancer patients treated in a single institution between 2007 and 2012. Only patients with tumors located in the rectum or left colon were included. The term left colon was defined as the large intestine, from the left 1/3 of the transverse colon distally. All patients had histologically confirmed disease, were over 18 years-old, and had had an electively performed surgical procedure. Patients with simultaneous right-sided colon cancer or patients with a history of other neoplastic diseases were excluded. Preoperative radiotherapy was used in 3 of the rectal cancer patients**.** All patients had no history of autoimmune diseases or recent infections. The group was composed of 25 women and 33 men, with a mean age of 66 (SD 11), in varying stages of disease (tab. I).

The surgical procedures were carried out according to oncological guidelines. Due to the changes of the TNM staging systems during the study period, all the specimens were re-staged according to the 7th edition of the TNM. The clinical and pathological data were recorded. Patients received postoperative chemotherapy if indicated. All patients were followed up for at least 5 years, or until death, and dates of death were verified by the census registry office.

All patients provided their informed, written consent. The study was approved by the Jagiellonian University Ethical Committee KBET no. 86/B/2007 and KBET no. 122.6120.128.2015. The study was registered at ClinicalTrials.gov, registration number NCT03640572.

Blood samples were collected prior to any interventional procedure in sterile EDTA vacutainers. Cell preparation was started 1–2 hours after a blood draw. Expression of HLA-A2 was determined by patient blood lymphocyte staining, using PE-conjugated mouse anti-human HLA-A2 mAb or PE-conjugated isotype-matched mouse immunoglobulins (both BD Pharmingen) as a negative control, followed by lysis of erythrocytes (FACS Lysing Solution, BD Biosciences) and flow cytometry analysis (FACS Canto).

Statistics

The statistical analysis was conducted using the software Statistica 13 (StatSoft Inc.). The Kaplan-Meier method was used for the calculation of survival probabilities and the Wilcoxon-

Table I. Clinicopathological characteristics of the patients

Tumor location	Number of patients
Left colon	27
Rectum	31
T1	0
T2	9
T3	39
T4	10
N0	25
N1	15
N2	14
Nx	4
M0	46
M1	12
Stage I	7
Stage II	18
Stage III	21
Stage IV	12
Grade 1	17
Grade 2	25
Grade 3	9
Grade not assessed	7
R0	44
R1	2
R2	12

-Gehan test for the comparison of survival curves between groups. The Cox proportional hazard model was used for multivariate analysis. The Chi-square test and the Fisher exact test were used to compare the clinical and pathological features between the HLA-A2-positive and negative groups. Mean patient age was compared using Mann Whitney's U test. A p--value of < 0.05 was established as statistically significant.

Results

Fifty-eight colorectal cancer patients were evaluated; 33 were found to be HLA-A2-positive (56% of whole study group). The distribution of clinicopathological characteristics of patients in HLA-A2+ and HLA-A2- groups are listed in table II.

Table II. Clinicopathological characteristics of patients in HLAA2+ and HLAA2- groups

	HLAA2+ n = 33	HLAA2– n = 25	p
Age	65.85 (32–82)	65.95 (52–89)	0.863
Gender M/F	21/12	12/13	0.234
T1	0	0	>0.05*
T2	5	4	0.930
T3	27	12	0.007
T4	1	9	0.001
N-	15	10	0.678
N+	18	15	0.678
M0	28	18	0.232
M1	5	7	0.232
Stage I	4	3	0.989
Stage II	11	7	0.664
Stage III	13	8	0.562
Stage IV	5	7	0.232
Left colon	20	7	0.014
Rectum	13	18	0.014
G1	10	7	0.847
G2+G3	23	18	0.847

The groups of patients with the presence or absence of HLA-A2 had similar structures in terms of age, gender, grade of differentiation (G), and TNM, and differed significantly only in terms of their T3 and T4 characteristics and location (left colon/rectum).

The analysis of clinicopathological features showed that in the group of patients with T3 tumors, patients with HLA-A2 expression predominated, while in the group of patients with T4 tumors most patients were HLA-A2-negative.

Among the patients with rectal tumors, the HLA-A2--negative phenotype dominated, while among patients with left-sided colon tumors, significantly more patients had HLA-A2 expression.

All the patients were followed-up for at least five years.

The 5-year survival rate for HLA-A2-positive patients in all stages was 72.7%, while for HLA-A2-negative patients it was 40% (fig. 1).

The Kaplan Meier plot (fig. 1) showed that in the entire study group HLA-A2-positive patients lived longer then

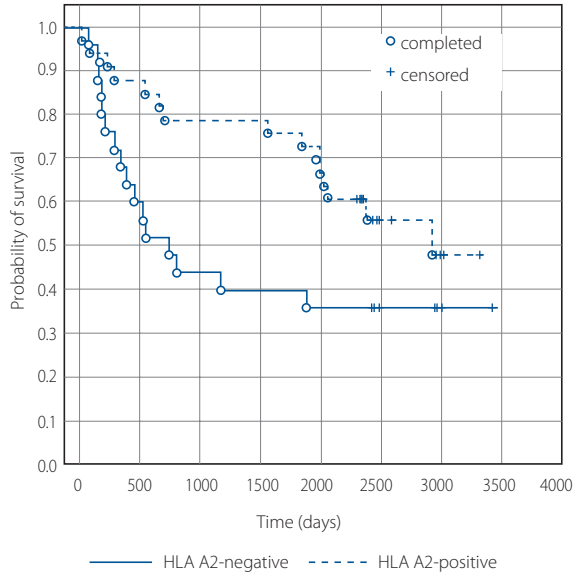

Figure 1. Cumulative proportion of survival for left-sided colorectal cancer patients in all tumor stages in HLAA2+ and HLAA2– groups

HLA-A2-negative ones. This difference was statistically significant (p = 0.027) according to the Wilcoxon-Gehan test.

Therefore, in our patient cohort, we found that the expression of HLA-A2 was associated with prolonged survival. In a group consisting of stage II and III CRC analyzed together, the 5-year survival rates were 75% and 36% for HLA-A2-positive and HLA-A2-negative patients respectively. The difference between the groups however was not statistically significant (fig. 2).

An analysis of the prognostic factors in locally advanced cancer was performed.

Variables with confirmed prognostic value, such as tumor stages I–III, radicality of resection, as well as HLA-A2 status were included in the Cox proportional hazard model.

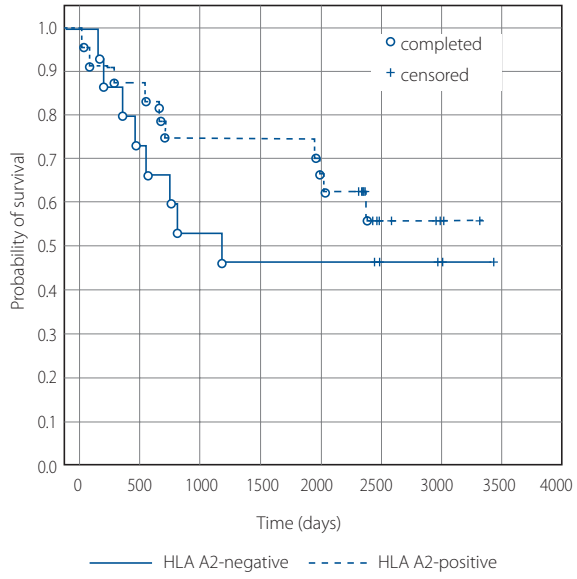

Figure 2. Cumulative proportions of survival for HLA-A2+ and HLA-A2– groups of left-sided colorectal cancer patients – tumor stages II+III

HLA-A2 status was an independent prognostic factor in this group of patients (p = 0.012; HR = 2.65; with 95% CI for HR: 1.23–5.72). This finding showed that the lack of expression of HLA-A2 was an independent negative prognostic factor.

Discussion

The results from this study show that the presence of HLA-A2 in patients with left-sided colon and rectal cancers is an important prognostic for their outcomes. HLA-A2 is among the 8 most frequent HLA alleles (HLA A*01, A*02, A*03, A*24, B*07, B*08, B*44, C*07) in the Caucasian population [23]. In our study, the expression of HLA-A2 was observed in 56% patients with CRC. This percentage is slightly higher than the prevalence of HLA-A2 antigens in the Caucasian population in Central and Western Europe, which is around 45% (42.6-51.3%), and also higher than in the results of the study by Kiewe et al. who found a frequency of exactly 50% of HLA-A2 expression. [2] However, these findings are not statistically significant.

The groups of patients with the presence or absence of HLA--A2 expression had similar structures in terms of age, gender, grade of differentiation (G) and TNM, and differed significantly only in terms of T3 and T4 characteristics and location (left colon, rectum). These patients were not preselected, and the researchers were not aware of their HLA status during patient recruitment.

The location of tumors does not influence survival, because, as previously mentioned, rectal and left-sided colon cancer patients have very similar prognosis. Moreover, only 3 rectal cancer patients received pre-operative radiotherapy (two HLA-A2-negative and one HLA-A2-positive). The depth of the invasion itself, the T feature, is not a potent prognostic factor until the tumor cannot be radically resected. In order to overcome the imbalance in the above mentioned features, a multivariate proportional hazard model was constructed.

In our analysis, there was a significantly higher survival rate for HLA-A2-positive patients, with 72.7% 5-year survival for the HLA-A2-positive patients and 40% for HLA-A2-negative patients. The difference between these groups was found to be statistically significant (p = 0.027).

Our results conflict with the study by Kiewe et al. who found no statistically significant difference in 5-year survival and overall survival between HLA-A2-positive and HLA-A2--negative groups of patients with colorectal cancer [2]. One possible explanation for these differences might be differences in the patient cohort.

In the group of patients with locally advanced cancer after radical surgery, the lack of expression of HLA-A2 was an independent prognostic factor which negatively affected survival (p = 0.012; HR = 2.65; with 95% CI for HR: 1.23–5.72). This phenomenon is not observed in all cancers. In breast cancer, HLA positive status is a favorable prognostic factor, however, in ovarian cancer it is a negative prognostic factor [7].

The 2015 Consensus of Molecular Subtypes (CMS) is considered the most robust classification system currently available

for CRC – with clear biological interpretability – and a basis for future clinical stratification and subtype-based targeted interventions. This study identified 4 consensus molecular subtypes: CMS1 (MSI-immune), CMS2 (canonical), CMS3 (metabolic), CMS4 (mesenchymal) [24]. In relation to the anatomical location of CRC, CMS1 dominates in the right colon, CMS2 in the left colon, and CMS3 and CMS4 tumors do not have a specific anatomic location.

The group of patients in our investigation was more homogenous than in other studies, as only left-sided colon and rectal cancer patients were included. Earlier studies analyzed a mixed population of colorectal [2, 25, 26], colon [27], or only rectal cancer patients [15, 28]. The authors of previously published papers did not take into account the fact that colorectal cancer may differ in biology, and thus the prognosis and response to treatment may vary, depending on the location of the tumor [18–21].

