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Mental adaptation to cancer diagnosis and the health locus of control in patients undergoing treatment

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Introduction. Cancer diagnosis and treatment perspectives pose a serious emotional and behavioral burden for the patient, and require adaptation strategies to be adapted.

Material and methods. The research consisted of 569 patients aged 19 to 91 undergoing oncological treatment. The study used the mini-MAC scale to measure mental adaptation to cancer and the MHLC scale to measure the health locus of control.

Results. The strategy of anxiety preoccupation was highest in breast cancer. The strategy of helplessness and hopelessness achieved the highest value in breast and reproductive organ cancers. The fighting spirit strategy showed the highest value in cancers of the digestive system. The positive re-evaluation strategy was the highest in cancers of the head and neck, and digestive system.

Conclusions. Patients with breast cancer and reproductive organ cancers seem to be at greater risk of developing destructive behavior, therefore extended psychological support has to be considered for these patients.

Key words: cancer, illness acceptance, quality of life, strategies for coping with the disease, pain management

Introduction

Cancer and the need for treatment are significant sources of stress for the patient and their family. The crisis of cancer and its treatment pose a serious emotional and behavioral burden for the patient, which may contribute to the development of anxiety-depressive disorders and the activation of destructive coping strategies. A patient with anxiety-depressive disorders and the feeling that they have no influence on their health often results in a lack of faith in the success of the therapy and low internal motivation for treatment; this may translate into difficulties in the relationship with the doctor. In such situations, encouraging the patient to comply with medical recommendations and health education does not bring the expected effect because it does not address all the causes of the patient's difficulties [1]. Understanding how patient psychologically adapts to cancer and identification

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of the type of health locus of control in the patient enables for better planning of cooperation between doctor and patient. Simultaneous patient education and psychotherapy, which can develop constructive strategies for coping with the disease, help increase patient's adherence to recommended treatment regimens and ensure they maintain them in the long term [2].

The theory of adaptation to neoplastic disease is based on the concept of stress in the cognitive-transactional current, according to Lazarus and Folkman (1984) [3]. The theory assumes that stress experienced as a result of the assessment of a stimulus as threatening (cancer disease), entails the use of maladaptive methods of coping with stress, which in turn may lead to poorer mental adaptation to the disease. Greer (2008) [4] defined a model of coping with stress that includes five main attitudes of adaptation to cancer: fighting spirit, avoidance / denial, fatalism / stoic acceptance, helplessness / hopelessness, anxious preoccupation. The results of studies by Greer et al. (1989) [5] indicate that different types of adaptation to a disease are associated with positive or negative reactions, motivation to treatment, sense of health control, and compliance with medical recommendations. The fighting spirit stance is associated with low external and high internal locus of control and high social support. The attitude of fatalism / stoic acceptance is related to the internal and external locus of control which can affect compliance with medical recommendations and cooperation with the attending physician. In this attitude, emotional state should be monitored as depressive disorders with resignation and emotional indifference may develop, which may falsely give the image of stoic acceptance. The helplessness / hopelessness attitude manifests itself in a patient with a sense of hopelessness and helplessness, passivity, anxiety, and depression, and is associated with a high external locus of health control and low social support. The attitude of anxious concern is manifested in the patient with an anxious attitude towards diagnosis, the diagnostic and therapeutic process, and often in hypochondriacal behavior. The avoidance / denial attitude is often associated with high anxiety, ambivalent reactions, difficulties in adherence to medical recommendations, and low motivation for treatment. In terms of the type of coping strategy and the course of disease process, it was found that people adopting attitudes classified as fighting spirit showed a higher level of compliance with medical recommendations and a longer period of remission and survival than people using the strategy of stoic acceptance or a sense of helplessness / hopelessness [5, 6].

The health locus of control and self-efficacy beliefs in crisis situations are considered to be one of the most important predictors of coping with a chronic disease, including cancer. Measure of the sense of health control is indicated by three main cognitive beliefs: one's own actions, the actions of others in the environment, and chance. The type of beliefs about the sense of health control is one of the psychological factors determining the quality of coping with the disease, the choice of health behaviors, and translates into the patient's involvement in the therapeutic process [7]. Rotter (1954) classified the site of health control as internal and external. The inner locus of health control manifests itself in assigning more responsibility for one's health as a result of one's own behavior and personal control over it. People with dominance of the internal sense of health control are more assertive in the doctor-patient relationship, autonomous in making decisions about their health, and have a higher sense of responsibility for their health condition. The internal locus of control is often associated with the pursuit of increasing the quality of life and health, as well as undertaking preventive behaviors aimed at maintaining health. The internal locus of control favors the initiation of pro-health behaviors by an individual and taking responsibility for their own health. The external locus of health control manifests itself in two attitudes: belief in the influence of others on one's health, and belief in the impact of an accident on one's health. The external locus of control favors the delegation of responsibility for one's health to others, which may lower one's own motivation to undertake preventive and pro-health behaviors. The external locus of health control is observed more frequently in chronically ill patients. The external locus of control may, however, positively affect the therapeutic process and compliance with medical recommendations by placing the responsibility for the health condition and all competences in this area onto the physician. From a therapeutic point of view, the best situation is when the patient shows an ambiguous locus of control, i.e. an undifferentiated type, because at the same time the patient has a strong conviction about the influence of others on his health (doctor, physiotherapist, nurse), which favors compliance with therapeutic recommendations and internal conviction, which mobilizes them to undertake effective pro-health activities and to remain in them [8, 9]. In Poland and around the world, the most frequently used tool for diagnosing the type of health locus of control is the MHLC Scale – Multidimensional Health Locus of Control Scale by Kenneth A. Wallston, Barbara S. Wallston, Robert DeVellis (1976; 1978) in the Polish adaptation of Zygfryd Juczyński (2012).

Many studies indicate that the emotional state of the patients and their way of coping with stress during the disease have a great influence on their engagement in therapy and the course of cancer treatment [10–14]. The assessment of depressive or anxiety disorders is insufficient in the psychological diagnosis of a patient, therefore, it was expanded to other dimensions. The aim of the study was to assess psychological adjustment to cancer in patients in the early stage of treatment, and to identify those who present maladaptive strategies and to provide them with psychological care. The screening assessment of the way of coping with stress and the type of localization of health control enables the selection of targeted psychotherapeutic methods. In turn, these translate into better cooperation between the patient and the medical staff and increases chances for the success of the oncological treatment. Therefore, the study

used readily available standardized research questionnaires examining mental adaptation to neoplastic disease and the health locus of control. The universality of the selected questionnaires allows for future replication of the study and the creation of an obligatory screening battery of tests to assess patient functioning in psycho-oncology clinics.

Material and methods

The study group

The study was carried out among 569 patients aged 19 to 91 undergoing oncological treatment. The study was conducted between January and December 2018. All patients included in the study received psychological support during their stay at the clinic. The study was voluntary, anonymous, and based on a one-time measurement.

Bioethics Committee

The research plan received a positive opinion from the Committee of the Science Department of the Maria Sklodowska-Curie National Research Institute of Oncology and was entered in the scientific plan, registration number 4.34/2018.

Variable measurement tools

The research questionnaire consisted of author-delivered sociodemographic survey questions and standardized tools. Mental adaptation to cancer was measured with the use of the Mini-Mental Adjustment to Cancer (mini-MAC) scale in the Polish adaptation of Z. Juczyński 2012.

The scale allows for a determination of what strategies the examined patient adopts in relation to cancer. The scale consists of 29 items including four scales:

- anxious preoccupation – perceiving the disease as something threatening, causing uncontrollable anxiety,
- fighting spirit – perceiving the disease as a challenge, which involves taking actions to combat the disease,
- helplessness / hopelessness – an attitude indicating passive surrender to the disease,
- positive reevaluation – a perception of the disease which, on the one hand, takes into account the seriousness of the situation, and on the other – allows one to find hope and appreciate past and present events in life.

The results of the mini-MAC strategy are in the range of 7–28 points, and the higher the score, the greater the intensity of a given cancer coping strategy. Using the mini-MAC scale, it is possible to also define two coping behaviors: constructive and destructive, resulting from a combination of the above. The constructive behavior includes the strategy of fighting spirit and positive re-evaluation, and the destructive behavior includes the strategy of helplessness / hopelessness and anxious preoccupation. The scale is used to assess adaptation to cancer, which translates into the behavior and emotions of the patient during the treatment and rehabilitation process.

The scale diagnoses adaptation strategies towards the disease: anxious preoccupation, helplessness / hopelessness, fighting spirit, positive re-evaluation. The results obtained from our research were referred to the mean results of analogous groups of patients included in the mini-MAC questionnaire manual. The results after conversion to standardized scale can be interpreted in the sten scale values from 1–10 sten, where results in the range 1–4 sten are interpreted as low, 5–6 sten as average and results in the range 7–10 sten are considered high.

The health locus of control was measured by the Multidimensional Health Locus of Control Scale (MHLC) by Kenneth A. Wallston, Barbara S. Wallston, Robert DeVellis (1976; 1978) in the Polish adaptation of Zygfryd Juczyński (2012), which measures 3 dimensions of the health locus of control: internal, external, i.e., the influence of others, and chance. The value of each of the dimensions is within 6–36 points, and the higher the score, the stronger the belief to which the analysis relates.

Statistical analysis

The study population was divided into subgroups according to the differentiation criteria based on the type of cancer. The obtained results were analyzed statistically with the use of statistical tests (t-student, single factor analysis of variance).

Results

569 patients (346 women and 223 men) aged 19 to 91 (mean age 54) were examined. The most numerous group of studied patients were those with breast cancer (30.05%) (fig. 1),

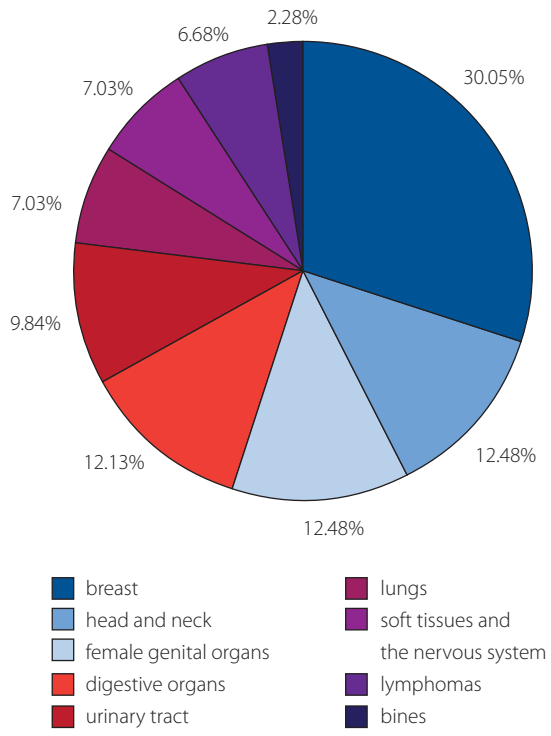

Figure 1. Tumor location

then: patients with cancers of the head and neck (12.48%), reproductive organs (12.48%), the digestive system (12.13%), and male genital (9.84%). The smallest groups were patients with lymphatic system neoplasms (6.68%) and bone neoplasms (2.28%). Almost 60% of patients (335 people) came for oncological treatment for the first time, while the remaining patients were re-exposed due to recurrence of the cancer. 167 patients (29.35%) were economically active during oncological treatment, 116 patients (20.39%) were on sick leave due to illness, 87 patients (15.29%) were on a disability pension due to disease, and 199 patients were retired (34.97%).

Figure 2 shows the mean intensity of stress coping styles in subgroups based on cancer type. The analysis of the adopted strategies as part of mental adaptation to neoplastic disease in the studied population of patients (fig. 2.) showed the mean value of fighting spirit rated as high, positive reevaluation was also rated high (21.6), anxious preoccupation rated medium (16.02) and helplessness / hopelessness rated low (12.67). The mean result in constructive strategies was 44.31 which correspondents to 7th sten (high intensity) and mean result in destructive strategies was 28.69 which corresponds to 4th sten (low intensity) (confidence level 0.01). Analysis of the level of coping strategies in relation to the treatment stage (fig. 2) showed that the anxious preoccupation was significantly (t-student p = 0.014) higher during the first treatment (19.4) than the next (15.41). No statistically significant differences were observed in the level of remaining strategies. The strategy of helplessness and hopelessness achieved a higher value during the next treatment due to recurrence of the tumor and was 12.70, while during the first treatment it was 12.65. The fighting spirit strategy was comparable during the first (22.86) and subsequent oncological treatment (22.5), and the positive reevaluation strategy was similar in the first treatment (21.58) as the subsequent treatment (21.68). Constructive strategies during the first treatment reached 44.63 and during the next treatment 44.14, which translates into 7th sten. The destructive strategies reached a value of 29.10 during the first treatment, and a value of 28.11 during the next treatment, which translates into 4th sten.

Figure 3 presents the coping strategies in subgroups based on cancer type. The analysis of coping strategies in relation to the type of neoplasms (fig. 3) showed that anxious preoccupation was highest in breast cancer (18.1) and lowest in lymphatic system neoplasms (ANOVA p = 0.003). The strategy of helplessness and hopelessness achieved the highest value in breast (13.8) and reproductive organ cancers (13.74) (ANOVA p = 0.003). The fighting spirit strategy showed the highest value in cancers of the digestive system (23.86) and the lowest value in lung cancers (21.1), however, the observed differences were not statistically significant. The positive re-evaluation strategy was the highest in cancers of the head and neck (22.27), and digestive system (22.06), and the lowest value was found in cancers of the lung (20.85) and the lymphatic system (20.91). The differences were not statistically significant.

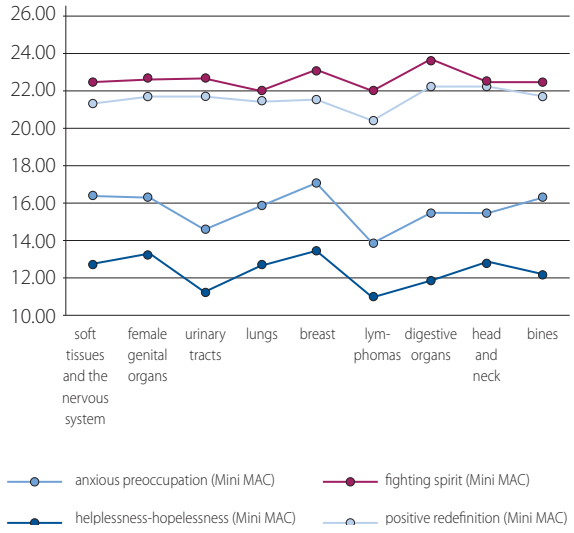

Figure 2. Cognitive coping responses by cancer type

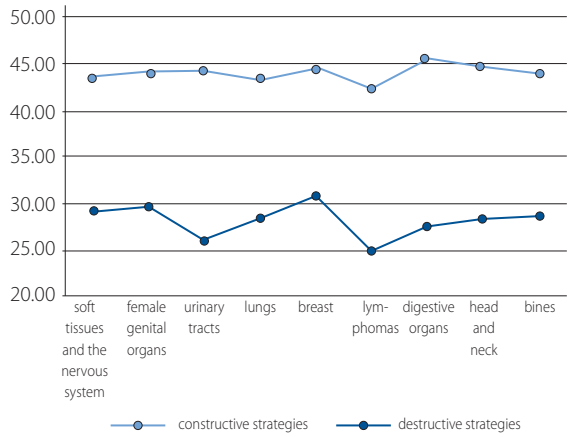

Figure 3. Coping strategies by cancer type

Constructive strategies (fig. 3) showed the highest levels in tumors of the digestive system (45.60) and the lowest in lung tumors (42.9). No statistically significant differences between the groups were present. The highest levels of destructive strategies were achieved in breast cancers (30.68) and cancers of the reproductive organs (29.76), and the lowest values were found in cancers of the lymphatic system (24.92) (ANOVA p = 0.001).

Figure 4 shows the health locus of control in subgroups based on cancer type. The analysis of the locus of health control (fig. 4) showed that the mean severity of the internal sense of health control was 24.83 and that the external locus of health control was 26.92, while the belief that health control depends on the influence of chance reached a mean value of 24.17 in the study population. The conviction about internal control (fig. 4) was highest in patients with head and neck (26.8) and lung cancer (25.9), and lowest in patients with cancer of the lymphatic system (23.16) (ANOVA p = 0.014).

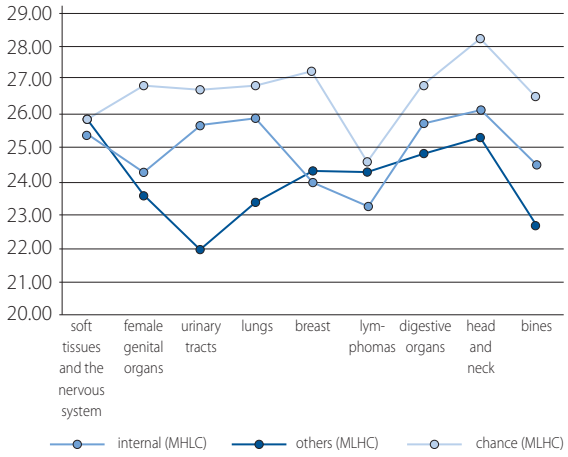

Figure 4. Health locus of control by cancer type

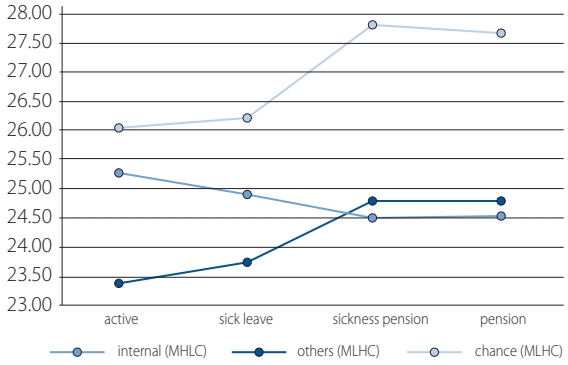

Figure 5. Health locus of control by professional activity

The belief about external control (fig. 4) was highest in patients with head and neck cancers (28.9) and lowest in patients with lymphatic system tumors (24.55) (ANOVA p = 0.033). The belief that health control (fig. 4) depends on chance was highest in patients with neoplasms of soft tissues and the nervous system (25.98), and the lowest level was achieved in patients with neoplasms of the urinary system (21.8) (ANOVA p = 0.039).

Figure 5 shows the dimensions of health locus of control in subgroups based on professional activity. The conviction about internal control (fig. 5) was highest in professionally active patients (25.31) and the lowest in patients who were on a pension (24.51) or retired (24.53) (no statistical significance). Belief about an external control (fig. 5) was highest in patients on a pension (27.78) and the lowest in professionally active patients (26.04) (ANOVA p = 0.002). The belief that health control (fig. 5) depends on the case was the highest in patients on disability (24.80) or retired (24.78), and the lowest level was achieved in professionally active patients (23.41) (no statistical significance).

Discussion

Cancer diagnosis and the prospect of oncological treatment have a negative impact on a patient's emotional state, causing an increase of anxiety. The stress associated with the disease requires developing adaptation strategies [15]. Most often, patients run two extreme strategies: constructive and destructive. Patients with a constructive strategy are positive, fight the disease, and are oriented towards a cure. Roesch et al. (2005) [16] found that better mental adaptation to cancer is associated with the use of task-oriented strategies. This result is analogous to those obtained in the presented study, which shows that the use of adaptive strategies such as focusing on planning or focusing on the positives are associated with a positive attitude towards the disease and, at the same time, with a lower intensity of negative emotions. In the study, the attitude of the fighting spirit was highest in patients with diagnosed cancers of the digestive system, while the attitude of positive re-evaluation was achieved in patients with head and neck neoplasms.

The second, destructive attitude is characterized by anxiety, a sense of helplessness / hopelessness, which translates into a lack of faith in recovery and low involvement in the therapeutic process. A study by Wootten et al. (2007) [17] indicates that focusing on emotions is associated with poorer mental adaptation. A similar result was obtained in the presented study – the use of strategies such as catastrophizing, rumination, and blaming oneself and others is associated with a higher severity of anxiety and a greater tendency to perceive the situation as threatening, and thus with poorer adaptation to the disease. The passive strategy was related to the external locus of the sense of control, which means that the patient has a low sense of their own influence on the situation, and expects that the medical staff will be directive and will take care of them. On the other hand, in the case of failure of oncological treatment, patients hold third parties responsible. In the study, the attitude of helplessness / hopelessness was highest in breast and reproductive organ cancers, and anxious preoccupation was also the highest among breast cancer patients.

High anxious preoccupation and a sense of helplessness / hopelessness in the case of cancers related to female sexual characteristics can have multiple causes. The disease strictly affects the perception of a woman's body, her attractiveness, physicality, quality of life in a sexual sense, and the possibility of having children, as well as disturbing the hormonal balance. It should also be taken into account that cancers related to female characteristics also affect intimate relationships, which may translate into a fear of rejection and loneliness.

A study by Chojnacka-Szawłowska (2012) [3] confirmed that patients initiating constructive strategies of coping with cancer were characterized by a higher quality of life and a better prognosis in terms of both survival and remission periods. These studies also confirmed that active and confrontational strategies have a greater impact on increasing the quality of life than strategies with a predominance of passivity and resignation. The research by Watson (1999) [18] showed that the type of attitude taken by patients towards the disease, as well as the rates of depression, correlate with the survival of patients with neoplastic diseases. Breast cancer patients adopting an attitude of helplessness / hopelessness or showing a high

level of depression have a significantly lower quality of life and have a significantly lower chance of 5-year survival. A study by Ośmiałowska (2021) also shows that breast cancer patients choosing constructive strategies of coping with the disease achieve a higher quality of life score compared to those who chose destructive coping strategies [19].

It was found in the study that professionally active people show the highest sense of internal locus of control and agency, and achieve the lowest values of external sense of health control and the influence of chance. This result indicates that patients working professionally during treatment function better emotionally and have a better network of social support, which ultimately translates into belief in their own agency. This group of patients also shows a lower preoccupation with anxiety and a sense of helplessness / hopelessness compared to patients who are not professionally active for various reasons.

During the first treatment, patients were most often anxious, while during the second treatment, the helplessness / hopelessness strategy was most often presented. Clinically, this translates into the fact that when confronted with a cancer diagnosis, patients need psychological support and education, while during recurrence, therapy very often requires psychiatric treatment due to the development of a depressive syndrome.

The obtained results indicate the good mental adaptation of patients to the disease, especially in its first stage. Thus, the results provide guidance on what actions should be taken into account when planning medical and psychological interventions to support the process of treatment. First, it is worth encouraging patients to deal with the disease in a constructive way – planning further actions, learning about the course of the disease, and the treatment process. It is also worth encouraging patients to look at current events in a broader context, not to treat the current disease as a situation in which they are helpless. When patients are willing to blame themselves or others for the situation, it is worth redirecting their attention to other less stressful events, reevaluating and looking for positives despite the disease. Patients are recommended to join associations of cancer patients, where they will receive support, a corrective positive experience of functioning with the disease, and with others whom they co-create a support group. However, the relationship between acceptance of illness, quality of life, and pain still needs further investigation. It has been constantly confirmed that patients with breast cancer and female and male genital cancers who have a high level of illness acceptance and a positive illness perception display a better quality of life and overall functioning [20–22].

A study by Kulpa et al. (2019) [23] indicates that constructive coping strategies translate into the ability to better coping with illness-related stress, internal locus of health control, higher quality of life, and greater patient confidence in treatment success. Patients with low self-efficacy often have comorbid anxiety and depressive disorders. Anxiety strategies are associated with an external locus of health control, anxiety disorders, and depressive disorders, as well as greater sensitivity to pain and more frequent episodes of intractable pain. The internal locus of control is associated with a sense of empowerment and higher decision-making; this is important because during treatment, patients often have to make what is referred to as an "informed consent" decision about medical and therapeutic procedures. Patients with an internal locus of control over their health and a high sense of self-efficacy make decisions faster and are consistent in those decisions. Self-efficacy is associated with an internal locus of control and intrinsic motivation, which translates into higher patient engagement in the treatment process and a positive attitude toward it; moreover, it is also associated with lower rates of treatment interruptions or treatment withdrawal due to patient decisions. Analysis of the results from our research shows that the assessment of the type of coping strategies and the health locus of control in cancer patients are important factors influencing their functioning. The finding of maladaptive strategies and the external sense of health control in the patient should be an indication for psychological care because the consequences of such strategies are reactive and anxiety-depressive disorders. This will enable the patient to be provided with clinical assistance before major depressive disorders develop. The possibility of modulating the onset of depressive symptoms, especially in high-risk oncology patients, has been previously noted by Ghanem et al. (2020) [24]. Screening patients with the mini-MAC and MHLC tests should be one of the most important elements in the prevention of depression and anxiety disorders in patients.

Conclusions

- Patients with breast cancer and reproductive organs cancers seem to be at greater risk of developing destructive copying strategies, therefore, extended psychological support has to be considered for those patients.
- Because professionally active patients use more constructive coping strategies, it would probably be beneficial to support oncological patients in staying occupationally active, at least partially.
- Education and psychological support during first treatment should focus on interventions addressing anxiety, while during next treatments coping with helplessness / hopelessness should be taken in account.
- The type of implemented coping strategy and the health locus of control in cancer patients are important factors influencing their functioning during the treatment of the disease.
- Screening patients with the mini-MAC and MHLC tests should be one of the most important elements in the prevention of depression and anxiety disorders in patients.

Conflict of interest: none declared

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Very high and very low levels of preoperative absolute monocyte count indicate poor long-term survival outcomes in patients with pancreatic adenocarcinoma. A preliminary study

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Introduction. We aimed to assess the prognostic significance of preoperative absolute monocyte count (AMC) in baseline peripheral blood samples among pancreatic cancer (PC) patients as possible manifest signs of non-optimal immunity status.

Material and methods. PC patients who underwent palliative surgical treatment without earlier chemo- or radio--therapy (n = 59).

Results. Median AMC was comparable in each subgroup, showing no significant differences. We have adopted an arbitrary trichotomic AMC division: low (<0.4 G/l, n = 9), medium (>0.4 and ≤0.6 G/l, n = 36) and high (>0.6 G/l, n = 14). Optimal (medium AMC) and non-optimal (both low and high AMC) was independent and a statistically significant predictor of OS. Resectability and optimal AMC constituted best Cox proportional hazard model, being equivalent predictors of OS.

Conclusions. Baseline AMC status may be an independent predictor of OS in this group of patients. Further research is needed to explain the biological nature of this phenomenon more widely.

Key words: pancreatic cancer, immune system, monocytes, lymphocyte-to-monocyte ratio (LMR), monocyte-to-lymphocyte ratio (MLR)

Introduction

Pancreatic cancer (PC) is one of the most malignant cancers, with the 5-year survival rate approaching 9% [1]. Late onset of symptoms, difficulties in pre-surgical diagnosis confirmation and low chemosensitivity justify the notoriety of PC [2]. Little is known about the exact role of the immune response in driving the poor prognosis of PC, apart from the fact that it is considered relatively low immunogenic [3]. The prognostic value of pretreatment AMC as well as the lymphocyte-to-monocyte ratio were studied in PC without an unequivocal conclusion. Some cancers can secrete GM-CSF and G-CSF, influencing directly the white blood cell counts, but this phenomenon has not been explored in cases of PC [4]. High pretreatment absolute monocyte count (AMC) generally drives poor prognosis factors in many cancers, including PC [5]. There is significant evidence that monocytes may influence the course of PC, but

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their role cannot be easily translated into simple hypothesis linking them to pancreatic cancer. In terms of quantity, AMC represents the state of the whole organism's monocyte-associated immune forces, associated with the course of neoplastic disease with numerous bonds. Therefore, we hypothesize that both relatively low and high pretreatment AMC could be linked to a poorer course of PC, as it generally reflects the non-optimal immunity status of the patient.

Material and methods

We retrospectively collected data of consecutive PC patients with disease preoperatively qualified as resectable, who underwent surgical treatment in the General and Transplant Surgery Department between the years 2013–2016 without earlier chemo- or radio-therapy. Additional inclusion criterium was having PC confirmed in postoperative material (n = 59). We analysed their sex, age, preoperative AMC (from routine venous blood tests taken one day prior to surgery, after admission), tumour location (head/body-tail), type of performance (resection/non resectable) and overall survival (OS). Laboratory norm for AMC was $<0.8 \times 10^9$/l. The study was approved by the local Ethical Committee.

Statistical analysis was conducted using Statistica 13 PL. We used the Kaplan-Meier method to estimate survival functions and the log-rank test to compare survival curves. To describe the size of effect we used hazard ratios (HR) from proportional hazard Cox regression models both for uni- and multivariate analysis.

Table I. Tested parameters in the study group – basic characteristics

Features	Number of patients (%)	AMC median, range
age:		
≥60	21 (35.6%)	0.58 (0.20–1.07)
<60	38 (64.4%)	0.56 (0.29–1.00)
sex:		
male	29 (49.2%)	0.60 (0.29–1.07)
female	30 (50.8%)	0.50 (0.20–0.80)
location:		
head	39 (66.1%)	0.52 (0.20–1.07)
body-tail	20 (33.9%)	0.57 (0.50–0.60)
resectability:		
resection	33 (56.0%)	0.54 (0.20–0.90)
non-resectable	26 (44.0%)	0.60 (0.21–1.07)
AMC:		
<0.4 (low)	9 (15.3%)	–
0.4–0.6 (optimum)	36 (61.0%)	–
>0.6 (high)	14 (23.7%)	–

Results

Table I contains detailed study group characteristics. Median AMC was comparable in each subgroup, showing no significant differences. According to our hypothesis, we searched optimal cut-off values using the visual method (based on the OS *vs.* AMC chart, fig. 1). We have adopted an arbitrary trichotomic division:

- low (<0.4 G/l, n = 9) AMC,
- medium (>0.4 and ≤0.6 G/l, n = 36) AMC,
- high (>0.6 G/l, n = 14) AMC.