HLA-A2 expression is investigated in patients in several ways. One of the approaches uses the identification of HLA-A2 on the surface of cancer cells, other approaches identify its expression on somatic cells.

In publications, HLA status is mostly characterized in terms of the tumor environment, and its involvement in the evasion of the immune response, by analysis of its expression by the immunohistochemistry in tumor-infiltrating immune cells or in tumor cells. On the other hand, HLA status is detected in host peripheral blood cells, reflecting its role in the recognition of tumor antigens, by identifying the HLA protein using techniques such as immunoassays, flow cytometry etc., or the gene alleles, mainly by polymerase chain reaction (PCR) [10].

The interpretation and comparison of studies examining HLA class I antigen expression are generally very difficult, because the methods used for the analysis of HLA class I antigen expression vary substantially [29]. According to a recently published study, exposure to an inflammatory environment might be responsible for upregulating HLA class I gene expression in tumor cells, but the presence of HLA class I molecules at the cell surface is precluded by defects in other components of the antigen processing machinery. Besides, RNA expression analysis can detect HLA class I not only in tumors but also in immune and other stromal cells expressing this HLA. Therefore, HLA class I phenotypes should be supported by genetic data confirming mechanistic defects, while RNA expression level appears insufficient to determine HLA class I tumor status [30].

Although there are some studies assessing HLA-A on CRC tumor surface in the available literature [15, 25–28, 30], HLA-A2 expression on somatic cells in patients with CRC has not been extensively studied in the past [2].

In this study we decided to determine HLA-A2 expression on somatic cells from the peripheral blood, and therefore, it is very difficult to compare our findings with those of other studies. It would be interesting to assess HLA-A2 expression on somatic and cancer cells simultaneously, but unfortunately this was not possible due to organizational and financial constraints.

Tumor cells do not present distinctly different HLA class I antigens than the host cell, however, it should be noted that one mechanism of cancer escape from the control of the immune system is the loss, or reduction, of the expression of HLA class I antigens on cancer cell surfaces. Therefore, tumor cells may differ from somatic cells in this respect. The loss of HLA class I is rather rare (16–20%) among MMR-p (MSS) tumors which dominate in the left half of the colon, which was confirmed on a larger cohort by Ijsselsteijn et al. [30]. The conclusion from their study, that HLA class I is an important determinant of metastatic homing in CRCs, is in-line with our observation of better prognosis for patients with left-sided colorectal cancer and HLA-A2 expression.

Recently, Löffler et al. [23] provided comprehensive data on the HLA presented antigenic repertoire of CRC cells. They identified a set of 758 HLA class I and 310 HLA class II presented peptides (ligandome), exclusively expressed on colorectal carcinoma tissue, and proposed 12 naturally presented HLA class I ligands out of 38 preselected peptides (five peptides each were selected for the seven most frequent HLA allotypes in the Caucasian population and three additional peptides were selected for HLA-C*07), as putative candidates for future anti-CRC vaccination. Although among them only one HLA-A2 was presented, one cannot exclude the possibility that other non-selected peptides, including those related to HLA-A2, may be effective in the induction of an adaptive anti-tumor immune response, thus increasing the survival of HLA-A2 positive patients. Still more translational studies should be performed in order to understand CRC and immune system interactions.

Conclusions

In summary, the results of our study show that:

1. Patients with left-sided colorectal cancer and HLA-A2 expression lived statistically longer than HLA-A2-negative patients.
2. Lack of HLA-A2 expression was a negative prognostic factor in the group of patients with radical resections without metastases.
3. HLA-A2 status may affect the clinical course of patients with left-sided colon and rectal cancer, even though these tumors are considered less immunogenic than right-sided cancers.

The question remains whether we should consider the status of HLA-A2 expression when qualifying patients for adjuvant treatment and choosing between more or less aggressive therapies to improve their treatment results.

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Abbreviations

APC – antigen presenting cell

CI – confidence interval
CIN – chromosomal instability
CRC – colorectal cancer
HLA – human leukocyte antigen
HLA-A2 – human leukocyte antigen A2
HR – hazard ratio
MHC – major histocompatibility complex
MMR – mismatch repair
MMR-d – mismatch repair deficient
MMR-p – mismatch repair proficient
MSI – microsatellite instability
MSS – microsatellite stable
MUC1 – mucin 1
OS – overall survival
TAA – tumor-associated antigen
TIL – tumor-infiltrating lymphocyte

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A straightforward estimation of cardiac substructure exposure for clinical practice: example of breast rotational intensity modulated radiation therapy

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Introduction. Mean heart dose (MHD) is the most widely used dosimetric parameter for cardiac sparing during treatment planning. Specific cardiac substructure exposure could be more clinically important, but MHD cannot provide the radiation oncologist with precise insight at the substructural level.

Materials. We propose a straightforward method for estimating cardiac substructure exposure based on linear regressions between mean dose delivered to cardiac substructures and MHD. We focused on breast irradiation with intensity modulated radiation therapy as an application example. Correlations between mean dose to cardiac substructures and MHD were statistically significant and usually moderate ($r > 0.5$) or strong ($r > 0.7$), allowing the use of such linear regression models to estimate cardiac substructure exposure from MHD for clinical practice.

Conclusion. This method can be extrapolated to other clinical situations for daily practice, albeit with some restrictions.

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Key words: cardiac substructure exposure, cardiotoxicity, intensity modulated radiation therapy, breast cancer

Introduction

Adjuvant radiation therapy decreases breast cancer mortality but poses cardiotoxicity risks [1]. Fortunately, recent techniques efficiently spare the heart [2], such as rotational intensity modulated radiation therapy (IMRT) or proton radiation therapy. However, the heart is a complex organ made of multiple histologically-diverse substructures and the widely used mean heart dose (MHD) cannot provide a precise insight at the substructural level. In this perspective, we propose a straightforward method for estimating mean doses to cardiac substructures when only MHD is known (which is the case for clinical practice), focusing on locoregional breast cancer irradiation using rotational IMRT as an application example.

Materials

Thirty breast cancer patients having undergone breast conservation surgery and subsequently irradiated with rotational IMRT (volumetric modulated arc therapy or helical tomotherapy) were selected by random sampling from our institutional database. Sixteen patients were treated for left-sided breast cancers and 14 for right-sided breast cancers. Target volumes included the whole breast with a boost, homolateral axillary lymph nodes and internal mammary chain. Half of the radiation schedules were hypofractionated: hypofractionated regimens delivered 52.2 to 56 Gy to the tumour bed (in 18 to 23 fractions) while normofractionated regimens delivered 63 to 66 Gy. Cardiac substructures were delineated according to published international guidelines [3]. Mean doses to the heart (MHD),

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cardiac cavities, left ventricular walls and coronary arteries were retrieved. For each substructure, a simple linear regression was performed between the mean dose to the considered cardiac substructure and the MHD.

Results

For all substructures, MHD was a significant explanatory variable (with the exception of the first two right coronary artery segments for left-sided irradiation). The cardiac substructures which were the most sensitive to MHD variation were the left ventricle anterior wall ($\beta = 1.8$, $p < 0.001$) for left-sided irradiations and the right auricle ($\beta = 1.3$, $p < 0.001$) for right-sided irradiations. The coronary artery segments which were the most sensitive to MHD variation were the mid segment of the left anterior descending coronary artery ($\beta = 2.9$, $p < 0.001$) for left-sided irradiations and the proximal segment of the right coronary artery ($\beta = 1.6$, $p < 0.001$) for right-sided irradiations.

For right-sided irradiations, the correlations were usually strong ($r > 0.7$). Correlations were somewhat weaker for left-sided irradiations, but the correlation coefficient was still usually greater than 0.5. The greatest correlation with the MHD was found for the distal circumflex artery segment for left-sided irradiations ($r = 0.88$, $p < 0.001$) and for the left ventricle septal wall ($r = 0.95$, $p < 0.001$) for right-sided irradiations.

Discussion

Based on simple linear regressions, this method for estimating cardiac substructure exposure is straightforward and convenient when only MHD is available, which is often the case in daily practice since cardiac substructures are usually not

Table I. Provides the equations estimating the mean dose delivered to each substructure from MHD

a. Linear models for cardiac substructure

	Cardiac substructure					
	Left-sided breast irradiation			Right-sided breast irradiation		
	Mean dose	r	p value	Mean dose	r	p value
Left ventricle (LV)	= 1.0 x MHD – 0.4	0.84	<0.001	= 0.7 x MHD – 0.7	0.95	<0.001
LV anterior wall	= 1.8 x MHD – 2.1	0.73	<0.001	= 0.7 x MHD + 0.1	0.81	<0.001
LV apical wall	= 1.4 x MHD + 0.7	0.35	0.031	= 0.6 x MHD – 0.5	0.76	<0.001
LV lateral wall	= 1.0 x MHD – 0.9	0.81	<0.001	= 0.6 x MHD – 0.7	0.94	<0.001
LV inferior wall	= 0.6 x MHD – 0.3	0.76	<0.001	= 0.6 x MHD – 0.7	0.87	<0.001
LV septal wall	= 0.9 x MHD – 0.1	0.85	<0.001	= 0.9 x MHD – 0.9	0.95	<0.001
Right ventricle	= 1.0 x MHD + 0.2	0.80	<0.001	= 1.0 x MHD – 0.6	0.92	<0.001
Left auricle	= 0.6 x MHD + 0.3	0.70	<0.001	= 1.0 x MHD – 0.7	0.91	<0.001
Right auricle	= 0.5 x MHD + 0.8	0.77	<0.001	= 1.3 x MHD – 0.3	0.80	<0.001

b. Linear models for coronary artery segmentation

	Coronary artery segmentation					
	Left-sided breast irradiation			Right-sided breast irradiation		
	Mean dose	r	p value	Mean dose	r	p value
Left main coronary artery	= 0.8 x MHD + 1.0	0.59	0.001	= 1.0 x MHD + 0.3	0.77	<0.001
Left anterior descending artery (LADCA)	= 2.6 x MHD – 1.2	0.64	<0.001	= 0.8 x MHD + 0.3	0.73	0.001
LADCA proximal segment	= 2.4 x MHD – 5.3	0.70	<0.001	= 0.7 x MHD + 1.3	0.70	0.001
LADCA mid segment	= 2.9 x MHD – 1.3	0.53	0.004	= 0.9 x MHD + 0.7	0.55	0.007
LADCA distal segment	= 2.0 x MHD + 5.5	0.27	0.069	= 0.8 x MHD – 0.6	0.68	0.001
Circumflex artery (CxA)	= 0.8 x MHD – 0.7	0.86	<0.001	= 0.7 x MHD – 0.5	0.86	<0.001
CxA proximal segment	= 1.0 x MHD – 0.5	0.65	<0.001	= 0.8 x MHD – 0.2	0.76	<0.001
CxA distal segment	= 0.7 x MHD – 1.0	0.88	<0.001	= 0.6 x MHD – 0.5	0.83	<0.001
Right coronary artery (RCA)	= 0.7 x MHD + 0.9	0.52	0.004	= 1.2 x MHD – 0.2	0.86	<0.001
RCA proximal segment	= 0.6 x MHD + 3.3	0.24	0.070	= 1.6 x MHD + 1.3	0.76	<0.001
RCA mid segment	= 0.5 x MHD + 2.8	0.09	0.215	= 1.5 x MHD – 1.5	0.81	<0.001
RCA distal segment	= 0.5 x MHD + 0.2	0.50	0.004	= 0.9 x MHD – 1.0	0.72	0.001
RCA posterior descending segment	= 1.1 x MHD – 1.9	0.67	<0.001	= 0.6 x MHD – 0.6	0.78	<0.001

r is the correlation coefficient, **p** values are adjusted for multiple testing with Holm-Bonferroni method.

routinely delineated. This approach, illustrated herein for breast rotational IMRT, can be extrapolated to other clinical situations where cardiac radiation exposure is concerned.

And yet, these linear models based on MHD must be used with some caution. While correlations between MHD and mean dose to cardiac substructures were strong for right-sided irradiations, they were more moderate for left-sided irradiations: in this case, a part of the substructure exposure cannot be explained by MHD variation, generating an uncertainty in its estimation. In addition, MHD provides no information on high doses to cardiac substructures. The histological diversity of the cardiac substructure (muscle, nerves, epithelial tissues, and lymphatic and blood tissue) explains the broad range of described radiation-induced adverse cardiac events [4]: specific cardiac substructure doses may thus be more important than MHD. For instance, atrial dose correlates with specific cardiotoxicity for lung cancer patients [5–6]. Even though substructure dose constraints are not precisely known yet, toxicity studies taking into account cardiac segmentation may help clarifying them.

Conclusions

Clinical practice and cardiotoxicity trials would gain by considering cardiac substructure exposure; relying solely on the MHD for cardiac sparing may be simplistic, but linear regression models can help in estimating cardiac substructure exposure when only MHD is available.

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Oncogeriatrics (part 6.)

The usefulness of routine preoperative investigations in the qualification of an older patient for elective surgery

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Medical history, physical examination and a Comprehensive Geriatric Assessment remain the most important elements in preparing an older patient for surgery, to determine the number of preoperative additional tests, and remain the strongest predictors of postoperative outcome. The additional 40-60 minutes devoted to its implementation at the time of qualification for surgery, is well worth the chance to significantly reduce the risk of complications in the postoperative period. The patient's chronological age alone is not a criterion for the type and number of additional tests. Routine biochemical blood serum tests (with the exceptions of haemoglobin, creatinine, albumin and HbA1c in diabetic patients) and other preoperative static investigations have not been shown to affect the risk of postoperative complications, no more so in the older population. It is also misleading to believe that a large number of preoperative tests will protect the attending physician from legal liability.

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Key words: older patient, preoperative investigations, elective surgery, elderly

Advances in medicine and other areas of life have caused the number of people over 80 years old to increase by 70% over the past few decades. Elderly patients account for half of the adults operated on, but about 80% of peri- and postoperative complications are in this age group [1]. As a result, the costs of preoperative diagnostics and treatment is increasing significantly; therefore we should use our resources wisely.

All the below recommendations are based on the guidelines of scientific societies, supplemented, whenever possible, with studies on older surgical patients [2–5].

Preoperative investigations are used to detect disorders in asymptomatic patients in order to prevent unexpected problems. Many surveys conducted among physicians show that additional tests are very often performed without indications, or if they are already carried out, have no effect on patient management [6]. In this context, it is also interesting to observe the results of the study "Less is more" by Wijeysunder et al., in which 100,000 patients, who underwent internal consultation with various medical implications, were included in the study. The authors observed that there was a perceived necessity to perform further, often unnecessary tests, thereby changing the date of surgery and, what is more, increasing the 30-day risk of death related to the explanatory procedures carried out [7]. Furthermore, in the Ramesh B et al. study, including 300 people >65 years old, operated on due to oncological reasons, only 12.7% of patients had abnormalities in routine biochemical

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blood tests. There was also no significant connection between these abnormalities and increased risk of postoperative complications [8].

Therefore, any decision regarding the necessary biochemical tests, imaging and consultations should be made individually, taking into consideration the patient's current general condition, comorbidities and estimated surgical risk, which is an indicator of the 30-day risk of death due to cardiovascular reasons resulting only from the type of surgery, and excluding the patient's associated diseases (tab. I).

For elective surgery, pre-operative assessment and testing should be done early enough to clear potential abnormalities. It is currently accepted that this time should not be longer than 6 weeks from the date of the planned surgery [5].

A properly taken medical history, physical examination and Comprehensive Geriatric Assessment remain the most important elements in preparing an older patient for elective surgery and determining the number of additional tests it is necessary to perform. Unfortunately, as shown in surveys conducted among physicians, a detailed medical history and full physical examination is rarely carried out at the time of qualification [8].

In the older population, there are common abnormalities in the results of laboratory tests that do not change preoperative procedures in any way and, more importantly, do not correlate with the frequency of postoperative complications, even in the oldest age groups (80–100 years). Therefore, age alone should not determine the need for routine biochemical testing of these patients [6].

A complete blood count should be performed in ASA patients scored 1–4 before each high-risk procedure and should be considered in patients with ASA 3–4 who have qualified for intermediate risk surgery with known cardiovascular and/or renal disease, if they have previously undiagnosed symptoms. In all other cases, a complete blood count is not routinely recommended [2].

Electrolytes, urea and creatinine should be performed in patients with ASA scored 1–4 who have qualified for high risk procedures, ASA 3–4 in all types of surgery and if the patient is taking diuretics, is diagnosed with chronic kidney disease, diabetes or when preparing the patient for surgery may change their value significantly (preoperative bowel preparation). However, it should also be stressed that the determination of serum creatinine is of great value in identifying patients with cardiac risk. Serum creatinine >170 mmol/l or >2 mg/dl or creatinine clearance <60 ml/min/1.73m^2 is one of the six independent risk factors for perioperative cardiac complications [9].

In all older patients, pre-operative fasting blood sugar measurement should be performed. This will detect previously unknown or incorrectly treated diabetes or impaired glucose tolerance, which significantly correlates with the risk of postoperative complications. The determination of glycated hemoglobin (HbA1c) is recommended in patients with diagnosed diabetes who have not had it checked in the last 3 months [2].

Levels of alanine transaminase and aspartate transaminase are not routinely recommended but should only be performed for patients with suspected or diagnosed liver and biliary tract disease. It has also been shown that asymptomatic abnormalities in liver enzyme results do not change the perioperative management and are not prognostic in postoperative course. Patients with liver cirrhosis have a significantly increased risk of death and postoperative complications. However, this risk is proportional to the severity of liver cirrhosis measured by the Childs-Pugh classification, and not to the level of the above-mentioned enzymes [10, 11].

It is advisable to check the level of serum albumin concentration in all elderly patients qualified for high risk surgery. Preoperative albumin concentration is one of the most important indicators of perioperative risk of complications and death (this correlation is linear and becomes statistically significant at serum albumin <3.5g /dl). In patients scheduled for elective surgery, hypoalbuminaemia, with clinical compliance, is most often symptomatic of malnutrition. This condition significantly increases the risk of postoperative complications and requires nutritional treatment and postponement of elective surgery according to the guidelines [12].

There is no indication for the routine monitoring of coagulation parameters in all patients. This is due to the fact that

Table I. Estimated 30-day risk of death from cardiovascular causes resulting from the type of surgery without taking into account the patient's accompanying diseases [5]

Low risk <1%	Intermediate risk 1–5%	High risk >5%
– Superficial skin and subcutaneous tissue operations – Thyroid surgery – Breast surgery – Minor urological procedures, including transurethral procedures – Minor gynecological procedures – Minor orthopedic procedures – Cervical vascular surgery in asymptomatic patients	– Cholecystectomy, splenectomy, hiatal hernia surgery – Major urological (except bladder resection) and gynecological procedures – Major orthopedic procedures – Cervical vessels treatment in symptomatic patients – Endovascular procedures (including aortic aneurysm) – Minor thoracic surgery – Kidney transplantation	– Oesophageal, duodenal, pancreatic, biliary and liver surgery – Colorectal surgery – Adrenal resection – Total bladder resection – Open limb vascular procedures – Major thoracic surgery – Lung/liver transplantation

activated partial thromboplastin time, normalized prothrombin time and platelet count do not allow the detection of the most common abnormalities. A detailed history (regarding bleeding disorders in the past, epistaxis, intra-articular and soft tissue bleeding, prolonged bleeding after tooth extraction, excessive bleeding during menstruation, family history regarding such disorders, medications taken) is more sensitive and specific than the routine tests mentioned above, a fact which has been confirmed in studies involving very large groups of surgical patients. Therefore, coagulation parameters should be determined when the patient has a positive history in the aforementioned abnormalities and in patients with ASA scored 3–4 with chronic liver disease undergoing intermediate- or high-risk surgery. If the patient is taking novel oral anticoagulants, however, there are currently no simple tests to assess the coagulation system [13].

Thyroid stimulating hormone (TSH) level should be performed on all patients qualified for intermediate- and high-risk operations. Some studies have identified this parameter, along with complete blood count, as one of the most common abnormalities occurring in the older population [8]. In oncological patients, most often the level of the TSH in blood serum is taken before computed tomography.

It is not recommended to routinely perform a urinalysis prior to surgery except for patients with dysuric symptoms or when it is necessary to determine the baseline status before urological and orthopedic surgery. Artetial blood gas analysis is not routinely recommended for patients qualified for elective surgery [4].

Performing a pre-operative electrocardiogram (ECG) at rest is recommended for asymptomatic patients who have qualified for high-risk surgery, patients with more than one cardiac risk factor (coronary heart disease, heart failure, stroke or transient ischemic attack of the central nervous system, renal dysfunction, diabetes requiring treatment with insulin), and in the case of patients with ASA 3–4 also for low-risk procedures. An ECG at rest does not provide additional information when used as a screening method in elderly patients. Cardiac echocardiography should be performed on all patients with recently detected heart murmurs, dyspnoea, syncope and heart failure symptoms. The results of resting echocardiography do not correlate with perioperative cardiovascular complications. Echocardiography may be considered in patients with no clinical symptoms, with no ECG changes, who are undergoing high-risk procedures [14, 15].

A chest X-ray is not recommended as a routine pre-operative examination because it has very limited value. The procedure is recommended only if the result may have an impact on the change in perioperative management (pneumonia, suspected anatomical abnormalities). The sensitivity of this test in heart disease is low and rarely effects a change in perioperative management, which is why it is not recommended as a routine test [16].