Low AMC corresponded to a high percentage of resection – 77.8%, (respectively: medium MC – 55.3%, high MC – 35.7%). There was no statistically significant correlation between AMC and age (r = 0.0013, p = 0.992), as well as between the AMC subgroup and resectability (p = 0.12).

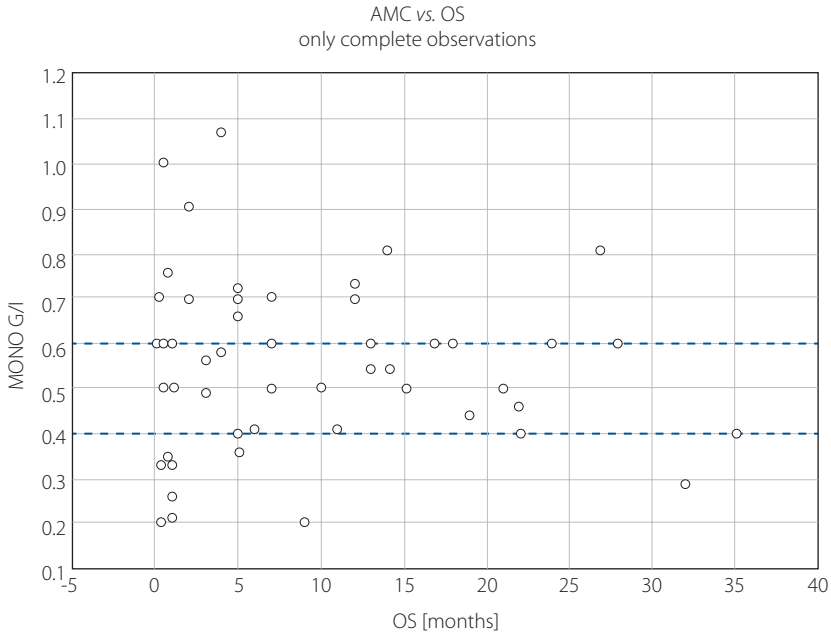

Figure 1. AMC distribution among all patients. Dotted lines corresponds with the cut-off points adapter

Table II. Characteristics of the study subgroups in the context of tested parameters and AMC levels

Parameter (n; %)	Low AMC	Medium AMC	High AMC
sex:			
male	4 (44.4%)	15 (41.7%)	10 (71.4%)
female	5 (55.6%)	21 (58.3%)	4 (28.6%)
age:			
≥60	6 (66.7%)	24 (66.7%)	8 (57.1%)
<60	3 (33.3%)	12 (33.3%)	6 (42.9%)
resectablity:			
resection	7 (77.8%)	21 (58.3%)	5 (35.7%)
non-resectable	2 (22.2%)	15 (41.7%)	9 (64.3%)
6-months survival:			
yes	2 (22.2%)	24 (66.7%)	5 (35.7%)
no	7 (77.8%)	12 (33.4%)	9 (64.3%)
12-months survival:			
yes	1 (11.1%)	20 (55.6%)	2 (14.3%)
no	8 (88.9%)	16 (44.4%)	12 (85.7%)

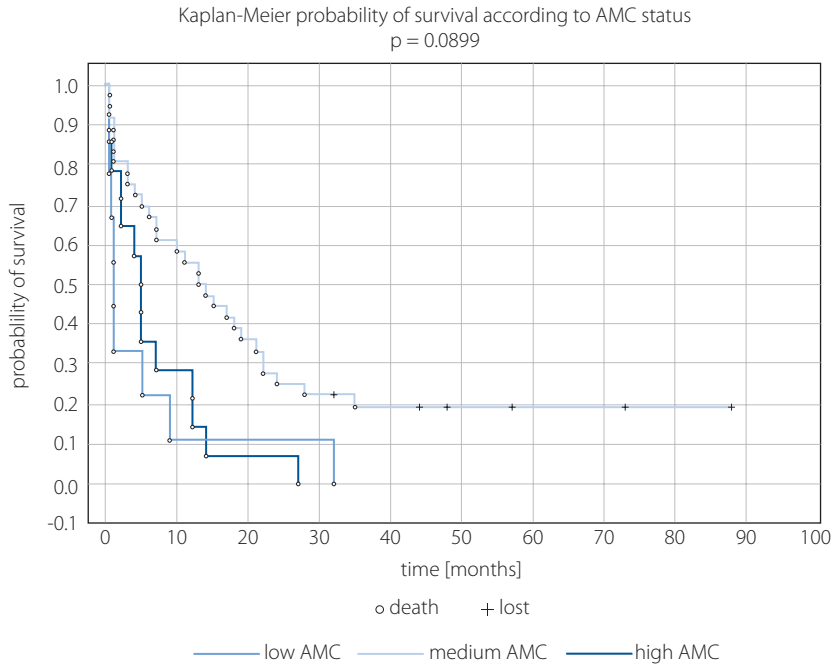

Figure 2. Survival curves for pancreatic cancer patients of low, medium and high AMC. Log-rank p = 0.0899

Survival analysis

The median survival time for low, medium and high AMC was respectively: 1; 13.5; 5 months (p = 0.0899; tab. II, fig. 2). AMC divided in this way was not a significant predictor of OS, but redefined into optimal (medium AMC) and non-optimal (both low and high AMC) statistically significant determinants of OS (p = 0.009) and an independent predictor of OS. Resectability and optimal AMC constituted the best Cox proportional hazard model, being equivalent predictors of OS (tab. III, fig. 3).

Discussion

We postulate two main causes for observed low AMC phenomenon in our study group: a specific, but of little quantitative effect – the process of monocytes migration to the tumour tissue and a non-specific, but responsible for a major part of this symptom, decrease of monocytes production.

A low monocyte count may be both isolated monocytopenia as well as other forms of leukopenia. Leukopenia, which is a secondary immunodeficiency state, may develop in some cases of malnutrition [6]. A white blood cell count below the normal range was found in 39.7% of anorexia nervosa patients [7] and in 62% of hunger-strike patients [8]. 85% of PC patients experience a reduction in their body weight [9]. Immune system stimulation lead to raising the AMC. High AMC patients tend to be younger than others, suggesting that personal maximum is a function of the organism's ava-

Table III. Cox proportional hazard regression – univariates and the best multivariate model

Parameter (n; %)	HR (range)	p
	univariate	
sex	0.99 (0.58–1.72)	0.984
age ≥60	0.76 (0.43–1.33)	0.343
resectablity	0.37 (0.21–0.67)	0.0009
low, medium, high AMC	1.07 (0,62–1.87)	0.786
optimal AMC	0.39 (0.22–0.70)	0.001
	multivariate	0.00002
resectablity	0.34 (0.18–0.62)	0.0005
optimal AMC	0.36 (0.20–0.65)	0.0007

ilable resources [10]. The phenomenon of GM-CSF secreting tumours also could be responsible for the special prognostic role of high monocyte count in patients with PC, but this is not in line with our results, as the secretion of GM-CSF was linked with an antiangiogenic and antitumour effect, resulting in lower mortality; as it has been not investigated in PC yet, this option remains only a theoretical possibility [4].

Absolute monocyte count was reported to be a predictor of outcome, dichotomizing patients into groups with a good and bad prognosis. As the rationale comes from AMC translation into the general anticancer immunity state, in our opinion it is justified to read them in context with each other, independently from the studied malignancy type. Until now there was only one study discussing this issue in PC patients (cut-off 0.6, p = 0.23) [5]. The approach of other authors was either dichotomic, or trichotomic, depending on the number of the prognostic group. The trichotomic approach assumes an optimal AMC group with good prognosis and extrema (low and high AMC) of bad prognosis groups. Bruckner et al. described it for the first time in patients with gastric cancer in JAMA (1982) [11]. In 2013 Herishanu et al. postulated on it in his work on chronic lymphocytic leukemia [10]. Our study hypothesis, results and conclusions come in line with their papers (cut-offs respectively: 300 and 900; 250 and 750 – the exact cut-offs are different, probably because of the study group size and specific features, but their middle value stays similar). Other authors proposed following single cut-off values: for myeloproliferative diseases: 630, 700, 800, 1000, 1500 and for solid tumours: 300, 408, 700, 800, 900 [12–19]. Although the statistical significance in the Kaplan-Meier survival analysis was generally reached, these results cannot be considered reproducible. A possible explanation is the skewness of AMC distribution (asymmetrical distribution of low and high AMC patients) in the studied group and considering only one cut-off point idea. Schmidt et al. did not include patients with AMC below the norm into his malignant melanoma study, which constitutes a bridge between the dichotomic and trichotomic approach, as well as can be the result of search for statistical significance when it is impossible to reach with single cut-off point with those patients included [20].

LMR prognostic ratio context

The pretreatment lymphocyte-to-monocyte ratio was a widely tested prognostic factor in many types of cancer, including pancreatic cancer. Their general idea of a bad prognosis blood phenotype can be presented as following:

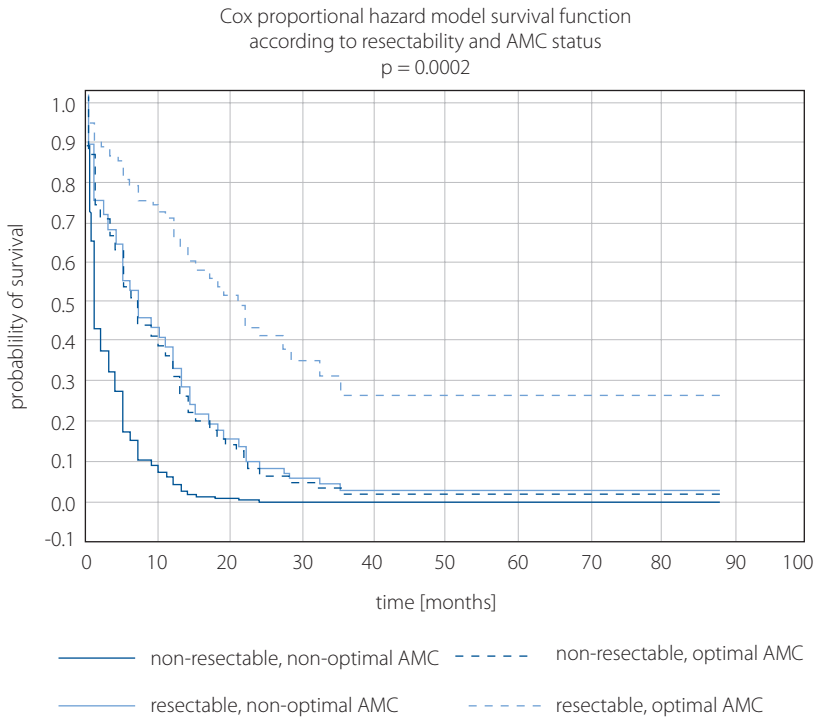

Figure 3. Chart illustrating Cox proportional hazard model survival function according to resectability and AMC status

$$\frac{lymhocyte\ count}{monocyte\ count} > k$$

$$lymhocyte\ count > k \times monocyte\ count$$

Where k is the cut-off point set for the particular study group, so it is kind of an unfavourable balance between white blood cell type counts in peripheral blood. The results are partially repeatable (with relatively similar HR 0.34–0.78 but with a wide range of proposed cut-off points 2.05–4.62) [21–28].

Laboratory norms for monocyte ($<0.8 \times 10^9$/l) and lymphocyte ($1.0–4.5 \times 10^9$/l) counts suggest that a healthy adult organism has a few times more lymphocytes than monocytes in their peripheral blood. The way of thinking laying under the LMR idea raises several doubts. First, any complete theory or hypothesis explaining the reason of observed phenomenon was presented since now, even though the outcome of many studies seems still statistically significant. Secondly, the LMR idea omits the problem of patients with very low white blood cell counts, which as a form of immunodeficiency has obviously undeniably bad prognosis. Thirdly, it puts over the cut-off points great deal of the norm. In light of this study's results, bad prognosis of high LMR values can just speak for blood morphology phenotypes of good prognosis existence, that are not describable using simple linear functions. It is possible that their nature is not about the mutual relationship of different white blood cell types, but about their raw, effective count and even more importantly, their function. A better understanding of the immune system's importance for pancreatic cancer patients will probably lead to finding new, precise biomarkers to better personalize treatment [29–30].

Limitations of the study

Although the study group size was enough to find our hypothesis statistically significant, it still can underestimate some nuances, for example, the exact comparison of low *vs.* high AMC. We also did not analyse the data about chemo- or radio--therapy regimens used postoperatively, so we cannot exclude that the study is biased by some treatment-related factors. As we did not collect the exact TNM, grade, comorbidity or BMI, our results cannot be assessed in this context yet.

Conclusions

We are the first to describe the association between preoperative non-optimal AMC and the course of the disease in pancreatic adenocarcinoma patients. As the monocyte count seems at least a potential predictor of OS, the need for further research in this field is crucial. We postulate on not only the existence of good prognosis blood morphology profile, but also search for a universal marker of the current state of immune system--cancer interaction.

Conflict of interest: none declared

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Cardiotoxicity in patients with early breast cancer treated with adjuvant trastuzumab

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Introduction. Breast cancer is the most common cancer among women in Poland. The aim of this study was to evaluate the incidence of cardiotoxicity in patients treated with adjunctive trastuzumab, as well as to determine risk factors for cardiotoxicity.

Material and methods. The study covered 100 patients who completed one year of trastuzumab therapy or discontinued treatment due to acute cardiac complications. They underwent an oncological, cardiological, questionnaire and laboratory follow-up.

Results. Acute cardiac complications (CC(+)) occurred in 11 (11%) patients. Patients in the CC(+) group were more likely to have hypertension, ischemic heart disease, hypothyroidism, and were more likely to smoke compared to the group without cardiac complications (CC(–)). They had a lower left ventricular ejection fraction before, during and after trastuzumab therapy, and larger left ventricular dimensions in systole and diastole after treatment. The CC(+) received a higher dose of anthracyclines compared to CC(–). The NT-proBNP value remained elevated in the CC(+) group after treatment, despite normal LVEF values, and was higher than in the CC(–) group.

Conclusions. Based on the study, type II cardiotoxicity, diagnosed early and treated appropriately, was found to be reversible.

Key words: cardiotoxicity, anthracyclines, trastuzumab, breast cancer

Introduction

Breast cancer treatment outcomes have improved in recent years. In many countries, despite an increase in incidence, a decrease in mortality from this cancer has been achieved [1]. This improvement is due to earlier detection of breast cancer, as well as more intensive treatment. The introduction of systemic perioperative treatment (radiotherapy, chemotherapy, immunotherapy, and hormone therapy) has reduced the risk of recurrence and increased overall survival time for patients with early breast cancer. However, this success has been associated

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with an increased risk of early and late complications. The use of anthracyclines – cytostatics with high efficacy in the treatment of breast cancer – is inextricably related to the problem of cardiotoxicity, which can be exacerbated by the use of trastuzumab, a human monoclonal antibody directed against the HER2 receptor [2]. Therefore, it is very important to correctly qualify for various treatments, use possible prophylaxis, and monitor the patient's condition during and after anticancer treatment. Such management is aimed at effective treatment of the cancer with as few complications as possible.