Spirometry is not routinely recommended for patients qualified for elective surgery except patients with ASA 3 and 4 with suspected or known respiratory disease and who are eligible for high risk surgery [17].

Indications for coronary angiography are based on an evaluation algorithm that takes into account the following data: the urgency of the operation, the patient's clinical stability, the cardiac risk of the operation, the patient's performance, clinical cardiac risk factors and the level of induced ischemia. A detailed description of the algorithm is available on the website of the Polish and European Society of Cardiology.

The patient's chronological age alone is not a criterion for the type and number of additional tests. Routine biochemical blood serum tests (except for haemoglobin, creatinine, albumin and HbA1c in diabetic patients) and other preoperative investigations have not been shown to affect the risk of postoperative complications in the older population. The key is a proper medical history and physical examination, extended by the Comprehensive Geriatric Assessment. In our opinion, the 40–60 minutes devoted before surgery to its implementation, is well worth the chance of significantly reducing the risk of complications in the postoperative period, which are often associated in the case of elderly people with prolonged hospitalization, the risk of disability, dependence on the care of others, and an increased risk of death, not to mention the costs. It is also misleading to believe that a large number of preoperative tests will protect the attending physician from legal liability.

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Pulmonary toxicities of immune checkpoint inhibitors

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Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many malignancies. Toxicities of immunotherapy are variable, can involve almost every organ, therefore appropriate diagnosis and management of Immune Related Adverse Events (irAEs) is important. Immune-mediated pneumonitis is an uncommon, but potentially life-threatening toxicity of ICIs. Pre-existing lung disease, a history of lung radiotherapy, age >70 years and male gender are suggested as the risk factors of pneumonitis. Dyspnoea, dry cough, fever and chest pain are typical symptoms. Diagnostic algorithms recommend radiological investigation with a chest computed tomography scan. Additional diagnostic procedures – such as pulse oximetry, spirometry, measurement of carbon monoxide diffusing capacity, bronchoscopy with BAL may be helpful. The therapeutic approach is determined by the intensity of the symptoms and CT findings. Corticosteroids and antibiotics are the drugs of choice. Hospitalisation is necessary in severe cases, and other forms of immunosuppression (infliximab, mycophenolate mofetil) may be considered. Continuation of immunotherapy can be considered with caution in patients with G1-2 toxicity, when clinical improvement was achieved and steroids were tapered.

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Key words: pneumonitis, immune related adverse events, immune checkpoint inhibitors

Introduction

In recent years, immune checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD-L1) have been accepted in the treatment of some malignant tumours. Ipilimumab (anti–CTLA-4 antibody), nivolumab, pembrolizumab (anti PD-1), atezolizumab and durvalumab (anti PD-L1) are widely used in clinical practice in the treatment such neoplasms as melanoma, non-small-cell lung cancer, head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, Hodgkin's lymphoma, hepatocellular and renal cell carcinoma [1].

The ICIs affect the immune system – restore the T cell-mediated immune response – and in consequence can lead to autoimmune complications. A broad range of immune-related adverse events (irAEs) involve almost every organ but mostly affect the endocrine system, skin, digestive system, and lung [2].

Immune-mediated pneumonitis is an uncommon but potentially life-threatening toxicity of ICIs. 35–40% deaths of fatal irAEs are connected with pulmonary complications [3].

This paper discusses the issues concerning the pulmonary toxicity of ICIs-epidemiologic data, symptomatology and diagnostic and management recommendations.

Incidence of pneumonitis

Incidence of pneumonitis in clinical trials with anti–PD-1/PD-L1 was variable – from 0% to 10% and was less common reported in trials with anti-CTLA-4- 1% [1]. The incidence was higher when combined treatment was given – nivolumab plus

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ipilumumab or ICIs with chemotherapy [4]. A meta-analysis of 23 trials involving 12,876 patients showed significant increased risk of pneumonitis related to PD-1/PD-L1 versus chemotherapy (RR, 5.64 95% CI: 1.94–16.38, p < 0.001) [5].

The risk of pneumonitis is higher in patients with non-small- cell lung cancer (NSCLC) than in those with melanoma (odds ratio [OR], 1.43; 95% CI, 1.08–1.89; p = 0.005) and higher in patients with renal cancer than patients with melanoma (OR, 1.59; 95% CI, 1.32–1.92; p = 0.001) [6].

A meta-analysis of 112 trials involving 19,217 patients showed all toxicity-related death rates of 0.36% (anti-PD-1), 0.38% (anti-PD-L1), 1.08% (anti-CTLA-4), and 1.23% (PD-1/PD-L1 plus CTLA-4). Pneumonitis was the most common cause of death in anti-PD-1/PD-L1-treated patients – 35% from 333 incidents [3].

Some data from clinical practice suggests that the incidence of pneumonitis related to ICPs can be more common than those reported in clinical trials. In a retrospective analysis of 205 patients with advanced NSCLC 39 (19%) patients experienced immune-related pneumonitis during follow-up and 8 of them died (20%) [7]. Another analysis of 167 NSCLC patients showed the incidences of all-grade and grade 3–4 pneumonitis at 13.2% and 4.2%, respectively, and the mortality rate was 18.2% [8]. Combined treatment has a higher risk. In NSCLC stage III, concurrent chemoradiotherapy and adiuvant immunotherapy with durvalumab is the new standard of care. The phase III PACIFIC showed significant clinical benefit, but pneumonitis occurrence was higher in durvalumab (33.6%) *vs.* placebo (24.9%) patients [9].

The median onset of pneumonitis symptoms ranges from 5 to 12 weeks, but it can be observed even after 24 months of therapy [1, 7]. There are no defined risk factors for irAE of respiratory tract to date, but some data are conflicting. A history of lung radiotherapy, age >70 years, male gender, smoking and low serum albumin are suggested as the risk factors for immune-mediated pneumonitis. [7, 8, 10]. In particular, interstitial lung diseases may form a background for CIP development as autoimmune mechanisms are related. In a prospective study, Fujimoto et al. presented safety of nivolumab in patients with defined mild lung fibrosis [11]. However, in another study the lung fibrosis score was found to implicate anti-PD-1 related pneumonitis [12]. The autoimmune diseases seem not to predict development of pneumonitis [13]. There was no relation beween CIP incidence and the presence of antinuclear antibodies in the study on 83 NSCLC patients treated with single ICI [14].

Many patients with lung cancer suffer from chronic obstructive lung disease (COPD) and ILD, which are *per se* a risk for the development of NSCLC. The recognition of CIP in COPD or ILD is difficult, as the symptoms are very similar and may mimic exacerbation of primary disease. The doctor should know the patient and he must know himself. The course of the complication of treatment could be worse in patients with chronic lung diseases, especially in the elderly [15]. The help of a chest physician and a multidisciplinary team in patient management is essential.

Symptoms and diagnostics

Pulmonary toxicity is referred as checkpoint inhibitors pneumonitis (CIP) [16], ICI- pneumonitis (ICI-P) [4] or some authors prefer interstitial lung diseases (ILD) to underline similarity to the group of interstitial diseases [17]. The term CIP seems to be appropriate as it includes the relationship to ICIs and involvement of parenchymal tissue. The definition of CIP includes new symptoms from the respiratory tract and new changes in chest imaging. The clinical symptoms suggestive of CIP are not specific. Thus, it is highly important for proper diagnosis to connect new symptoms in the respiratory tract with ICI use and to state a time relationship.

The distressing respiratory symptoms of CIP are: dyspnoea and cough, fever, and chest pain. They may be accompanied by desaturation in effort. In about 30% of patients, the course of CIP is asymptomatic, with only new abnormalities visible in the chest CT [18]. In differential diagnosis of the symptoms like dyspnoea, chest pain, and fatigue, other respiratory tract diseases should be taken into account. Especially a patient history including COPD, asthma, ILD, risk factors for pulmonary embolism, previous tuberculosis, and any destructive changes need to be analysed. On the other hand, other types of irAE could be responsible for these symptoms, such as: cardiovascular, neurological or endocrinological toxicity [19]. The more - pulmonary irAE could be accompanied by these.

In clinical status, assessment and the severity of symptoms are taken into account in the appropriate classification according to the Common Terminology Criteria for Adverse Events (CTCAE) grading (tab. I.). The clinical signs like tachypnoe, tachycardia, cyanosis, a range of changes in auscultation – crackles and the time of changes developing are important. Oxygen saturation measurement (and a blood gas analysis if needed) is helpful in making a decision on medical care and hospitalisation.

Chest imaging with high-resolution computed tomography (HRCT) is of great importance in the recognition of respi-

Table I. Clinical grading of pulmonary toxicity during immune checkpoint inhibitor administration (CTCAE criteria) [19]

Grade 1, mild
Asymptomatic or mild symptoms, intervention not required
Grade 2, moderate
Symptomatic, medical noninvasive intervention needed, limiting normal activity
Grade 3, severe
Respiratory symptoms limiting self-care ADL, hospitalisation, oxygen therapy indicated
Grade 4, life threatening
Required urgent intervention, intubation, ventilatory support
Grade 5
Death of irA

ratory tract ICI toxicity. A CT scan with contrast to eliminate pulmonary embolism is suggested by some authors [7].

Generally, the parenchymal infiltrations are visible with the most frequently seen ground-glass opacities, consolidations, interlobular septal thickening and intralobular lines, micronodules, bronchiectasis and architectural distortion [4, 17, 18]. The changes are often overlapping, bilateral and separated from the primary lung tumour [16]. The classification of interstitial lung diseases (ILD) has been used to describe the CIP pattern by some authors, and the nonspecific interstitial pneumonia (NSIP), cryptogenic organising pneumonia (COP) – like pattern, acute interstitial pneumonia (AIP) are mentioned [4, 17, 18]. Pleural effusion and mediastinal adenopathy are rare. The histological reports of CIP are rather scanty. However, in some histopathological reports the NSIP, COP, AIP pattern was described in the majority of cases. The special kind of pulmonary changes after ICIs is sarcoid-like granulomatosis.

Clinical symptoms and lung changes visible in CT scan in patients treated with ICI sometimes need rapid diagnosis and an immediate decision. The main direction of differential diagnosis is progression of malignant disease or infection (fig. 1). In the first step, the analysis of CT is needed to refer to the last imaging and possible progression of the primary tumour or metastases from another body site. An analysis of possible toxicity of previous treatment: chemotherapy and radiotherapy is needed. Next, a broad spectrum of microbiological tests of sputum/material from bronchoscopy or blood should be performed. After exclusion of infection, the recognition of pneumonitis is probable. The course of pulmonary complications is very often rapid, demanding an urgent therapeutic decision. Thus, a bronchoalveolar lavage (BAL) fluid examination might be very helpful [20]. BAL is a relatively low invasive method of respiratory tract examination, and is realised by instillation to the airways and next immediate aspiration of 100–200 mL of saline via bronchofiberoscope. BAL fluid analysis allows the recognition of infection (also opportunistic), the presence of malignant cells, and confirmation of interstitial lung disorder [20]. The normal constituents of BALf are macrophages, lymphocytes and granulocytes in the following proportions: 80, <20, <5%. The predominance of lymphocytes is suggestive of active non-infectious inflammation. Delauney et al performed BAL in 55% of patients with pulmonary complications and in 80% of them lymphocytic alveolitis was observed [17]. In our experience, the BALf evaluation by microscopic examination of slides stained with haematological and histological methods could be very helpful in the differential diagnosis of new lung infiltrations in the course of ICI administration. The more frequent use of flow cytometry allows the local immune response to be characterised, which could be helpful in the choice of treatment [21, 22, 23]. Very importantly, conclusive results are obtained during some hours (unpublished data).