The aim of this study was to determine the incidence of cardiac complications in patients with early breast cancer treated with adjuvant trastuzumab, as well as to identify risk factors predisposing to cardiotoxicity.

Material and methods

The study, conducted between 2012 and 2014, included 100 patients (99 women and 1 man) with a diagnosis of HER2--positive breast cancer who received trastuzumab after surgery as an adjuvant treatment, and who consecutively reported to the oncology clinic for a follow-up visit. The patients were aged between 34 and 77 years, with a mean age of 55.7 years. 95 patients received postoperative chemotherapy, the other five were not treated with cytostatics due to contraindications.

After chemotherapy, patients received trastuzumab at a saturating dose of 8 mg/kg body weight *i.v.*, followed by a maintenance dose of 6 mg/kg body weight *i.v.* every 21 days. Complementary treatments used in the study group are shown in table I.

During the follow-up visit, each time a subjective examination (asking about comorbidities, addictions, medications taken, oncological treatment used, and internal medicine, as well as family history of cancer), physical examination, laboratory tests, taking into account potential biomarkers of cardiotoxicity (glucose, total cholesterol, TSH, hs-Tnt, NT-proBNP were determined), and electro- and echocardiographic tests were performed. In apical projections, the left ventricular ejection fraction was calculated based on the biplanar method.

Table I. Type of adjuvant treatment used in the study group of patients

Type of treatment	Number of patients (%), n = 100
chemotherapy	95 (95%)
AC x 4 ± paclitaxel/docetaxel	63 (63 %)
AC x 6	27 (27%)
TAC or FAC x 6	5 (5%)
radiotherapy	61 (61%)
left side	31 (31%)
right side	30 (30%)
complementary hormonal treatment	53 (53%)
tamoxifen	46 (46%)
aromatase inhibitors	7 (7%)

AC – doxorubicin, cyclophosphamide; FAC – fluorouracyl, doxorubicin, cyclophosphamide; TAC – docetaxel, doxorubicin, cyclophosphamide

Symptoms of cardiotoxicity during trastuzumab therapy were considered to be: a decrease in the left ventricular ejection fraction (LVEF) to less than 50% , symptoms of heart failure, and cardiac arrhythmias.

A retrospective evaluation of the cardiovascular system during cancer treatment was conducted based on the echocardiographic results performed before and during trastuzumab therapy.

Statistics

The statistical package statistica.pl ver. 10 and the Excel 2010 program, which is part of the Microsoft Office package, were used to perform statistical analysis of the results.

During the statistical analysis of the results, the following statistical tools were used: elements of descriptive statistics, comparisons of structure indicators, correlations between values of statistical characteristics.

Results

Among the 100 patients who participated in the study, trastuzumab treatment was discontinued in 11 (11%) due to: asymptomatic decrease in LVEF to less than 50% (in 9 patients) or symptoms of heart failure (in 2 patients). No other symptoms of cardiotoxicity were observed.

All patients who developed cardiac complications had a left ventricular ejection fraction of at least 50% before therapy, and there were no contraindications to anthracycline treatment. During trastuzumab therapy, the left ventricular ejection fraction dropped below 50% in 9 patients, to the lowest value of 20%, and 2 patients had symptoms of heart failure despite normal LVEF values. The patients received between 1 and 12 administrations of trastuzumab (an average of 6), before they developed symptoms of cardiotoxicity (tab. II). Patients with cardiac complications received a significantly higher dose of anthracyclines compared to patients without cardiac complications: 441.82 *vs.* 382.3 mg.

Echocardiographic evaluation of patients

The left ventricular ejection fraction is one of the parameters that determines the left ventricular systolic function. It was above 50% in all patients participating in the study before and after trastuzumab therapy. Its mean value was statistically significantly higher in the group without cardiac complications both before and during treatment, 73.21% *vs.* 68.55%; $p = 0.0074$ and 64.58% *vs.* 40.27%; $p < 0.0001$, respectively. There were no statistically significant differences between the mean LVEF values in both groups after treatment.

A decrease in the mean left ventricular ejection fraction value was observed during trastuzumab therapy, followed

Table II. Characteristics of the group of patients who developed symptoms of cardiotoxicity

Patient	LVEF before treatment	LVEF during treatment	LVEF after treatment	CHTH used	Radiotherapy	Number of trastuzumab administrations
1	73	30	50	6 x AC + docetaxel	L	6
2	65	20	68	4 x AC	P	4
3	71	25	50	4 x AC + paclitaxel	P	6
4	78	47	70	4 x AC	L	12
5	65	45	65	4 x AC	P	10
6	69	40	60	6 x AC	–	10
7	65	57	51	6 x AC + docetaxel	–	1
8	72	60	77	4 x AC	–	2
9	71	35	60	4 x AC	–	1
10	55	30	60	6 x AC	L	11
11	70	40	78	6 x AC	P	6

LVEF – left ventricular ejection fraction; L – left side radiotherapy; P – right side radiotherapy; AC – doxorubicin, cyclophosphamide; CHTH – chemotherapy

by an increase after the completion of treatment. However, the mean LVEF value after completion of targeted therapy was significantly lower in both the group with and without cardiac complications than the LVEF value measured before trastuzumab therapy (tab. III).

After completion of oncological treatment, during follow-up visits, a larger left ventricular dimension in both the systole and diastole was observed in the group of patients who had cardiac complications compared to the group of patients without cardiac complications (tab. IV, V).

Biomarkers (NT-proBNP, hs-Tnt)

The group without cardiovascular complications had a statistically significantly lower mean NT-proBNP value (154.28 pg/ml) than the group with cardiovascular complications (369.80 pg/ml), based on results from measurements during the follow-up visit ($p = 0.0038$).

No statistically significant differences were observed in hsTnt levels in the group with and without cardiac complications during the follow-up visit (8.81 *vs.* 8.61 pg/ml).

Radiotherapy

61 patients received adjuvant irradiation, seven from the group with cardiac complications (63.64%) and 54 from the group without cardiac complications (60.67%). Irradiation to the left side of the chest was used in three patients in the group with cardiac complications (27.27%) and 28 patients in the group without cardiac complications (31.46%). Irradiation to the right side of the chest was used in four patients in the group with cardiac complications (36.36%)

Table III. Comparison of mean left ventricular ejection fraction (LVEF) values between groups with and without cardiac complications

Period	Group without cardiac complications (%)	Group with cardiac complications (%)	Standard (%)
before treatment	73.21	68.55	50.00
during treatment	64.58	40.27	50.00
after treatment	66.69	62.18	50.00

Table IV. Left ventricular internal dimension in diastole (LVIDD) values after completion of treatment

Period	Group without cardiac complications (mm)	Number of patients (n)	Group with cardiac complications (mm)	Number of patients (n)	Standard (mm)
echo 1	42.59	89	48.95	11	39.00–59.00
echo 2	41.55	32	49.05	7	39.00–59.00
echo 3	42.80	8	48.48	5	39.00–59.00

Table V. Left ventricular internal dimension in systole (LVIDS) values after completion of treatment

Period	Group without cardiac complications (mm)	Number of patients (n)	Group with cardiac complications (mm)	Number of patients (n)	Standard (mm)
echo 1	27.28	89	35.74	11	21.00–40.00
echo 2	26.96	32	34.15	7	21.00–40.00
echo 3	26.66	8	34.27	5	21.00–40.00

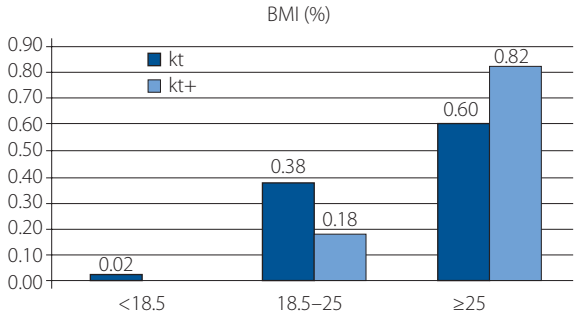

Figure 1. Distribution of the study population by body-mass index (BMI) and the presence of cardiac complications

and in 26 patients in the group without cardiac complications (29.21%).

Risk factors

The mean age in the study population was 55.71 ± 9.71 years and was statistically significantly higher in the group with cardiac complications than in the group of patients without complications (60.18 ± 6.31 *vs.* 55.16 ± 9.94 years), median age 61 *vs.* 56 years. Overweight (BMI > 25) was found more often in the group of patients with cardiotoxic symptoms than in the group without cardiac complications (82% *vs.* 60%) – figure 1.

Statistically, there were significantly more smokers ($p = 0.0177$), patients with hypothyroidism ($p = 0.0215$), hypertension ($p = 0.0042$), and ischemic heart disease ($p < 0.0001$) in the group with cardiac complications than in the group without cardiac complications.

Discussion

Over-expression of the HER2 receptor in breast cancer is associated with a poor prognosis, short time to recurrence, and short overall survival. When a human antibody directed against the HER2 receptor was developed in the late 20th century, it was initially introduced to treat advanced, then early breast cancer. The addition of trastuzumab to anthracycline-based chemotherapy proved successful. However, an increase in time to progression by 67% and an increase in response by 50% in disseminated disease, as well as an increase in disease-free time by about 50% and overall survival by about 30% in early breast cancer were associated with a risk of cardiovascular complications [3, 4]. Therefore, the problem of cardiotoxicity has become the main subject of research, not only by oncologists, but also by cardiologists.

One of the objectives of our study was to determine the incidence of acute cardiac complications among patients treated with trastuzumab.

Among the 11 patients with cardiotoxicity (11% of the study group): two patients had heart failure symptoms in NYHA class III/IV with preserved EF, five patients had decreased EF below 40%, another four patients had EF values in the range of 40–49%.

In the present study, the analysis of cardiotoxicity was conducted based on historical standards for diagnosing cardiovascular incidents in oncology [5]. In 2016, the European Society of Cardiology, in its first expert position statement on cardiovascular toxicity associated with anticancer treatment, indicated the diagnosis of cardiotoxicity when the left ventricular ejection fraction EF decreases by more than 10 percentage points to below normal, i.e., less than 50% [6]. In December 2021, a new definition of cardiotoxicity proposed by the International Cardio-Oncology Society was published [7]**.** For the first time, the diagnosis of the severity of myocardial damage caused by cancer drugs was standardized. Any decrease in EF below 40% was defined as severe cardiotoxicity. Such a situation occurred in 5 patients in the study population. The term severe cardiotoxicity (exactly: cancer therapeutics related cardiac dysfunction) is associated with an unfavorable prognosis. Indeed, it was shown in a large European registry (CARDIOTOX registry) that such EF was significantly associated with the risk of premature death from any cause (shorter overall survival) [8]. Moderate cardiotoxicity was proposed to include the onset of heart failure symptoms requiring intensification of cardiac treatment – it should be assumed that this was the case for 2 patients in the analyzed population who experienced NYHA III/IV symptoms despite a normal EF. However, moderate cardiotoxicity can also be diagnosed on the basis of echocardiography, when EF decreases to the range of 40–49% and this was the case in another 4 patients (two of whom had borderline EF = 40%).

It should be noted that modern echocardiography was not used in the analyzed population along with assessment of GLS (global longitudinal strain), i.e. a global longitudinal strain of the left ventricle. Indeed, mild cardiotoxicity can be diagnosed when GLS decreases by more than 15% from baseline and/or there is an increase in biomarkers defined as an increase in cardiac troponin I/T above the 99th percentile, BNP ≥ 35 pg/ml, NT-proBNP ≥ 125 pg/ml.

In the analyzed study, the group without cardiac complications had statistically significantly lower NT-proBNP levels than the group with cardiac complications, while no differences were observed in troponin levels. According to recent standards, it would be necessary to check how many patients with normal EF and no clinical symptoms had an increase in biomarkers or GLS changes during oncological treatment.

A number of risk factors for cardiotoxicity were found in the analyzed study, their identification is consistent with results from other publications. Through the knowledge of these risk factors, specific algorithms for the baseline assessment of patients before potentially cardiotoxic anticancer treatment were developed [9]. Baseline risk stratification is currently determining the frequency of follow-up testing (echocardiography, biomarkers) during and after active cancer treatment [10, 11].

Initial cardiovascular status prior to the start of oncology treatment is undoubtedly the most important factor determining the successful completion of potentially cardiotoxic therapy. Comorbidities, addictions, and habits shape overall health status. The co-occurrence of certain features in one patient may increase the risk of cardiotoxicity during cancer treatment, while the same features in another combination may have no effect on the cardiovascular system.

The study results on the role of trastuzumab in breast cancer treatment (HERA, Kremer et al., Pein et al.) highlighted the problem of cardiotoxicity of anti-HER2 therapy, which was inextricably related to the cumulative dose of doxorubicin [12–14]. In the present study, the mean cumulative dose of anthracyclines was significantly higher than the dose above which the risk of cardiotoxic complications increased (doxorubicin > 300 mg/m^2 according to Kremer's study) and was 387 mg/m^2 [13].

The BCIRG 006 trial is a study in which in one arm patients received trastuzumab without anthracycline treatment (6 courses of TCH), while other patients were treated sequentially with an AC regimen and docetaxel with or without trastuzumab [15]. In our study, 5 patients treated with trastuzumab did not receive anthracycline-containing chemotherapy due to cardiac contraindications or previous chemotherapy for second breast cancer. It is noteworthy that the BCIRG 006 trial showed similar efficacy of chemotherapy with and without anthracyclines (TCH regimen), with a higher safety profile of chemotherapy containing carboplatin and docetaxel [15].

More than 50% of breast cancer cases are diagnosed between the ages of 50 and 69, at which time the incidence of cardiovascular disease also increases. In the Slamon study of advanced breast cancer [16], as well as the Russo study [17] and the NSABP B – 31 [18], older patients treated with trastuzumab were more likely to be diagnosed with cardiotoxic complications. In Serrano's study, conducted in 2012 on adjuvant treatment of breast cancer in women over 70 years of age, older age and associated internal medicine (heart disease, diabetes) increased the risk of cardiovascular disease in patients treated with trastuzumab [3]. This was confirmed by Russo, who added impaired glomerular filtration in the kidneys, which increases with age, to the list of risk factors [17]. In contrast, in the Naumann study mentioned above, age was not an independent factor in the occurrence of cardiac incidents, but in a subgroup analysis of patients who experienced cardiac complications (15.72%), an inverse correlation was observed between age and time to complications [14]. Similar conclusions were drawn on the basis of our study, the age of the patients remained unaffected by cardiovascular risk. However, in the subgroup analysis, patients over 60 years of age predominated among those with cardiac complications (72.73%).

Conclusions

According to our study, the return of LVEF to normal and the alleviation of heart failure symptoms in all patients indicate the reversibility of type II cardiotoxicity. Regular echocardiographic examinations during trastuzumab therapy are extremely important. Rapid detection of asymptomatic and symptomatic complications as well as immediate implementation of cardiac therapy can prevent permanent heart damage. Therefore, it seems crucial to search for new diagnostic methods to isolate the group of patients at high risk of cardiac complications in order to safely carry out oncological treatment.

Conflict of interest: none declared

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Prehabilitation as an extra approach to usual care for cancer patients

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Prehabilitation seems to be an important issue in oncology. The main purpose of prehabilitation is to improve a patient's physical and psychological condition at the beginning of and during cancer treatment. Prehabilitation also reduces the risk of potential complications, average length of stay at hospital, stress and risk of depression, and improves quality of life. Prehabilitation activities should be individualized. Multimodal prehabilitation is more recommended and it can include a spectrum of interventions like: general conditioning exercise, targeted exercise, nutritional interventions, psychological interventions, smoking cessation and education. There is a lack of clinical trials concerning prehabilitation. Therefore new studies are still needed to standardize protocols for different types of cancer and clinical situations, and to estimate the efficacy of prehabilitation programs.

Key words: prehabilitation, cancer, exercise, psychological interventions

Introduction

Cancer diagnosis is a difficult and stressful time for a patient. The cancer patient undergoes aggressive diagnostic procedures followed by severe, strenuous, prolonged treatment (surgery, chemotherapy, radiotherapy, immunotherapy, hormone therapy) depending on the cancer type, localization, and clinical stage. Cancer treatment affects the patient's physical, emotional, and nutritional status due to medical and psychological complications [1]. The cancer itself and oncological treatments are associated with a loss of appetite, weight loss, weakness, loss of muscle mass and muscle function [2]. Cancer treatment complications may delay or preclude further treatment, reduce patients' quality of life and generate increased costs for the health service. The unawareness of patients may increase the rate of psychological distress. Cancer rehabilitation is well established. It is well-known that exercise programs during and after therapy can improve quality of life and reduce depression in cancer patients [3]. However, special person-centered care seems to be necessary for cancer patients to support their physical, emotional, informational, spiritual, and social needs from the point of diagnosis, during treatment, and to follow-up [4].

Proper perioperative care was recognized as an important component of comprehensive surgical treatment back in the 1990s. The first perioperative care protocol to improve surgical outcomes was done for colorectal surgery (Enhanced Recovery After Surgery – ERAS) [5]. This protocol has been revised, improved, and adapted for surgery in other locations [6]. It includes, among other things, nutritional interventions, smoking and alcohol cessation, encouragement of physical activity and relaxation, anemia management, and detailed patient information about various aspects of treatment. ERAS

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recommends implementation of preparations for surgery from the first visit to the surgical outpatient clinic and optimal use of time to surgery to improve the patient's general condition.

Prehabilitation is a relatively new method in medicine, but it seems to be an important issue particularly in oncology. The first research concerning prehabilitation among cancer patients was published since about 10 years ago. Cancer prehabilitation is defined as "a process on the continuum care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and severity of current and future impairments" [7]. The main purpose of prehabilitation is to improve the patient's physical and psychological condition at the beginning and during cancer treatment. Effects of prehabilitation were determined in some studies. The authors identified the influence of prehabilitation on physical activity levels, muscle strength, muscle and bone mass, total muscle/fat ratio, BMI, mental well-being, quality of life, postoperative complications, morbidity, average length of stay at hospital, disease-free survival, and reducing costs [8–20]. Cancer diagnosis can affect patients to carry out critical behavior modifications (e.g., exercise, smoking cessation). People often rethink their lives and are open for lifestyle changes [21]. It also seems that there is a need for education, providing more information because patients often have problems with processing the information and making decisions at the time of diagnosis [22]. Certainly, prehabilitation should make patients feel cared for and guided by a schedule. But on the other hand Giles and Cumminis [23] claimed that patients are too upset and worried with their diagnosis to take part in training and they are not psychologically able to modify their lifestyle. A program conducted improperly may even occasionally worsen the psychological condition. The authors suggested that prehabilitation may increase the social inequalities in cancer survival due to less involvement of lower social classes [23]. It might be consider that additional activities could be an extra stress for patients. The question arises as to what interventions to introduce into patient's care: diet and/or exercises and/or smoking cessation and/or psychological consultations. Patients who receive too many recommendations and are unable to fulfill them may have a poorer quality of life. However, accurate informing of patients at the time of diagnosis seems to play a main role. Patients should not feel pressured, they should learn the purpose and potential effects of prehabilitation to avoid disappointment or blame for treatment failure due to noncompliance with the prehabilitation program.

Prehabilitation is also a challenge in practice due to the limited time from diagnosis to treatment and the need to organize effective activities based on patient compliance. Because of the limited time available for prehabilitation prior to oncological treatment, primarily surgery, patients need to be quickly included into a prehabilitation program and be motivated to adhere to it quickly and effectively.

There is a lack of clinical trials concerning prehabilitation. In many countries the health care system is unable to provide the prehabilitation programs as a routine practice due to financial and organizational constraints [24]. It is difficult to introduce quickly and provide prehabilitation interventions in a short interval between diagnosis and the start of therapy since there are no standardized methods. Moreover, it is challenging to establish a prehabilitation scheme that will have an effect, especially in the short term.

Types of prehabilitation

Prehabilitation may involve single or multiple interventions. Generally physical exercise is a crucial factor in multidisciplinary cancer care [25]. But the implementation of a nutritional and psychological intervention into a prehabilitation program may impact clinical outcomes [26–28]. Multimodal prehabilitation can include a broad spectrum of interventions like: general conditioning exercises, targeted exercises, nutritional interventions, psychological interventions, smoking cessation, and education [18]. There are some data that multimodal prehabilitation programs including psychological, nutritional, and physical intervention are associated with better functional outcomes when compared with single interventions. Patients better tolerate exercise programs together with dietary supplementation [29]. Psychological interventions could reinforce patient's motivation for physical and nutritional interventions, while physical exercise could reduce anxiety and depression [30].

Individualized prehabilitation should be provided. It seems to be important to educate and engage patients about the prehabilitation program.

Physical intervention

There are recommendations to combine exercises with standard oncological treatments to improve physical and psychological well-being for all types of cancer [16]. Physical interventions include general conditioning exercises or targeted exercises and could also be used as prehabilitation. General conditioning exercises and cardiovascular fitness are useful for strengthening and increasing tolerance to cancer treatment, as well as reducing postoperative complications. Exercise interventions may also include aerobic, yoga, Qi-gong, and Tai-Chi [31]. Targeted exercises concerning body region which could be related with dysfunction after treatment, for example bladder exercises to prevent post-operative urinary incontinence.

Patients may undergo physical training to improve therapy outcomes and health-related quality of life [11]. Better post-operative results and shorter length of hospital stay were associated with physical activities before surgery [10, 17]. Women

with breast cancer, physically active before surgery, have 85% greater chance of returning to a baseline physical condition 3 weeks after surgery than inactive patients [32]. Targeted exercises would be associated with a reduction in absences from work [33]. Rao et al. [14] showed lower anxiety among women with breast cancer who partook in yoga prior to surgery.

Prehabilitation training may improve the 6-minute walk test (6MWT), which is used to measure functional capacity. The results of 6MWT was associated with post-operative morbidity and complications [34]. Cavalheri et al. [35] showed that non-small cell lung cancer patients who exercised before surgery demonstrated greater 6MWT than inactive patients; they had decreased risk of pulmonary complications by 67%, shorter time with an intercostal catheter, and a reduced hospital stay. Morano et al. [36] also showed that preoperative exercise training among lung cancer patients significantly decreases the time of hospitalization, time of need for a chest tube, and pulmonary complications. Exercise intervention before operations reduced complications after abdominal surgery [37]. Significantly higher heart rate, oxygen uptake, peak power output were reported in the group of colorectal cancer patients who had undergone a 4-week course of aerobic exercise prehabilitation before surgery in comparison to patients who did not receive exercise training [38]. Physical prehabilitation may improve muscular strength and reduce the frequency of sarcopenia. Prehabilitation could change body composition. Analysis of body composition demonstrated that in a case of esophageal cancer, patients' exercise interventions reduced overall fat mass and reduced fat-to-muscle ratio [39]. It could influence the hospital stay, postoperative complications, the risk of infection, and the need for assisted ventilation related to additional medical costs and rate of readmission [8, 9].

Meta-analysis showed that aerobic high-intensity interval training (HIIT) in prehabilitation programs is effective, safe and feasible among cancer patients. HIIT is defined as a discontinuous endurance exercise characterized by a relatively short time of high-intensity exercises between periods of rest or low-intensity activity during recovery [40]. This method significantly improved cardiovascular fitness, measured by peak oxygen uptake in comparison to usual care. HIIT has been shown to have beneficial effects on quality of life, mood, emotional and pain state, as well as cognitive health [41–42].

VO_2 peak is an independent predictor for surgical complications and the survival of non-small cell lung cancer patients [43]. Recent studies showed that intervention combined with moderate- and high-intensive training (maximum heart rate 70–80%) is an optimal exercise program to improve 6-minutes walk distant (6MWT) and clinical outcomes of cancer surgery patients [44, 45]. High-intensity training is more effective to increase cardiorespiratory function in a limited time from diagnosis to operation [46].

However, there are no established schedule of exercises (type, duration, frequency, composition of activities) [47].

Nutritional intervention

It is recommended to assess nutritional status before major surgery. Perioperative nutritional support therapy is indicated in patients with malnutrition and those at nutritional risk. Patients with severe nutritional risk shall receive nutritional therapy prior to major surgery in a period of 7 to 14 days. Severe nutritional risk has been defined according to the ESPEN working group as the presence of at least one of the following criteria: weight loss >10% within 6 months, BMI <18.5 kg/m^2, SGA (subjective global assessment) grade C or NRS (nutritional risk screening) >5, serum albumin <30 g/l [48]. ESPEN recommend that the total energy expenditure of cancer patients is similar to healthy subjects and generally ranging between 25 and 30 kcal/kg/day [49]. According to ESPEN guidelines, protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day [49].

Nutritional supplementation in cancer patients is mainly aimed at increasing protein for higher efficiency of exercise and functional capacity [19]. Preoperative protein supplementation has a positive impact on outcomes, including bone mass increase and 6MWT improvement [19–20, 50].

Nutritional prehabilitation alone and in combination with exercise significantly shortens the length of hospital stay after colorectal surgery [51]. Results of randomized clinical trial and meta-analysis showed that among malnourished patients who received nutritional intervention before a gastrointestinal operation, complications after surgery were reduced by 20% [52]. Kabata et al. [53] conducted a prospective study among patients who underwent abdominal cancer surgery. Patients who partook in a nutritional intervention for 14 days prior to the operation had significantly less number and severity of complications in comparison to patients without nutritional intervention; their level of protein was stable after surgery.

Psychological intervention

Cancer diagnosis naturally influences the emotional well-being of patients. Patients often experience anxiety and shock at the time of diagnosis. Existential questions, self-blame, fears for the future, and loss of control usually accompanies cancer patients thoughts at this time. Distress during the wait for surgery may have an adverse effect on recovery and cause higher risk of mortality [54–55]. Psychological intervention provided immediately after cancer diagnosis could help patients to adjust to the current situation. The standard of care in US includes distress screening to assess the psychological functioning of patients [56]. It was reported that stress management training before surgery among women with breast cancer reduced depression, tiredness, and anxiety [14, 15]. Stress management includes relaxation techniques such as meditation, breathing, yoga, muscle relaxation and strategies for coping with stress and problem solving [57]. Distress connected with cancer surgery is correlated with education levels, family support, and preoperative education.

Depression, anxiety, and fear can have adverse impacts on recovery, with complications among patients who have abdominal surgery [58–59]. Patients with breast cancer, who partook in yoga or supportive care before treatment and continued after surgery and during radiotherapy and chemotherapy, experienced less anxiety [14].

Psychological prehabilitation programs based on stress management, relaxation methods delivered in at least four 45–60 minutes sessions appear to improve quality of life after surgery among cancer patients [60].

Changes in lifestyle

Smoking cessation is recommended after cancer diagnosis to reduce postoperative complications, infection, disease recurrence, and even mortality [61, 62]. It was noted that patients who stopped smoking before surgery demonstrated lower risk of complications and better functional status and well-being after operation [63]. Smoking cessation among breast cancer patients may improve adherence to adjuvant chemotherapy [64]. Female smokers after breast cancer resection with reconstruction showed a greater risk of complications, infection, and failure of reconstruction [65-67]. Smoking is noted as a predictive factor of distress [68].

Prehabilitation interventions in different cancer localizations

Prehabilitation research focuses on patients undergoing surgery for colorectal cancer, prostate cancer, and less often breast cancer, lung cancer, and bladder cancer patients. Mainly the prehabilitation program is introduced before surgery, but there are also some studies relate to radiotherapy and chemotherapy.

Colorectal cancer

Trimodal prehabilitation (exercise, nutritional and psychosocial counseling) used before colorectal cancer resection significantly improves functional capacity, physical fitness, and 6MWT [69, 70]. The results of randomized control trials in colorectal cancer patients treated by operation showed that physical fitness as measured by the 6-min walking test was significantly higher in patients with 4-weeks prehabilitation than in the group of patients who underwent rehabilitation first after operation [69]. In an international multi-center, prospective, randomized trial, the positive impact of 4 weeks multimodal prehabilitation (an individualized exercise programs, breathing techniques, dietician consultation, protein supplementation, smoking cessation program, psychological intervention after screening for anxiety and depression) on a group of 714 colorectal surgery cancer patients was established. Dimeo et al. [71] showed that 86% of patients with prehabilitation in comparison to 40% of patients without prehabilitation recovered to baseline function 4 weeks after operation ($p < 0.01$). By strengthening the functional capacity (6MWT) and postoperative complications, quality of life and survival may be improved [13]. But in other randomized clinical trials, the impact of multimodal prehabilitation (exercise, nutritional and psychological interventions) on postoperative complications among colorectal cancer patients was not confirmed [69, 72].

Targeted prehabilitation among colorectal cancer patients may influence strengthening functional capacity and result in better outcomes by reducing delays in beginning the adjuvant therapy [73]. Trépanier et al. [12] showed that 4 weeks trimodal prehabilitation (exercise, nutritional and psychosocial counseling) improved 5-year disease-free survival in patients with stage III colorectal cancer at ($p = 0.044$). Aerobic exercise seems to be an independent predictor of disease recurrence and mortality among colon cancer patients [74].

In the case of colorectal cancer surgery, patients who underwent any prehabilitation intervention had significantly shorter hospital stays [51].

Prostate cancer

Patients who were offered pelvic floor muscle training prior to a prostatectomy had significantly higher urinary continence one and three months after the operation, in comparison to patients who received usual care [75–77]. Continence-related quality of life was significantly improved at one and three months after the operation [76]. Patients who underwent physical therapy and a pelvic floor exercise program before and after a prostatectomy, and continued this program at home twice a day after surgery, were more likely to regain continence earlier then control group at 12 weeks post operation [75].

Burgio et al. [78] among patients using preoperative behavioral training prior to prostatectomy showed the significant decrease in time to achieve continence ($p = 0.03$) and a reduction in the number of patients with leakage at endpoint 6 months after operation ($p = 0.04$) in comparison to patients who started training first after operation. The impact on return to work and usual activities or quality of life was not reported. The preoperative biofeedback combined with a postoperative program of perineal physiokinesitherapy improved recovery of continence [76]. Prehabilitation also had an impact on anxiety among prostate cancer patients [79].