Treatment

The therapeutic approach is determined by the intensity of the symptoms according the CTCAE – table I [24]. Extensiveness of lung changes in the CT scans might be considered an additional risk factor [25]. Careful observation of patients and an appropriate therapy started immediately after occurrence

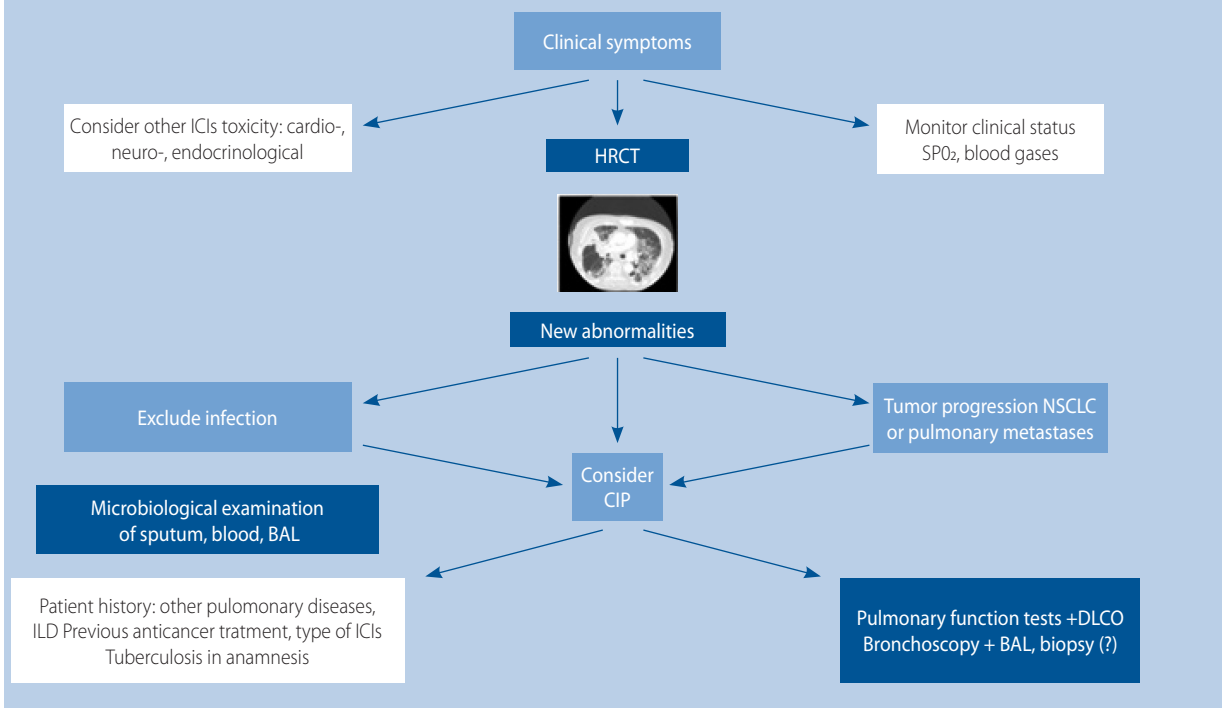

Figure 1. Diagnosis and differential diagnosis of checkpoint inhibitors pneumonitis (CIP). HRCT – high resolution computed tomography, BAL – bronchoalveolar lavage, $SP0_2$ – oxygen blood saturation, DLCO – diffusing capacity, ILD – interstitial lung disease, NSCLC – non-small-cell lung cancer

of the symptoms enable radiological regression and an improvement in the clinical status in most patients [18].

Several oncological societies have developed diagnostic and therapeutic recommendations. These are summarised in table II [1, 19, 24, 25].

Generally in asymptomatic patients with CT abnormalities (confined to one lobe of the lung or, 25% of lung parenchyma) observation and repeated CT scans are recommended. Immunotherapy can be continued or held until the resolution of radiological changes [1, 19, 24, 25].

In patients with moderate symptoms (grade 2) or abnormalities involving more than one lobe of the lung or 2550% of lung parenchyma, temporary holding of the ICI is indicated. [1, 19, 24, 25]. Chest X-ray, blood tests and microbiological tests (for viral, opportunistic or specific bacterial – such as mycoplasma and legionella) should be considered [24]. In the case of inflammatory suspicion (fever, CRP, neutrophil counts) empirical antibiotics should be given. [24]. Empirical antibiotics can be used based on local guidlines – amoxicilin or levofloxacin might be a first option for outpatients [26]. If no evidence of infection – steroids tretment with dose tapering by 5–10 mg/week over 4–6 weeks in case of clinical improvement. Clinical evaluation of the patient's state should be repeated after 72 hours of treatment. If no clinical improvement is achieved – hospitalisation is recommended, with intravenous corticosteroids and further diagnostic procedures. The continuation of ICI therapy is possible when complete clinical improvement was reached (and the prednisone dose reduced to 10 mg/day) [1, 19, 24, 25].

In patients with extensive CT changes involving all lung lobes or 50% of lung parenchyma and in patients with severe or life-threating symptoms – CTCAE grades 3 and 4 – hospitalisation is mandatory (also in the Intensive Care Unit). Bronchoscopy with BAL, and microbiological testing should be performed. Empirical antibiotics and steroids intravenously are necessary. In case of clinical improvement, the dose of steroids should be slowly reduced and finally stopped after at least another 6–8 weeks. If no clinical improvement in the patient's clinical status is observed after 48 hours of therapy with steroids, the administration of immunosuppressive agents should be considered (infliximab or mycophenolate mofetil).

Table II. Management of pneumonitis in patients treated with ICPs [1, 19, 24, 25]

SITC	– Consider holding ICI – Monitoring symptoms and oxygen saturation every 2–3 days; weekly clinic visits – CT prior to every cycle of ICI treatment (at least every 3 weeks) – Resolution of radiographic findings – consider continuation of therapy – No new change or sypmtoms – consider continuation of therapy with close follow-up	– Hold ICI – Pulmonary consultation for bronchoscopy with bronchoalveolar lavage methylprednisolone 1 mg/kg/day (*i.v.* or oral equivalent) – Improvement – steroid taper over >4 weeks – Worsening – treat as grade 3–4 – Consider continuation ICI when symptoms and imaging abnormalities resolve	– Discontinue ICI – Pulmonary consultation for bronchoscopy with bronchoalveolar lavage – Methylprednisolone *i.v.* 2 mg/kg/day – No clinical improvement (48–72 h) – infliximab, cyclophosphamide, mycophenolate mofetil or IVI Gy – Improvement – steroid taper over >8 weeks – Continuation ICI – G3, consider carefully only if symptoms and imaging abnormalities resolve – G4 – Permanently discontinue ICI
ASCO	– Hold ICI – Repeat CT in 3–4 weeks; – Monitor symptoms and pulseoximetry weekly – Continuation of ICI after radiographic improvement – No radiographic improvement – treat as G2	– Hold ICI – Consider bronchoscopy with BAL – Prednisone 1–2 mg/kg/d and taper by 5–10 mg/wk over 4–6 weeks – Consider empirical antibiotics – Monitor every 3 days – No clinical improvement after 48–72 hours of prednisone – treat as G3	– Permanently discontinue ICI – Bronchoscopy with BAL, consider lung biopsy – Empirical antibiotics; (methyl)prednisolone *i.v.* 1–2 mg/kg/d – No improvement after 48 hours – infliximab 5 mg/kg or mycophenolate mofetil *i.v.* 1 g twice a day or IVI G for 5 days or cyclophosphamide – Improvement – taper corticosteroids over 4–6 weeks
NCCN	– Consider holding ICI – Reassess in 1–2 weeks – Monitor symptoms and pulsoximetry – Consider CT scan in 4 weeks – Continuation of ICI after radiographic improvement	– Hold ICI – Consider bronchoscopy with BAL – Consider empirical antibiotics if ifnection has not been fully excluded – Prednisone/methylprednisolon 1–2 mg/kg/d – Tapering dose over 4–6 weeks	– Discontinue ICI – (methyl) prednisolone i.v. 2–4 mg/kg/day, taper corticosteroids ≥6 weeks – High resolution CT and respiratory review – Bronchoscopy and BAL – Empirical antibiotics – If no improvement after 48 hours consider infliximab 5 mg/kg (second dose after 14 days) or mycophenolate mofetil *i.v.* 1–1.5 g twice a day
ESMO	– Consider delay of treatment – Monitor symptoms every 2–3 days – If worsens – treat as grade 2 or 3–4	– Hold ICI – Empirical antibiotics if suspicion of infection – If no evidence of infection or no improvement with antibiotics after 48h – add in prednisolone 1 mg/kg/day orally, taper corticosteroids ≥6 weeks	– Discontinue ICPi – (methyl) prednisolone *i.v.* 2–4 mg/kg/day, taper corticosteroids ≥8 – High resolution CT and respiratory review – Consider bronchoscopy and BAL – Empirical antibiotics
Grade	1	2	3/4

Table III. Management of CIP – general guidelines

Grade			ICI		Treatment
	Symptoms	CT changes extension	Management	Resumption	
G1	Asymptomatic, radiological abnormalities	Confined to 1 lobe, <25% of parenchyma	Hold therapy or continue with monitoring	Yes if resolve radiological abnormalities	Nonspecific
G2	Mild symptoms, medical intervention indicated		Hold therapy	Yes if resolution to G1	– Prednisone 1–2 mg/kg – Taper steroids by 5–10 mg/week, over 4–6 weeks – Empirical antibiotics if infection suspicion – If no improvement after 48 h treat as G3
G3	Severe symptoms interfering with ADL, supplementation of oxygen required	All lung lobes or >50% of parenchyma	Discontinuation	No	– Methylprednisolne *i.v.* 1–2 mg/kg – Empirical antibiotics – Prophyllaxis (PCP, fungal) – Taper corticosteroids over 6–8 weeks – If no improvement after 48 h infliximab or mycophenolate mofetil
G4	Life-threatening respiratory failure, invasive support required				

In the case of CIP grade 3 or 4, a continuation of the immunotherapy is contraindicated. [1, 24, 25].