Breast cancer

Rehabilitation for breast cancer patients undergoing operation and radiotherapy is most commonly introduced after oncological treatment. It is focused on restoring the function of the shoulder and upper limb using mobility and flexibility exercises. The systematic review demonstrated that an exercise program conducted before breast cancer surgery may improve the shoulder's range of motion, grip strength, function recovery and reduce pain, but postoperative rehabilitation should be continued to aid recovery [80].

General conditioning exercises are also very important for well-being among breast cancer patients. Rao et al. [14]

showed that yoga, prior to breast operation, lower states and traits of anxiety. In Canada, Brahmbhatt et al. [81] carried out a study among 22 women who underwent breast cancer surgery, receiving individualized exercise (aerobic exercise and upper quadrant-specific resistance training) before breast operation. All participants subjectively noted beneficial effects and did not consider discontinuation from exercises and rather planned to continue the training program. Participants also claimed that they would recommend it to other patients before surgery. The 6MWT significantly increased from baseline to the preoperative assessment, there was a small decrease in 6MWT in the 6-week postoperative assessment and this again significantly increased 3 months after surgery. There are suggestions that psychological screening and intervention immediately after breast cancer diagnosis can help improve psychological and social status [82]. Breast cancer patients, who received stress management training before operations, experienced a reduction in depression and fatigue shortly after surgery [83].

A cardioprotective effect was observed in animals that underwent exercises in the prechemotherapy period. Kirkham et al. [84] showed that breast cancer patients who did aerobic exercise 24 hours before doxorubicin, experienced a less severe decline in cardiac function after chemotherapy.

In general, multimodal prehabilitation for breast cancer treatment (general conditioning and targeted exercise, nutritional optimization, stress reduction, smoking cessation) may reduce postoperative complications, enhance the effect of adjuvant therapy, enhance usual activities, facilitate a return to work, and mitigate psychological and physiological reactions to surgery [85–87].

Lung cancer

The results of a randomized controlled trial conducted by Liu et al. [88] showed that a 2-week multimodal prehabilitation program before surgery in lung cancer patients (aerobic and resistance exercises, respiratory training, nutrition counseling with protein supplementation, psychological guidance) was associated with higher perioperative functional capacity (as measured by 6MWT). But there were no differences in lung function, postoperative complications, and length of stay in hospital. Lai et al. [89] showed that pre-operative short-term (one week) comprehensive pulmonary rehabilitation training can improve the pulmonary resistance of patients with mild to moderate chronic obstructive pulmonary disease and accelerate rapid recovery of patients after surgery. Moreover, in a study published by Stefanelli et al. [90], high-intensity prehabilitation (3 weeks) improved the physical performance of patients with chronic obstructive pulmonary disease and non-small-cell lung cancer (NSCLC) undergoing surgical resection. Coast et al. [91] demonstrated significant improvements in the depression score among lung cancer patients after the prehabilitation program. However, most authors did not notice changes in the quality of life [89, 92, 93]. Significant quality of life improvements was observed only by Huang et al. [94] and Peddle et al. [92]. In the systemic review and meta-analysis from 2019, including 676 participants at stage I–IV NCSLC from 10 studies [95], significant positive results were found in functional capacity (6MWT, VO_2 peak, dyspnoea) and pulmonary complications among lung cancer patients who have undergone prehabilitation (moderate intensity aerobic, resistance, inspiratory muscle training). There were improvements regarding mental wellness, but the results were not statistically significant. The systematic review conducted by Garcia et al. [96] reported that preoperative exercise training in lung cancer patients significantly enhanced pulmonary function. Another systematic review [97] showed that moderate and intense preoperative exercise therapy among patients qualified to lung surgery had a beneficial impact, not only on physical fitness, but also on quality of life (not significant). Prehabilitation in lung cancer patients undergoing surgery may reduce postoperative complications [95–97]. Exercise training in lung cancer patients leads to a lower risk of pulmonary complication by 67% in comparison with the control group, improved 6MWT, and a shorter time of intercostal catheter need [98]. Among advanced lung cancer patients, physical capacity, anxiety and well-being, and quality of life were improved [99–100]. Prehabilitation for lung cancer patients decreased the length of hospital stay after surgery [96–97].

Other cancers

Minnella et al. [101], in a randomized clinical trial, showed that multimodal prehabilitation statistically improved perioperative functional capacity (as measured by 6MWT) in esophagogastric cancer patients. Patients got individualized home-based exercise training programs and aerobic exercise, food-based dietary advice was provided, and protein supplements were prescribed. Patients after prehabilitation more often experienced an improvement in their condition before operation in comparison to patients without prehabilitation (62% *vs.* 4%) as well as after surgery (52% *vs.* 6%). There were no statistically significant differences in complication rates and length of hospital stay.

In the case of head and neck cancer patients, prehabilitation includes some specific exercises: general stretching, motion exercises and specific swallowing exercises. Some trials showed positive functional outcomes, while other studies did not confirm that [102]. It seems that exercise should begin as soon as head and neck cancer is diagnosed, and should take place before surgery and continue after the operation [102].

There was no significant benefits for bladder cancer patients treated with radical cystectomy of peri-operative exercise [103]. However analysis from 2020 [104] showed a trend toward improved physical condition and psychological well-being with the use of prehabilitation in bladder cancer patients before radical cystectomy.

Prehabilitation *vs.* rehabilitation

Meta-analysis carried out by Treanor et al. [105], comparing prehabilitation with standard care for cancer patients, found that preoperative interventions significantly improved physical well-being, quality of life, mood, and immune function in prostate cancer patients, while reducing the length of hospital stay and post-operative complications among lung cancer patients. In breast cancer patients who underwent prehabilitation with psychosocial intervention, there was a significantly lower level of distress, anxiety, depression (3 months after surgery) and less distress related to losing the breast, the partner's response and worries one year after surgery were also reported [105].

Conclusions

There is growing evidence that multimodal prehabilitation (exercises, nutritional consultation with protein supplementation, psychological support and smoking cessation) may improve the treatment outcomes for cancer patients, especially surgery. The systemic reviews showed that use of prehabilitation programs is more effective than standard care for cancer patients before the start of cancer therapy [25, 41, 60, 105]. Prehabilitation is important not only in improving the patient's overall physical condition before cancer treatment, but also for reducing the risk of potential complications, stress and risk of depression, and improving the quality of life (tab. I). A structured prehabilitation program for cancer patients, implemented early on from diagnosis, allows patients to actively participate in preparing for treatment, gives them a sense of empowerment, increases motivation and helps them feel cared for. Prehabilitation is feasible and safe – no adverse effects of prehabilitation were noted [91]. However, there are no standardized prehabilitation guidelines. There is a huge heterogeneity in type, intensity, duration, timing, and supervision of prehabilitation programs. Multimodal prehabilitation is more recommended, but it seems that prehabilitation activities should be individualized.

Table I. Prehabilitation benefits

Benefits for patients	Benefits for health care system
improving general condition	fewer complications
improving nutritional status	reduction in length of hospital stay
reducing stress, anxiety	reducing the risk of re-hospitalization
shorter hospital stay	
fewer treatment complications	
shortening the time to adjuvant treatment	
improvement of quality of life	
a faster return to work	

New studies are still needed to standardize protocols in different cancer types and clinical situations and to estimate the efficacy of prehabilitation programs.

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Adjuvant radiotherapy post microvascular reconstructive surgery (MRS) for patients with locally advanced head and neck cancer – when and how?

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For many decades palliation (radiotherapy, chemotherapy or symptomatic treatment) was the only therapeutic solution for locally very advanced head and neck cancer. In the mid 70s, H. Buncke carried out pioneering microvascular reconstructive surgery (MRS) as a radical treatment. Since that time, the MRS has been accepted around the world as a successful radical therapy, not only for head and neck (H&N) cancers. A part of the H&N cancers need however post-MRS radiotherapy (RT). Based on the 20 year experience of the Institute of Oncology in Gliwice with MRS (about 2500 patients), D. Bula has defined local recurrence risk factors. Dutch studies convincingly documented the prognostic value of the estimated molecular profiles of the resected margins as additional risk factors. The use of conventional 2.0 Gy/fraction post-MRS-RT result in a high risk of the inserted reconstructive flap necrosis or rejection. Therefore, a novel IMRT-VMAT technique with 50 Gy given in 1.5–1.6 Gy/fraction has been designed which allows to almost eliminate the flap from the irradiated volume and therefore minimizes recurrence and/or flap rejection to almost zero. The present paper shows objectively selected a cluster of patients being the candidate to post-MRS safe and effective VMAT radiotherapy.

Key words: advanced head and neck cancer, microvascular reconstructive surgery, criteria for post-op. VMAT radiotherapy

When and why did MRS begin?

Worldwide, nearly 600 000 patients are annually diagnosed with squamous cell head and neck cancer and about 60% of them have locally very advanced disease with or without infiltration (destruction) of local bone structures [T4N0(+)]. Locoregional recurrence are the predominant most failure resulted from uncontrolled microdisease. For decades, palliative radiotherapy or symptomatic pain release therapy have been used as the only solution. As the result overall survival (OS) was only estimated but not the cure rate, because it has never been achieved [1, 2]. Generally, 5-year OS was low, on average about 10–15% (fig. 1, bottom survival curves) which raised to about 30–35% after radiotherapy combined with concurrent chemotherapy (usually single agent – cisplatin). The rate of patients with symptomatic therapy,

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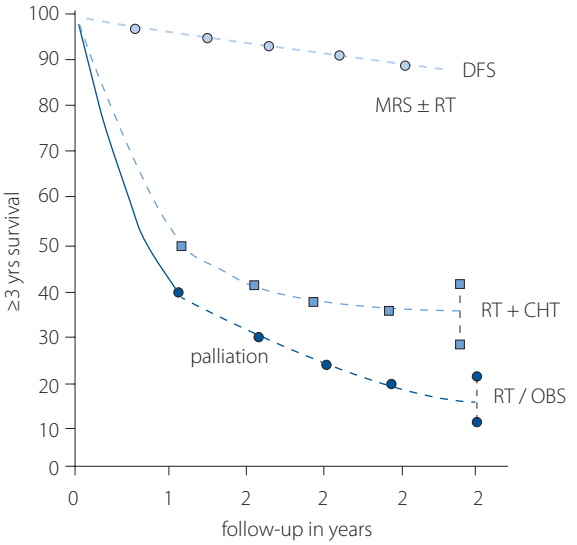

Figure 1. Survival after palliative radiotherapy (RT) or chemoradiation (RT + CHT) compared with disease-free survival (DFS) after microvascular reconstructive surgery (MRS) with or without adjuvant RT

mainly painkillers, has still remained pretty high and patients quality of life was usually very poor. Patients with advanced tumors, often accompanied with pathologic bone (mandible or maxilla) infiltration and local necrotic lesions had no chance to be cured.

Incidentally, large tumor regression after palliative chemoradiation led to radicalization of therapeutic procedures (surgery), which sometimes (rarely) resulted in local tumor control, however with a high risk of local recurrence. Therefore, the overall rate of local tumor control with disease-free survival was very low (a few percent) and lasted not longer than 2–3 years. For the majority of very advanced head and neck (H&N) cancer patients prognosis was not optimistic and although palliative therapy resulted in prolonged survival, their quality of life became worse and worse and was accompanied with increasing pain and deteriorating speech, in addition to problems swallowing and eating. Such poor perspectives for palliative therapeutic options lasted for many decades till the 70s.

In 1973, a significant breakthrough was initiated by Harry Buncke's pioneering work in which he transferred an island flap to reconstruct defect in the upper part of the feet. In the same year, Daniel and Taylor [3] repeated this reconstructive microvascular surgery. They, with many other pioneers [4–10] developed core principles of reconstructive microsurgery which are still pertinent today. This therapeutic procedure has quickly spread across US, European and Far South-East medical and oncology centers.

Microvascular reconstructive surgery (MRS) of locally advanced, not only head and neck cancers, should be considered as a milestone step because it has offered a radical outcome and long-term local tumor control, instead of the previous palliation and short-term survival. In the Institute of Oncology in Gliwice in 2000, the MRS has enriched methods and techniques of oncological surgery, and during the last 20 years about 2500 patients with advanced head and neck and other localization were successfully treated using the MRS. The overall 5-year disease-free survival rate increased to 88–90% (fig. 1, top curve) which clearly testifies to the tremendous improvements compared with previous results of palliative therapy. At the beginning of the MRS, the use of simple flaps gradually progressed into perforator, prefabricated, prelaminated, and chimeric flaps. Theoretically any tissue of any size from the body can be harvested using 135 different flaps, among which there are 65 types of free flaps. It allows the choice of a proper one for individual patient. Hidalgo et al. [11] pointed out that only seven free-flap donor sites are sufficient to solve 98% of microsurgical problems in oncology.

Although MRS has been a highly effective local therapy, there is still about 10–15% risk of local tumor recurrence and a few percent of postoperative local complications (flap necrosis). Thus, there is undoubtedly room for postoperative radiotherapy (RT), but it is still an open question whether all or only carefully selected patients need this RT as adjuvant therapy.

When should post-MRS radiotherapy should be applied?

Bula [12] analyzed the results of MRS in 119 patients with locally very advanced midface cancer, among which 85% were in stage T4N0(+) and in 63% of them four or more anatomical structures were involved. In 18 patients (10%), radicalism of surgical margins was defined as uncertain (very narrow margins?). One may ask what such uncertainty means. It is rather subjective than objective criterion for choosing post-op. RT. Using taxonomic statistics, the author established patient clusters with high and low risk of local recurrence. The cluster of patients with uncertain surgical margins, overweighed, with resection defect IIIA according Cordeiro scale [7, 8] and resected tumor size larger than 18 cm^2 strongly correlated with a high (about 90%) risk of local recurrence. On the contrary, cluster with radical margins (negative), normal weight, resection defect type IIA and a tumor size of about 4–8 cm^2 significantly ($p < 0.001$) correlated with almost no risk of local recurrence.

Therefore, patients from the first cluster likely seem to be candidates for postoperative RT. However, an important question arises as to whether the risk factor and parameters established by Bula can be considered as sufficient and adequate predictors for the post-MRS radiotherapy.

Studies of Nees et al. [13], Van Houten [14, 15] and Graveland [16], all from Vrije University Medical Center in Amsterdam (The Netherlands), have focused their studies on the molecular characteristics of minimal residual disease in surgical margins of head and neck cancer patients. Graveland [16] used two 5 µm sections from all surgical margins, which were histologically examined as to whether they were molecularly positive or negative. The specimens were used for immunohistochemical staining of the overexpression of the *p53* gene and *Ki-67* gene.