In the case of patients with toxicity G1–2 who continued treatment, the occurrence of a second episode of toxicity G ≥ 2 is an indication to persistence discontinuation of ICI [4].

Prolonged use of steroids is associated with the increased risk of complications (osteoporosis, gastritis, diabetes and others) and bacterial, fungal or viral infections [27]. Prophyllaxis of pneumocystis pneumonia (PCP) with cotrimoxazol (480 mg twice daily Monday/Wednesday/Friday) is indicated for patients receiving at least 20 mg methylprednisolone or equivalent for ≥4 weeks [24, 25, 27]. Prophyllaxis of fungal infections is questionable, some recomendations suggests fluconazol for patient who receiving at least 20 mg methylprednisolone or equivalent for ≥6 weeks [25].

Summary

Incidence of CIP in clinical trials have been reported <10%, higher rates have been reported for combinations of PD-L1 and CTLA-4 inhibitors. Some data suggest that incidence in clinical practice may be higher (about 20%). Unfortunately, this complication of immunotherapy brings with it the highest mortality. Preexisting lung disease, a history of lung radiotherapy, age >70 years, male gender, smoking and low serum albumin are suggested as the risk factors for CIP. The risk of pneumonitis is higher in patients with non-small cell lung cancer (NSCLC) than in those with melanoma or renal cell cancer. Early detection of CIP is crucial, but differential diagnosis can be problematic. Additional diagnostic procedures – such as pulse oximetry, spirometry, measurement of carbon monoxide-diffusing capacity, bronchoscopy with BAL may be helpful [28]. In the CT scans, parenchymal infiltrations with ground-glass opacities, consolidations, interlobular septal thickening and intralobular lines and micronodules are described. In most cases maintaining ICP and systemic corticosteroid therapy are effective (genaral guidlines are summarised in table III).

Continuation of immunotherapy can be considered with caution in patients with G1–2 toxicity when clinical improvement was achieved and steroids were tapered (dose <10 mg prednison/day). Pulmonary and infectious disease consultations should be considered in all symptomatic patients, especially in patients with G3–4 toxicity.

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An update on the epidemiology, imaging and therapy of brain metastases

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Introduction. The incidence of brain metastases (BM) is rapidly increasing, with most cases occurring in patients aged 50–80 years and in 10–40% of patients with systemic neoplastic disease. The Graded Prognostic Assessment (GPA) is the most impartial prognostic method, according to which the average survival rate of patients with brain metastases is only 7.18 months.

Purpose. To present a systematic review of the currently available evidence-based literature on the epidemiology, diagnosis, and treatment of BM.

Methods. The authors searched PubMed up to March 2020 using the phrases "brain metastases", "brain metastasis surgery", and "brain metastases treatment", which returned 65 citations.

Conclusions. The choice of imaging and therapy for brain metastases remains a significant clinical problem. MRI, including T1, T1 + C, T2, FLAIR, and SWI sequences, is the most sensitive method for solitary BM detection, while other techniques such as spectroscopy, perfusion imaging, or fractional anisotropy contribute to diagnosis precision and neurological deficit avoidance in cases eligible for surgery. According to current treatment algorithms, three main methods are used to manage BM: surgery, chemotherapy, and radiotherapy, depending on the expected effect and the patient's clinical condition. Surgery is most often used, offering neurological deficit remission in 60 to 90% of patients. Most chemotherapeutics do not cross the blood-brain barrier, so immunotherapy with antibodies such as pembrolizumab and ipilimumab, as well as antineoplastic vaccines, are a promising therapeutic prospect.

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Key words: brain, cancer, metastasis, imaging, therapy, surgery, immunotherapy

Key messages

- In spite of recent improvements in diagnostics and treatment, there are few data describing the incidence and prognosis of patients with BM.
- The diagnosis and treatment of BM still pose a major challenge for all oncology-related specializations.
- Traditional surgical excision has been used since the beginning of BM management and remains effective.
- Currently available targeted therapies still require further study but there are promising advances in the field.

Introduction

Cancer is the second most common cause of death in developed countries, with intracranial brain metastases (BM) the most common neurological complication of systemic cancer. BM are associated with significant morbidity and mortality [1, 2],

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and the number of patients admitted with BM has increased markedly over past few decades [3]. Amongst patients with systemic neoplastic disease, about half will develop BM during the whole period of the management of the disease [4].

Brain metastases appear as round, ring-enhancing lesions, usually at the white and grey matter junction, on magnetic resonance imaging (MRI) or computed tomography (CT). MRI is more sensitive at detecting BM than CT, detecting 20% more multiple metastases [1]. Patients presenting with headaches, seizures, or other neurological deficits are imaged by MRI with gadolinium contrast. However, only 30% of MRIs conducted at the time of neurologic diagnosis reveal solitary lesions [5]. Magnetic resonance spectroscopy (MRS) can contribute new information about BM metabolism and the surrounding edema.

Brain metastases are refractory to existing systemic therapies, mainly due to a unique set of brain growth factors promoting resistance and inefficient drug delivery due to the blood-brain barrier [6]. Treatment algorithms are based on prognosis and whether the aim of management is symptom palliation, prolongation of survival, or both [6]. As with all cancer management, there are three core therapeutic approaches to BM: surgery, radiotherapy, and chemotherapy. However, only a few chemotherapies penetrate the blood-brain barrier, a longstanding situation that has hampered progress in BM therapy [5]. However, newer innovative therapeutic strategies are being developed based on targeted molecular and immunological approaches. The newest clinical studies have shown that the central nervous system (CNS) should be treated as a different (but not isolated) immunological environment variant that requires the application of targeted therapy, such as immune check-point inhibitors (ICI) [4].

In spite of recent improvements in diagnostics and treatment, there are few data describing the incidence and prognosis of patients with BM. The aim of this review was to summarize the incidence, diagnosis, treatment possibilities, and prognoses of patients with BM.

Methods

The authors searched PubMed up to March 2020 using the phrases "brain metastases", "brain metastasis surgery", and "brain metastases treatment", which returned 65 citations.

Epidemiology

The incidence of brain metastases is increasing and, due to diagnostic problems, their exact incidence is unknown. The data on brain metastases incidence that are available in the literature are disparate and difficult to compare, originating from epidemiological, clinical, and autopsy studies.

An early population-based analysis of brain metastases conducted between 1954 and 1963 in Iceland reported an annual incidence of BM of 2.8 affected individuals per 100,000; the incidence proportion of metastatic brain tumors in all patients with primary systemic malignancies was less than 20% [7]. Ten years later, a US (United States) study reported an annual incidence of BM of 8.3 per 100,000 [8], while a population-based review of the Metropolitan Detroit Cancer Surveillance System from 1973 to 2001 found an incidence proportion of brain metastasis among all patients with systemic malignancies to be 9.6%. This probably represents an underestimate, because the authors only included lung, melanoma, breast, renal, and colorectal cancers [7]. A Swedish healthcare registry study from 1987 to 2006 found that the annual incidence rate of hospitalization for BM doubled during this period from 7 to 14 persons per 100,000. While these population-based studies were performed in different populations and without standardized treatment, they appear to indicate an increase in incidence [9]. This trend towards an increase in brain metastases incidence has also been observed in neurosurgical departments. In a retrospective cohort study of the Nationwide Inpatient Sample, there was an increase in the annual number of surgical resections for BM from 3900 in 1988 to 7000 in 2000 [10].

However, every population-based study must be regarded as an underestimate because of neurologically silent metastases. Autopsy studies have shown that up to a quarter of patients diagnosed with cancer have BM before death [11, 12]. It is estimated that there will be 1,762,450 new cancer cases in the US in 2019, 440,612 of whom will develop BM during their lifetime. Schouten and colleagues[8] reported that approximately 70% of cancer patients develop BM within the first year after diagnosis, meaning that at least 308,428 BM cases are expected in 2019 in the US. Compared to 258,886 reported BM cases in the same database in 2009: this represents an increase of about 20% [13, 14].

The origin and histotype of the primary cancer and improved survival rates from diagnosis are major factors affecting BM incidence. Sophisticated imaging techniques and better management of diffused neoplastic diseases (that leads to longer overall survival) are the main dimensions that contribute to the increase of BM incidence [15]. In order of decreasing frequency, the majority of BM arise from cancer of the lung, breast, kidney, and gastrointestinal (GI) tract and from melanomas [16].

The estimated annual incidence of lung cancer in 2019 was 228,150 [14], and lung cancer is the most frequent (30–60%) source of BM. Between 17% and 65% of patients with primary lung cancer develop BM [9, 16], most commonly from small cell lung cancer and adenocarcinomas. Lung cancer frequently presents with brain metastases as the first symptom of systemic disease. The median interval between initial cancer diagnosis and identification of a BM is shortest for lung cancer and ranges from 2 to 9 months, with 91% of patients with lung cancer being diagnosed with brain metastases within one year of initial diagnosis [9, 16]. The presence of an epidermal growth factor receptor (EGFR) mutation is associated with a higher incidence of brain metastases in patients with non-small cell lung cancer (NSCLC) [17]. From

these data, ~138,792 new lung cancer BMs are expected to be diagnosed in the US in 2019.

In contrast to lung cancer, brain metastases arising from breast cancer arise later in the disease course, a median of 2–3 years after the initial diagnosis. The estimated annual new incidence of breast cancer in 2019 is 271,270 [14]. Breast cancer is the most common source of BM in women, accounting for 5–30% of all metastatic brain tumors in women and occurring in up to 30% of women with primary breast cancer [18]. Younger age, human epidermal growth factor receptor 2 (HER2) positivity, estrogen receptor (ER) negativity, high tumor grade, high proliferative activity, and high burden of metastatic disease are all risk factors for BM in breast cancer [19–21]. Graesslin et al. developed a nomogram to predict subsequent BM in patients with breast cancer without brain metastatic disease based on these risk factors [22]. From these data, ~56,966 new breast cancer brain metastases will be diagnosed in the US in 2019.

The incidence of melanoma is also increasing, with an estimated 96,480 new cases in 2019 and a higher incidence in male patients. Approximately 37% of patients with stage IV melanoma develop BM, with autopsy series reporting an incidence as high as 90%. Melanoma BM are associated with the poorest outcome of all cancers. Although NCCN (The National Comprehensive Cancer Network) guidelines recommend a brain MRI for stage III (regional) and IV (metastatic) melanoma, Mustafa et al. suggested cranial evaluation for earlier-stage patients, even for localized disease [23].

There are estimated to be 101,420 new colorectal cancer cases in the US in 2019, again more commonly in men than in women [14]. Approximately 10% of patients with stage IV colorectal cancer have brain metastases, and the median interval between initial colorectal cancer diagnosis and identification of a BM is approximately 2–3 years [16]. We estimate the caseload of new brain metastases using the data in table I.

Imaging diagnosis and morphology

T1, T1 + C, T2, FLAIR, and SWI sequences are commonly used to study patients with possible BM. Gadolinium-based contrast agents (GBCA) are available for use in clinical applications of MRI. Increasing the GBCA dose increases the sensitivity for small (<5 mm) lesions [24] and, similarly, increasing MRI field strength improves metastasis detection; contrast dose appears to have greater impact than field strength, although half-dose contrast at double resonance field strength is reportedly superior to full dose at normal resonance field strength [25]. Due to the development of nephrogenic systemic fibrosis, high doses of gadolinium are now avoided, and in light of US Food and Drug Administration (FDA) warnings against the use of high-dose gadolinium, other potential enhancement methods for BM are needed. Increasing the time delay (by 15 minutes) between contrast injection and acquisition has been shown to result in at least one additional lesion being detected in 43% of patients with BM [26]. Moreover, the volume of metastatic lesions detected is greater after time delay [27]. A delay of 20 minutes appears to be optimal for maximizing the detection of small lesions. The distribution of contrast agent in BM can vary; typical well-defined ring-enhancing lesions are only apparent in 15% of BM. With this in mind, Dolgushin et al. subclassified BM into five groups: (I) target, with decay in the center of the tumor (26.9%); (II) heterogeneous, with multiple decay fields (13.9%); (III) ring (15.3%); (IV) ring and tissue (13.1%); and (V) homogeneous (30.8%) [28].

Although brain metastases typically exhibit well-defined margins delimited by a glial pseudo-capsule, recent studies have demonstrated that there is often surrounding brain infiltration. Brain colonization by metastatic cells could be promoted by the glial defense system in the adjacent brain parenchyma, neutralization of which seems to be a prerequisite for brain parenchymal colonization *in vivo* [29]. The impact of astrocytes on chemotherapy resistance and tumor cell proliferation has been reported [30, 31]. In an *ex vivo* organotypic brain slice co-culture mode, astrocytes and microglia accumulated at the metastasis/brain parenchyma interface, formed multiple protrusions, and interacted with the immortalized benign non-CNS (central nervous system) epithelial cells to subsequently induce apoptosis in these cells [32, 33]. Siam et al.

Table I. Estimated new cancer cases and deaths by sex, United States, 2019 [13]

	Estimated new cases			Estimated deaths			Estimated number of BM
	General	Male	Female	General	Male	Female	General
All sites	1,762,450	870,970	891,480	606,880	321,670	285,210	308,428
Colon	101,420	51,690	49,730	51,020	27,640	23,380	10,142
Lung	228,150	116,440	111,710	142,670	76,650	66,020	138,792
Melanoma	96,480	57,220	39,260	7,230	4,740	2,490	60,782
Breast	271,270	2,670	268,600	42,260	500	41,760	56,966
Kidney	73,820	44,120	29,700	14,770	9,820	4,950	Not enough data to estimate
Primary Brain Tumors	23,820	13,410	10,410	17,760	9,910	7,850	

proposed four types of metastatic infiltration: type 0, displacing growth without infiltration – non-infiltrating cancer cells with a significant glial reaction (typical for renal cell cancer); type 1, cluster/cohort infiltration – strands invade the adjacent brain parenchyma with detached infiltrating cohorts and clusters sometimes found in the Virchow-Robin space, but also without contact with the blood vessels; type 2, diffuse infiltration – single cells or mini-spheres infiltrating the brain parenchyma; and type 3, angio-cooptive – typically, infiltration into the adjacent brain parenchyma takes place along preexisting blood vessels (typical for melanoma) [33].

These studies strongly suggest that microscopic total resection should be favored over gross total resection to achieve clinical benefits. The tissue of the cavity wall should, where possible, be resected beyond the glial pseudo-capsule. Fluorescence-guided resections with preoperative 5-aminolevulinic acid (5-ALA) seem to be clinically beneficial. Recent studies have shown that material obtained from the fluorescent tissue of the cavity walls contains tumor cells in 33% of cases [34]. Patients with an infiltrative phenotype have poor prognostic outcomes. In addition, Ki-67 has a generally poor prognostic value, only being prognostic in NSCLC and RCC (renal cell carcinoma) [35].

The gold standard test for detection of BMs is MRI, since infiltrative areas can be missed with standard morphologic imaging. Perfusion imaging, spectroscopy, and diffusion-weighted imaging enhance the diagnostic accuracy, and diffusion-weighted imaging, apparent diffusion coefficient imaging, and fractional anisotropy imaging are used for tractography, which can prevent deficits after surgery.

Treatment of brain metastases

Brain metastases are a very common complication in oncology patients and pose a therapeutic challenge. The presence of BM usually heralds a dismal prognosis. The most objective evaluation of prognosis is the Graded Prognostic Assessment (GPA), which calculates an average survival rate for patients with BM of only 7.18 months [36]. The aforementioned index poses a useful tool while estimating a diagnostic-specific prognosis for patients with BM [37]. Specific factors taken into consideration vary, depending on the particular diagnosis and are strictly specified for the five neoplasms that most often cause BM: breast, renal, lung and gastrointestinal cancers, as well as melanoma. The GPA for different diagnoses can consist of several aspects: Karnofsky performance score, age, presence of extracranial metastases, number of BM and tumor subtype [38] (tab. II–IV). Diagnosis-specific Graded Prognostic Assessment (DS-GPA) is an extended version of the GPA index. DS-GPA includes primary tumor type, gene status and subtypes of breast cancer (tab. II–IV).

However, the molecular and histological features of the tumors have a big impact on survival rates. For instance, patients with breast cancer brain metastases and positive HER2 status can survive over five years with multimodal therapy and good control of the systemic disease [41]. In melanoma or NSCLC, the median survival is poor, and even young patients with good life quality generally survive less than a year [35]. Management should consider tumor histology where possible, available

Table II. Significant factors taken into consideration while estimating prognosis for particular neoplasms most frequently causing BM [7, 39, 40]

Type of neoplasm	Significant prognostic factors
Lung carcinoma	– Age – KPS – Number of BM – EGFR mutation – ALK remodelling
Breast cancer (adenocarcinoma)	– Age – KPS – ER, PR, HER2 mutations
Hypernephroma	– KPS – Number of BM
Melanoma	– KPS – Number of BM – BRAF mutation
Colon adenocarcinoma	– KPS – Age – Number of BM – Presence or absence of extracellular matrix

Table III. Graded prognostic assessment

Factors		Score
Age	>60	0
	50–59	0.5
	<50	1.0
KPS	<70	0
	70–80	0.5
	90–100	1.0
Number of CNS metastases	>3	0
	2–3	0.5
	1	1.0
Extracranial metastases	present	0
	absent	1.0

Table IV. Median survival time for the GPA

GPA score	MST [months]
0–1	2.6
1.5–2.5	3.8
3.0	6.9
3.5–4.0	11.0

elective treatment, the patient`s age, Karnofsky performance status, the volume of brain metastases, and extracranial disease activity [41]. The main treatment methods include surgery, whole brain radiotherapy (WBRT), stereotactic radiosurgery, and chemotherapy.

Whole brain radiotherapy alone has been compared to surgery plus WBRT for the treatment of newly-diagnosed brain metastases [42, 43], with good quality evidence of the benefits from the application of the combined regimen (median survival 4–6 and 10 months, respectively). Furthermore, disease-free survival and CNS recurrence rates are improved with multimodal treatment [41].

Most surgery produces good clinical results. 60–90% of operable patients benefit from symptom remission [44]. The application of perioperative techniques such as preoperative MRI, neuronavigation, and intraoperative electrophysiological techniques have extended the range of possible surgeries, improved the ability to perform radical resection, and improved safety [45]. Only 20% of non-radical tumor removal cases are visible on postoperative MRI. A lack of gross total resection of metastases is the biggest risk factor for local recurrence [46]. From the surgeon's perspective, the choice of technique and the impact of the operative method used on neurological function are important considerations, although a large retrospective study examining surgical effectiveness and safety showed that it is possible to remove a single brain metastasis with no neurological decline, even in eloquent regions [47].

Recent reports have shown that surgery of two or even three brain metastases has similar effectiveness to the surgical treatment of a single metastasis, albeit in patients with good overall neurological condition and well-controlled systemic disease [48].

Over the past few years, stereoradiosurgery (SRS) has emerged as a promising method [49]. Stereoradiosurgery allows the very precise irradiation of a tumor mass, with the convergence of superinduced rays accumulating the dose in one place and sparing the surrounding brain tissue. Stereoradiosurgery is particularly useful for the treatment of small metastases and lesions that are hard to reach by surgery [50]. The aforementioned method can be divided into stereotactic fractionated radiotherapy (SFRT) and single-dose SRS. Due to recommended dose limits, some tumors must be treated with fractionated doses. Single-dose SRS applied to no more than three brain lesions has been shown to achieve local control, defined as a lack of growth or a decrease in tumor mass after one year, in about 80–90% of cases [51]. The effects of treatment on metastases considered to be radio-resistant (melanomas or hypernephromas) are similar to those that are radio-sensitive. Another advantage of SRS is the possibility of using it on the elderly (>80 years old) [51–53]. Reports on WBRT combined with SRS have only shown improved outcomes in patients with high GPA (3.5–4) (WBRT combined with SRS *vs.* WBRT alone was 21.0 *vs.* 10.3 months). In patients with a worse GPA, there is no major difference between WBRT and WBRT combined with SRS [54]. Of note, SRS toxicity does not depend on the total number of metastases but only on their aggregate volume [53]. This method can also be used in combination with preoperative immunotherapy with anlotinib (anti-VEGF – vascular endothelial growth factor). In a multicenter clinical study, Wang et al. have proven that anti-VEGF factors substantively reduced brain edema, which led to better surgery tolerance and the enhancement of SRS effects [49].

Nowadays, more clinicians acknowledge the necessity of postoperative adjuvant methods. There are two complementary therapies which are becoming the newest standards: WBRT and SRS delivered to the resection cavity [56]. Moravan et al., in their study, claim that both methods have similar overall survival (OS), while SRS is marked by two significant advantages: longer cognitive – deterioration-free survival (dysfunction after 6 months in patients who underwent SRS *vs.* WBRT: 52% *vs.* 85%) and major reduction of local tumor recurrence (12-month period exempt from recurrence: 72% *vs.* 43% comparing postoperative SRS and no adjuvant therapies applied, respectively) [56]. The newest NCCN guidelines advocate the application of SRS alone as an adjuvant therapy amongst patients whose total metastases volume is limited; addition of WBRT significantly aggravates neurological and cognitive declines [23, 57]. For cavities larger than 5 cm total in volume, single-fraction adjuvant SRS should not be applied [23].