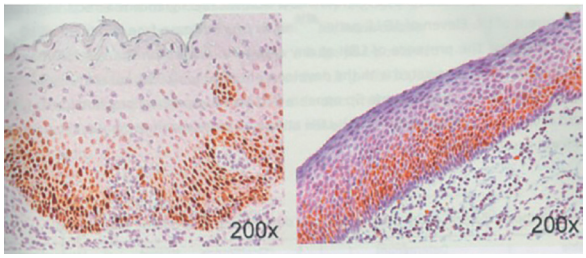

Figure 2. Example of immunohistochemical staining with: (A) a p53 positive field and (B) positive Ki-67 immunostaining [reprinted from Graveland et al. [16] with permission]

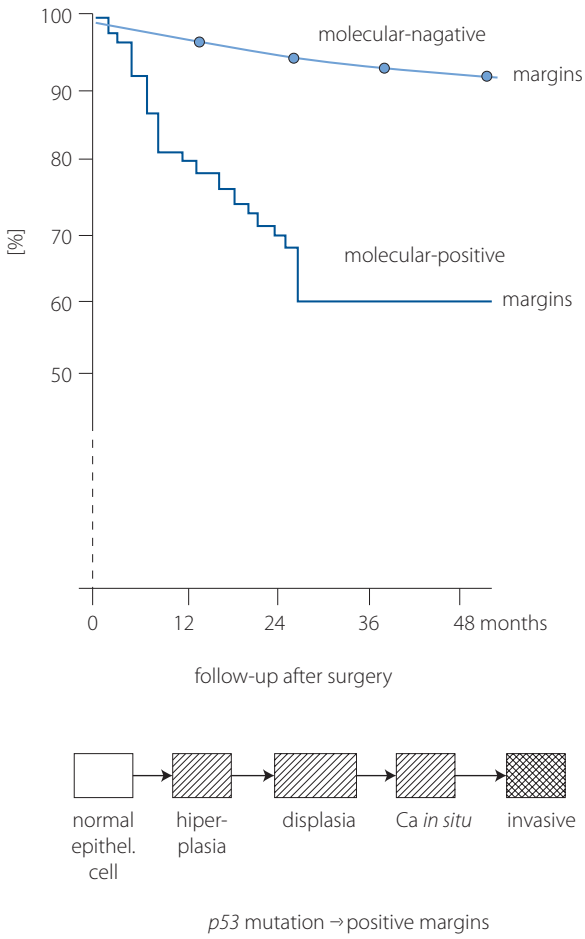

Figure 3. Local recurrence-free survival in relation to the molecular margin status (reprinted from Van Houten et al. Clin Cancer Res 2006; 6: 3803–3816, with permission)

A representative example of *p53* and *Ki-67*-positive fields is shown in the figure 2.

The *p53* and *Ki-67*-positive but histologically negative margins are the results of the cascade amplification of the EGFR, cyclin D1, cathepsin D, Cox-2, 9 p51, 3p, 17p 13, 11q 11 genes with LOH (loss of heterozygosity) which lead to gradual alteration of normal epithelial cells through hyperplasia and dysplasia to cancer cells (fig. 3, bottom part), clinically occurring as local recurrence of the primary tumor, although it has incorrectly been diagnosed the second primary tumor (SPT). Such local

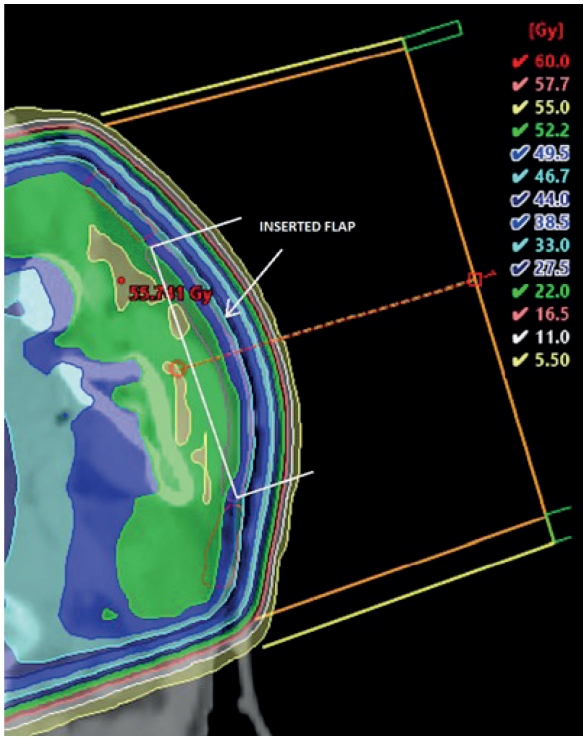

Figure 4. Simple a single- or two field post-MRS stationary irradiation using 30 fractions of 2.0 Gy

recurrences (LR) develop from preneoplastic fields consisting of genetically altered normal mucosa cells that were not completely excised and they occur very early, during the first 10 months of the follow-up [13]. The results of the studies of Van Houten et al. [14, 15] have convincingly shown that cases with histologically negative but molecularly (*p53*, *Ki-67*, HPV) positive margins result in a significant ($p < 0.017$) decrease of the 5-year disease-free survival by about 30%, compared with cases with both molecular and histological negative margins (fig. 3).

Results of the Dutch studies clearly encourage to supplement surgical margins with molecular staining as a significant predictor of high risk of local recurrence after the MRS, which is more precise of the LR than the "uncertain margins" defined by Bula [12]. Together with the high risk cluster factors defined by this author, they could increase the precision of individual selection of high LR risk patients to post-MRS radiotherapy.

Methods and technique of post-MRS radiotherapy

Traditionally, the beam(s) of a single-or-two-field stationary irradiation of post-reconstructive area cover(s) both the inserted flap (block of healthy tissues) and the block of normal tissues surrounding the flap (fig. 4). It sounds illogical to include the flap into the irradiated area because it is a locus of minor resistance (*locus minoris resistantiae*) of normal tissue island. Although the risk of the LR may decrease, on the other hand, the uncreased risk of the post irradiation flap necrosis and/or rejection significantly increases, after conventional 2.0 Gy fractionated radiotherapy.

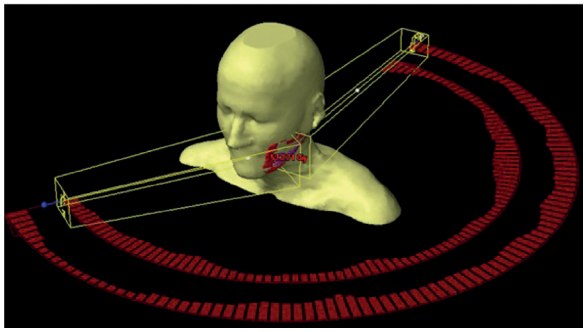

Figure 5. Example of VMAT radiotherapy technique with a single arc dose planning

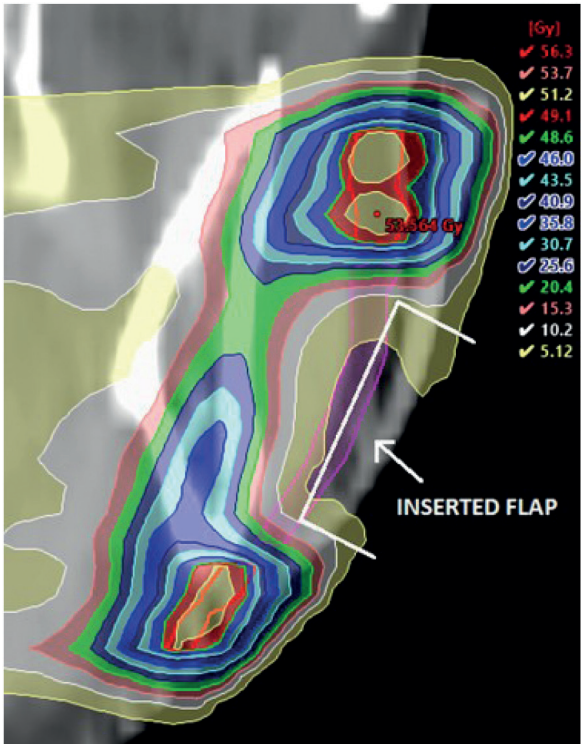

Figure 6. Example of vertical VMAT dose distribution of 50 ± 5 Gy in 30–31 fractions within the ring of normal tissues surrounding the inserted flap and sharp dose fraction gradient to above ≤0.35 Gy per fraction deposited in the periphery of the flap tissue

Modern linear accelerators offer the use of a variety of intensity modulated RT (IMRT) techniques with non-uniform dose distribution using multileaf collimators (MLC). One such sophisticated technique is volumetric-modulated arc therapy (VMAT), which produces satisfactory dose distribution (fig. 5) to optimize the field shapes and beam intensities using a number of gantry angles. A significant advantage of the VMAT delivery is a reduction of the overall treatment time compared with conventional IMRT. For post-MRS adjuvant radiotherapy, the VMAT technique seems to be an optimal solution. This technique allows to plan the highest dose deposited in a ring of normal tissues surrounding the inserted flap likely containing microlesions of normal cells with potential genetic progression into cancer cells, and a sharp dose gradient dose to almost zero within the inserted flap (fig. 6). An important point of such dose planning is that the dose per fraction should be not higher than 1.5–1.6 Gy which results in of dose per fraction reduced to 0.35 Gy within margins of the inserted flap. It allows to minimize or even eliminate the risk of the flap necrosis or rejection.

Summarizing, the recurrence risks factors defined by Bula [12] supplemented by an estimation of the molecular status of the respective margins increase the objective selection of patients as proper candidates to post-MRS adjuvant radiotherapy. The choice of the VMAT technique with the GTV_S (ring of normal tissues surrounding the inserted reconstructive flap) total dose of about 50 Gy in 1.5–1.6 Gy dose per fraction seems to be the optimal solution for post-MRS radiotherapy as it likely lowers (even to zero) the risk of the inserted flap necrosis or rejection, and provides long term disease-free survival of patients with locally advanced head and neck cancer.

Conflict of interest: none declared

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Immunotherapeutics and other anticancer agents in the management of advanced gastric cancer

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Advanced gastric cancer (AGC) is characterized by high mortality. The survival is estimated as 14.2 months. The treatment of choice in the early stages of GC is surgery. Due to high potential of malignancy, postoperative chemotherapy is usually administered. Novel methods of treatment involve immunotherapeutic agents (IA). The new therapies seem to be a hopeful perspective for patients with advanced GC. In this review, we present the outcomes of clinical trials in GC treatment with IA and their mechanisms of action. Furthermore, we present the benefits and shortcomings of immunotherapy and describe potential directions for future research.

Key words: advanced gastric cancer, immunotherapeutic agents, monoclonal antibodies, immune checkpoint inhibitors

Introduction

Gastric cancer (GC) is the fifth most common diagnosed malignancy with 1.1 million new cases in 2020 [1]. A surgical procedure is a crucial part of the treatment [2]. Adjuvant chemotherapy is usually administered postoperatively. Advanced gastric cancer (AGC), defined by extensive infiltration of adjacent tissue or metastasis, has a poor prognosis. Currently, chemotherapy plays a key role in AGC management. The median overall survival of AGC is estimated as 14.2 months [3]. Due to the low effectiveness of chemotherapy, immunotherapy is considered as a promising, novel part of AGC treatment. The aim of this paper is to report outcomes of several clinical trials in phase I, II, and III. We have made an attempt to present the mechanisms of action of various IA and provide valuable insights into the clinical implementation of these state-of-the art treatment agents.

Strategy for advanced gastric cancer treatment

For the first line treatment, it is recommended to use a platin agent (e.g. cisplatin) and fluoropyrimidine (e.g. 5-fluorouracil) in human epidermal growth factor receptor 2 (HER2) negative tumor. Cisplatin and oxaliplatin share similar efficacy. However, they differ in terms of adverse events (AE). Cisplatin treatment is associated with renal dysfunction and thromboembolic complications while oxaliplatin may cause neuropathy and diarrhea [4]. In HER2-positive cancer, trastuzumab is added to standard chemotherapy. Trastuzumab is an anti-HER2 monoclonal antibody. It was proven that combined therapy increases overall survival compared to chemotherapy alone in the ToGa trial [5]. In the second line treatment ramucirumab – an anti-vascular endothelial growth factor (VEGFR) monoclonal antibody may be administered. [6]. Third line

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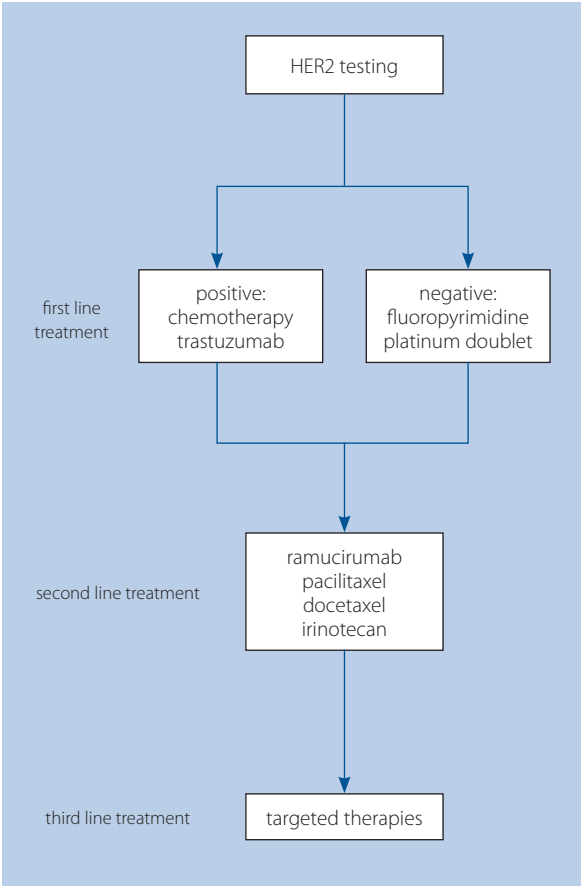
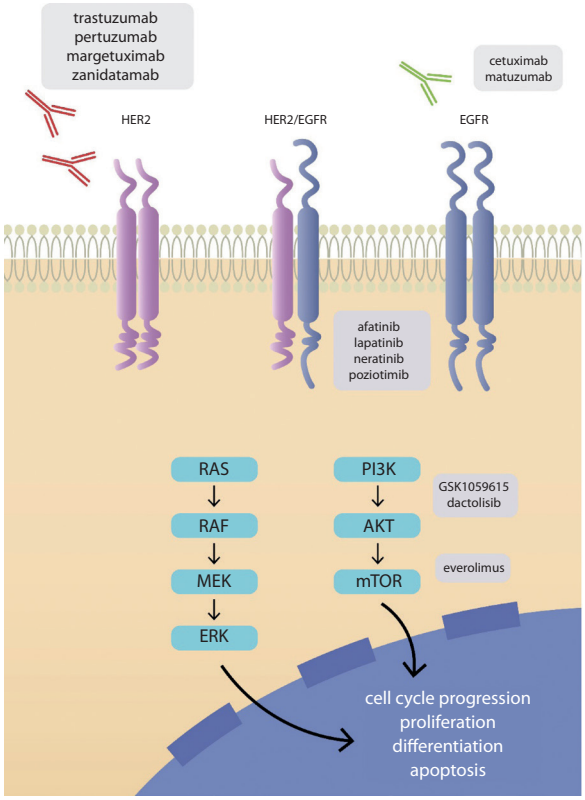


Figure 1. Treatment strategy for advanced gastric cancer according to the National Comprehensive Cancer Network (NCCN)



HER2 – human epidermal growth factor receptor 2; EGFR – epidermal growth factor receptor; ERK – extracellular signal regulated kinase; PI3K – phosphatidylinositol-3--kinase; mTOR – mammalian target of rapamycin

Figure 2. Epidermal growth factor signaling of receptors and target therapies

treatment may be considered in progression of the disease despite prior therapy. Figure 1 presents the strategy of AGC treatment based on guidelines of the National Comprehensive Cancer Network (NCCN) [7].