In view of the presence of the blood-brain barrier, metastatic tumors do not respond well to systemic chemotherapy, which is used to control systemic disease. However, there are some exceptions. EGFR-positive NSCLC radiologically responds to erlotinib, gefitinib, and osimertinib [45], targeted EGFR inhibitors. In addition, several other pathways are being examined as therapeutic targets, such as PI3K/Akt/mTOR (phosphoinositide 3-kinase/ protein kinase B/ mammalian target of rapamycin pathway), HER3 (human epidermal growth factor receptor 3), VEGF and polymerase inhibitors (PARPi).

Classical chemotherapeutics avoid the blood-brain barrier in three different ways, all of which are associated with barrier transport mechanisms. (1) Absorbing transcytosis, which is a phenomenon that describes the connection between positively charged molecules with brain endothelial cells (on which there are negatively charged caveolae or corrugations covered with clathrin). Chemotherapeutics, being positively charged, increase the distribution through the blood-brain barrier. Unfortunately, the occurrence of negatively polarized cell membranes throughout the body contributes to the significant toxicity of this method [55]. (2) Paclitaxel transport with the use of transport proteins turned out to be effective in animal models [58]. (3) Receptor transport, where endocytic transport is contingent on the ligand. This method allows the transport of large molecules. Attempts to exploit this method include the use of monoclonal antibodies and the approach has been applied to Alzheimer's and Parkinson's disease [59].

In view of the immunological privilege of the brain, immunotherapy represents a challenging but promising therapeutic. Most recommended targeted therapies are those which use anti-VEGF factors and checkpoint inhibitors, such as pembrolizumab [60]. Wang et al. suggest that inhibitors of PD-1 and PD-L1 (programmed death receptor-1/programmed death ligand 1) activate the antineoplastic effect of the T cells located in the tumor microenvironment (TME), previously inhibited by the tumor. Therefore, in comparison to methods routinely used in managing BM, those therapies feature reduced neurotoxicity [38]. What`s more, there are strong reasons to believe that immunocytes are able to comprehensively relocate into or out of the CNS [38]. For example, pembrolizumab (an anti-PD-1 immunotherapy) had a positive impact on intracranial melanoma or NSCLC metastases in 20–30% of cases [38]. Furthermore, in 55% of melanoma treatments, therapy with nivolumab and ipilimumab (anti-PD1 and CTLA-4- cytotoxic T-lymphocyte--associated protein 4) led to intracranial tumor remission [60, 62, 38, 63]. As a result, the latest NCCN guidelines recommend the application of nivolumab as a routine therapy for patients with initial or recurrent stage III/IV melanoma disease [23]. In a 2018 phase III clinical trial KEYNOTE-189, patients with NSCLC and BM were divided into two groups: one treated with chemotherapy alone and the other, whose treatment consisted of chemotherapy and pembrolizumab. The second group elicited a markedly better survival outcome than the patients on monotherapy [61].

There is also recent research in antineoplastic vaccines, since overexpression of the antigens that participate in carcinogenesis causes immunization. The most promising vaccine for patients with brain metastases in stage I/II of clinical research is PERCELLVAC3. Moreover, there is interest in the use of oncolytic viruses, which results in an immunological response not only to the virus but also the tumor, and which has been tested with anti-PD-L1 therapy and resulted in improved outcomes [64].

Conclusions

The incidence of metastatic brain tumors is increasing. The diagnosis and treatment of BM still pose a major challenge for all oncology-related specializations. Traditional surgical excision has been used since the beginning of BM management and remains effective. Currently available targeted therapies still require further study but there are promising advances in the field.

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Status of derivative works of scientific publications under copyright law and publication standards

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Introduction. The article aims to present the principles of derivative works (including translations) of original and others' scientific publications in copyright law and publication standards.

Material and methods. The analysis concerns the legal status of derivative works as so-called derivative (dependent) works under copyright law, with the indication of the practice of regulating dependent rights relevant to derivative works in publishing contracts and publication guidelines.

Results and discussion. Works prepared on the basis of original work and translations of works have a special status in copyright law. On the one hand, they are subject to the personal and economic copyrights of the person who created them, while on the other, the exploitation of such derivative works is subject to the consent of the author of the original work based on the construction of the so-called dependent copyrights. In practice, this category of work may create uncertainty as regards the proper grounds for exploitation of such modified scientific publications by other authors, as well as problem of unreliable duplication of one's scientific achievements in the form of modified versions of previous work.

Summary. The condition for the authorised preparation and exploitation of derivate works by other authors requires an awareness of the regulations concerning this category of work, as well as consideration of previous contractual provisions concerning the disposal of dependent rights to the original works on which they were based.

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Key words: derivative works, translations, modification of scientific publications, copyrights and translations, dependent copyrights.

Introduction

The characteristic of scientific research activities in the field of medicine, the interest in accessing translations of recent foreign medical publications, and the dissemination of one's works abroad are conducive to the preparation of modified or translated versions of scientific texts. This is due to the scientific and application attractiveness of updated research results (even if the initial results have already previously been described) and the universal applicability of medical discoveries, methods of treatment and diagnosis, which makes it possible to publish the same scientific papers in different language versions.

In terms of copyright law and publishing standards, the derivate works raise several important issues. Firstly, it should be clarified whether the elaboration (translation) of someone else's work has the nature of independent creative activity and results in the acquisition of copyright on such results, and whether it is necessary for the author (the entity authorised to do so) to the original work (translated or modified) to agree on such exploitation. Secondly, it is important to determine

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whether regulations concerning this kind of creativity are required in contracts with publishers. Thirdly, the problem of qualifying various versions of scientific works (translations) as competitive publishing positions, duplicating scientific achievements or even constituting so-called self-plagiarism, arises in relation to derivate works.

Material and methods

According to the standard provided by international regulations [1], copyright law protects not only original works but also so-called derivative works, including translations. A regulation in this respect is expressed in Article 2 Section 1 of the Act on Copyright and Related Rights of 14 February 1994 [2], which states that the development of someone else's work, in particular translation and modification, is subject to copyright, without prejudice to the right to the original work. Within the meaning of this provision, the derivate work is a recognisable appropriation of the content and often the form of the original work [3], which takes place by taking the creative elements of the original work and adding other creative elements by the person who prepares the derivate work. The creative contribution may be a result of the addition of new descriptions and comments, the selection of certain elements and their ordering, and so on. Creative elements are not the pure research data contained in the work, which as such are not protected by copyright. From the copyright point of view, there is a freedom to reprint them (e.g. as the results of final research, despite the previous publication of preliminary research) in subsequent scientific publications. Therefore, only updating the results of research contained in a work, as well as making editorial changes, corrections, shortening the text without any substantive changes, or changing the form of the original work, do not constitute a derivative work.

One type of derivative work is the translation of someone else's work, in relation to which it is assumed that a person making even a literal translation has a certain scope of freedom and creatively contributes to the translation. In practice, translations of foreign-language medical articles are often accompanied by additional comments, which adds additional creative input and may result in joint ownership of an article. A scientific publication that is inspired by someone else's work, including a work devoted to the same medical problem, describing similar research results, based on a similar methodology, and so on, is not a derivate work.

Results and discussion

The special legal status of derivate works (translations) in copyright law is a result of the difficult construction of so-called dependent copyrights linked with this type of intellectual creation. The exploitation and contractual regulation of such may lead in practice to certain misunderstandings, disputes about copyright infringement, or allegations of unreliable reproduction of the results of scientific activity.

On the one hand, preparing a derivative work of one's own or someone else's work means creating an independent copyright work, to which the authors of the study have moral and economic copyrights. From the legal point of view, the new version of an earlier scientific publication (including the language version) is, therefore, a subsequent, but separate, independent work. However, a different qualification in this respect may result from the standards for the evaluation of scientific achievements. According to these, derivative works as being devoid of new scientific character are those that duplicate the scientific achievements, and their demonstration may give rise to an allegation of scientific unreliability, and are sometimes wrongly qualified as self-plagiarism [4]. On the other hand, derivative works have the status of so-called dependent works due to their connection with the original work. This is expressed in the obligation to obtain the consent of the author of the original work to use and dispose of the derivative work (but not to make the study/translation itself), as well as to respect personal copyrights, including mention of the name of the author and the title of the original work in the copies of the modified work (art. 2 sec. 2 and 5 of the copyright law). Special rules of exploitation of studies (translations) as dependent works are a consequence of the author of the work being entitled not only to personal and economic rights, but also so-called dependent copyrights. These guarantee the author both the acquisition of rights to the original work, but also rights to "secondary" works created on its basis, including derivate works such as *e.g.* translations. The consent to use the dependent rights to a work should result from an explicit contractual provision or the explicit consent of the holder. In practice, it is a common mistake to assume that regulating the use of an author's economic rights to the original work (under transfer agreement or licence agreement) results in the freedom to modify, develop or translate it. In this respect, Article 46 of the Copyright Act should be borne in mind. It states that even if, on the basis of a contract, the transfer of all economic copyrights to a work takes place, unless the contract provides otherwise the author retains the exclusive right to permit the exercise of dependent copyright to the work.

Summary

To avoid potential problems with scientific works constituting derivative works, including translation of other works, the following proposals may be helpful to authors and those who publish, make available or disseminate modified or translated scientific work.

Firstly, for the authorised use of the derivate work based on one's own or someone else's original work, having the economic rights to the original work or a licence is not sufficient. Concerning someone else's work as developed or translated, it is necessary to have permission to exercise the rights dependent on the author of the original work or the entity that holds them (which also applies if the publisher commissions

its translators to translate scientific texts). In the case of one's own works, the provisions of previous agreements on the disposal of dependent rights to the original work should be respected (it should be ensured that the dependent rights to the original work have not been transferred to another entity (e.g. the publisher) or consent to the exercise of subsidiaries has not already been given).

Secondly, the exploitation of rights to a derivative work requires the assurance of personal copyrights by placing the name and title of the work on the study next to the author(s) of the derivative work. Using and disposing of a derivative work without meeting the conditions does not affect the creation of copyrights to the such work, but may result in an allegation of infringement of the rights to the original work, including the prohibition of use and a claim for compensation [5].

Thirdly, in the case of regulating dependent rights in publishing agreements, a conflict of interest for the author of a scientific work may arise in relation to keeping dependent rights to the work and the publishing house, which may be interested in securing its rights and acquiring dependent rights to eliminate a potentially competitive publication in the form of a study (translation) of such work elsewhere.

Fourthly, the qualification of derivate scientific works as independent works within the meaning of copyright is an issue that should be distinguished the existing restrictions on the publication and indication of such works as a part of scientific achievement. They are a result of the publishing rules applied by publishers, as well as codes of ethics relating to standards of scientific creation, based on the criterion of "originality of the work", scientific value, or competitiveness of the published content [6]. In this respect, ethical standards of publishing may apply, according to which the re-publishing of the same scientific work (or its essential parts) should be accepted by the publisher and should include a reference to the first publication of the work. Moreover, according to these standards, derivative works and their essential parts should be treated as a single publication in the author's scientific achievements [7].

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