Anti-HER2 inhibitors

HER2 is a member of epidermal growth factor receptors which are tyrosine kinases. HER1, HER3 and HER4 are other members of this group. All receptors have an extracellular domain, transmembrane region and intracellular tyrosine kinase with carboxy--terminal region. While ligands of HER1, 3, and 4 receptors have been identified, ligands of HER2 are still unknown (fig. 2) [8, 9]. HER2 is a proto-oncogene, and its function is to stimulate cell proliferation and inhibit apoptosis. Expression of this tyrosine kinase was found in the gastrointestinal tract, breast, kidney, and heart. Overexpression of HER2 is present in types of breast and GC (range from 4.4% to 53.4%) [10]. To identify HER2 over--expression in GC, immunohistochemistry and fluorescence *in situ* hybridization (FISH) is used. Expression is classified into three groups: negative: 0+/1+; equivocal: 2+ or positive: 3+ [11].

Trastuzumab

It is considered that patients with HER2 overexpression IHC2+ or IHC3+ are eligible to be treated with trastuzumab [12]. It is an IgG1 anti-HER2 monoclonal antibody that binds to the extracellular domain of the receptor and suppresses cancer cells proliferation and survival. Furthermore, trastuzumab indirectly stimulates antibody dependent cellular cytotoxicity (ADCC) [13]. Since trastuzumab was evaluated as safe and efficient in the ToGa trial, several other agent combinations with trastuzumab are currently being assessed. However, it still remains the only target therapy in the first line treatment. Based on the outcomes, the Food and Drug Administration (FDA) has approved trastuzumab in HER2-positive GC. Despite the promising results of the ToGa trial, poorer survival has been observed in routine clinical use of trastuzumab [14]. Xelox is composed of oral capecitabine and intravenous oxaliplatin. This combination is one of the most frequently applied regimens [15]. Two phase II clinical trials evaluated the outcomes of combination XELOX + trastuzumab (tab. I) [16, 17]. Favorable toxicity and promising outcomes were reported (OS 21 *vs.* 13.8 months). A recent phase II study evaluated the efficacy of trastuzumab in combination with docetaxel and capecitabine as a first line treatment. It has shown high efficacy (median overall survival 20.9 months) and safety (absence of major AE other than neutropenia, leukopenia, and hand-foot syndrome). Moreover, tumor shrinkage was observed in most of the patients [18].

Table I. Representation of currently recruiting or ongoing clinical trials with the use of anticancer agents mentioned in this review

ID	Treatment agents	Study design	Number of participants	Treatment line
NCT05152147	zanidatamab/ tislelizumab/ tislelizumab + chemotherapy	phase III	714	first
NCT03929666	zanidatamab + chemotherapy	phase II	362	first
NCT05274048	neratinib + trastuzumab deruxtecan	phase I	18	one prior line of chemotherapy + HER2 directed therapy
NCT04768686	pembrolizumab + FLX475	phase II	90	second and third
NCT04745988	pembrolizumab + lenvatinib	phase II	30	first
NCT03321630	pembrolizumab + lenvatinib	phase II	24	second or further
NCT04249739	pembrolizumab	phase II	93	first
NCT04592211	pembrolizumab + olaparib + pacilitaxel	phase Ib/II	71	second
NCT04882241	pembrolizumab + chemotherapy *vs.* placebo + chemotherapy	phase III	120	first
NCT03488667	pembrolizumab + mFOLFOX	phase II	40	first
NCT04782791	nivolumab + SOX *vs.* nivolumab	phase II	30	first
NCT03784040	nivolumab + OTSGC-A24 *vs.* nivolumab + OTSGC-A24 + ipilimumab	phase Ib	40	–
NCT05111626	nivolumab + bemarituzumab nivolumab + bemarituzumab + mFOLFOX6 *vs.* placebo + nivolumab + mFOSFOX6	part 1: phase Ib part 2: phase III	702	–
NCT03995017	nivolumab + rucaparib + ramucirumab *vs.* rucaparib + ramucirumab	phase I phase II	61	second or third
NCT03443856	nivolumab + ipilimumab *vs.* chemotherapy	phase II	240	second
NCT03979131	avelumab + chemotherapy	phase II	37	–
NCT03966118	avelumab + ramucirumab + pacilitaxel	phase II	59	second
NCT04893252	durvalumab + vactosertib	phase II	55	third
NCT04817826	durvalumab + tremelimumab	phase II	31	first

Trastuzumab deruxtecan

Trastuzumab deruxtecan (DS-8201) is a novel treatment agent composed of a HER2 monoclonal antibody covalently connected to the topoisomerase I inhibitor. The mechanism of action is based on inhibition of DNA replication. [19]. Shitara K. et al. performed phase I and phase II clinical trials to evaluate the effect of trastuzumab deruxtecan on patients with GC. Both studies proved that conjugate monoclonal antibodies have manageable toxicity and high efficacy. In the latter, the objective response rate in the study group was 43% and 12% in the control group. Furthermore, in both studies tumor shrinkage was observed. The most frequent non-hematopoietic AE were nausea and decreased appetite, while decreased neutrophil count and anemia were the most common hematopoietic AEs [20, 21].

Trastuzumab emtansine

Trastuzumab emtansine (TE) is another novel agent composed of an anti-HER2 antibody and microtubule inhibitor (DM1). After internalization and lysosome destruction, cytotoxin is released and DM1 binds to tubulin which causes apoptotic cell death (fig. 3) [22]. A large randomized control phase II/III trial (GATSBY) assessed the trastuzumab emtansine efficacy in 107 centers. However, there was no improvement of overall survival in patients treated with TE compared to taxane (docetaxel). Possible explanations include primary or acquired resistance of cancer cells (e.g. due to efflux of emtansine) or disruption of binding to the tubulin [23]. Several treatment agents are being developed for cancers resistant to trastuzumab emtansine.

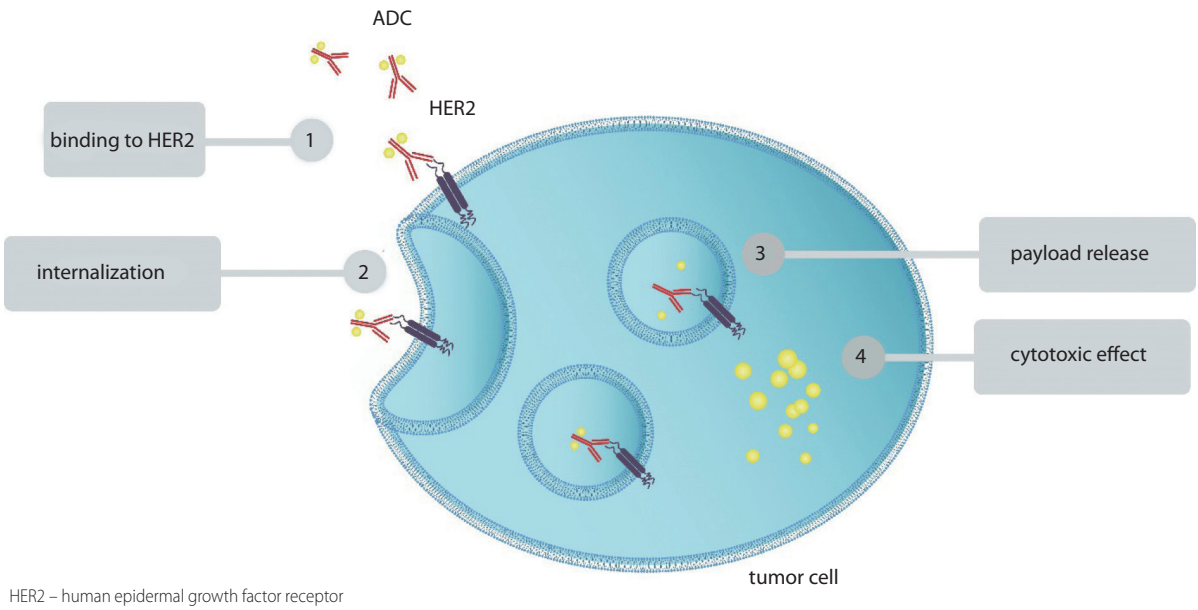


Figure 3. Mechanism of antibody drug conjugate (ADC)

XMT-1522

XMT-1522 is a novel antibody drug conjugate (ADC) composed of an anti-HER2 antibody that binds to different regions of the HER2 epitope (not competing with trastuzumab) and F-hydroxypropylamide (AF-HPA) which is an inhibitor of tubulin polymerization. According to the study performed by Le Joncour V. et al., XMT-1522 proves high efficacy against breast and GC cells resistant to TE in mouse xenograft models and *in vitro* [24].

Trastuzumab duocarbazine

Trastuzumab duocarbazine (SYD985) is an ADC agent composed of a monoclonal antibody and duocarmycin payload. It contains DNA binding and alkylating molecules and eventually causes cell death [25]. According to the study with mouse xenograft models, 1 mg/kg SYD985 equals to 5 mg/kg of trastuzumab in antitumor activity [26].

Zanidatamab

Zanidatamab (ZW25) is a novel anti-HER2 bispecific antibody which is considered effective in various types of cancers. It binds to two HER2 epitopes: ECD2 (pertuzumab binding domain) and ECD4 (trastuzumab binding domain) [27]. These novel anti-HER2 antibodies and ADCs should be considered in patients resistant to trastuzumab. Several clinical trials have evaluated the efficacy of zanidatamab in GC (NCT05152147, NCT03929666).

Dactolisib

Dactolisib (BEZ235) is a dual PI3K/ mTOR inhibitor which specifically targets HER2(+) GC cells. It has shown high efficacy in xenograft models compared to trastuzumab. Furthermore, some modest synergy with trastuzumab was observed [28].

Pertuzumab

Pertuzumab is another drug that might be combined with trastuzumab. It is a monoclonal antibody that binds to the ECD2 epitope of HER2. It suppresses heterodimerization of HER2 with other members of epidermal growth factor receptors (HER1, 3, 4). Thus, combined with trastuzumab, efficacy could be increased [29]. In phase III, a randomized, placebo-controlled JACOB trial study group was composed of pertuzumab, trastuzumab, and chemotherapy while the control group included placebo, trastuzumab, and chemotherapy. Progression-free survival was significantly increased in the study group (8.5 *vs.* 7.0; $p = 0.0001$), while no statistical difference was observed in overall survival (17.5 *vs.* 14.2; $p = 0.057$). Overall, the most common AE, was diarrhea. Neutropenia was the most frequent grade 3–5 AE [30]. Phase II randomized INNOVATION trial is currently being performed to assess the efficacy of pertuzumab + trastuzumab with chemotherapy *vs.* trastuzumab + chemotherapy *vs.* chemotherapy [31].

Margetuximab

Margetuximab is a novel monoclonal anti-HER2 antibody which is a trastuzumab derivative. It binds to the same domain as trastuzumab. However, its Fc1 region has been engineered to have increased affinity to stimulatory CD16A on NK cells. In addition, it has weaker affinity to suppressing CD32B found on macrophages and NK cells. Thus, it improves the immune identification of cancer cells [32]. Results of the phase Ib–II CP-MGAH22–05 study with the use of margetuximab with pembrolizumab (anti-PD1 antibody) suggest that a new chemotherapy-free treatment strategy might be considered [33]. Currently, the MAHOGANY phase II/III trial is being performed

which will evaluate margetuximab + retifanlimab + chemotherapy / no chemotherapy *vs.* margetuximab + tebotelimab + chemotherapy as a first line treatment for GC [34].

Tyrosine kinase inhibitors (TKI)

Tyrosine kinases regulate cell functions and constitute a heterogenous group of proteins. They take part in cell cycle and angiogenesis processes. Abnormal function of tyrosine kinases is associated with neoplastic development. Treatment agents targeting tyrosine kinases are called pan-HER inhibitors.

Afatinib

Afatinib, an inhibitor of receptor tyrosine kinases. Its mechanism is based on suppression of autophosphorylation in EGFR dimer which inhibits the signaling pathway [35]. An *in vitro* study has proven its suppressing mechanism on tyrosine kinases in overexpressed HER2 GC cells. In addition, it is suggested to use afatinib in case of trastuzumab resistance [36]. Afatinib, in combination with cisplatin and 5-fluorouracil, as a first line treatment did not increase efficacy in the phase II clinical trial. However, a favorable safety profile was observed which may replace toxic chemotherapeutic agents [37].

Lapatinib

Lapatinib is another tyrosine kinase inhibitor. It binds to the cytoplasmic ATP-binding site of HER1 and HER2 kinases which inhibits signaling cascades. Dual targeting of lapatinib may overcome resistance to anti-HER2 antibodies and achieve higher efficacy compared to mono-targeting agents [38]. In a phase II randomized placebo-controlled trial (EORTC 40071), the addition of lapatinib to ECF/X (epirubicin, cisplatin, 5-fluorouracil / capecitabine) did not provide any improvement in efficacy [39]. Furthermore, two phase III clinical trials (LOGIC, TyTAN) showed that lapatinib combined with capecitabine, oxaliplatin or pacilitaxel do not increase overall survival [40, 41].

Neratinib

Neratinib is an irreversible pan-HER inhibitor. While it has been approved in the treatment of breast cancer, limited studies evaluated its effect on GC. In GC cell lines study, promising results were obtained. Comprehensive HER inhibition reduced cell proliferation and decreased the invasive character of cancer cells [42].

Poziotinib

Poziotinib (HM781-36B) is another pan-HER inhibitor which achieved promising results in phase I clinical trial in patients with solid organ tumors. The maximal tolerated dose was established as 24 mg/day and 18 mg/day in intermittent or continuous dosing schedule respectively [43]. In a phase I/II clinical trial, poziotinib combined with pacilitaxel and trastuzumab showed good efficacy and beneficial toxicity. Furthermore, 62.5% of patients experienced tumor shrinkage [44].

Programmed cell death 1

PD-1 (CD279), discovered in 1992, is an inhibitor of innate and adaptive immune responses. It is similar in 15% and 20% to CD28 and CTLA4 respectively. PD-1 is located on macrophages, NK cells, B cells, T cells and dendritic cells [45]. PD-L1 (CD274) and PD-L2 (CD273) are ligands of PD-1. PD-L1 is expressed on hematopoietic and non-hematopoietic cells (e.g. heart, muscle, lung, liver) while PD-L2 is mainly expressed on antigen presenting cells (APC) [46]. PD-1 stimulation after binding to PD-L1 leads to T cells' immunological tolerance (fig. 4). This mechanism involves kinases dephosphorylation (SHP2) which inhibits TCR and CD28 signaling [47]. Expression of CD274 was found in various types of tumors. Therefore, tumor cells create an immunosuppressive environment which allows to avoid lysis [48]. Overexpression of PD-L1 in GC cells is associated with several factors such as lymph-node metastasis, depth of infiltration, microsatellite instability, and EBV

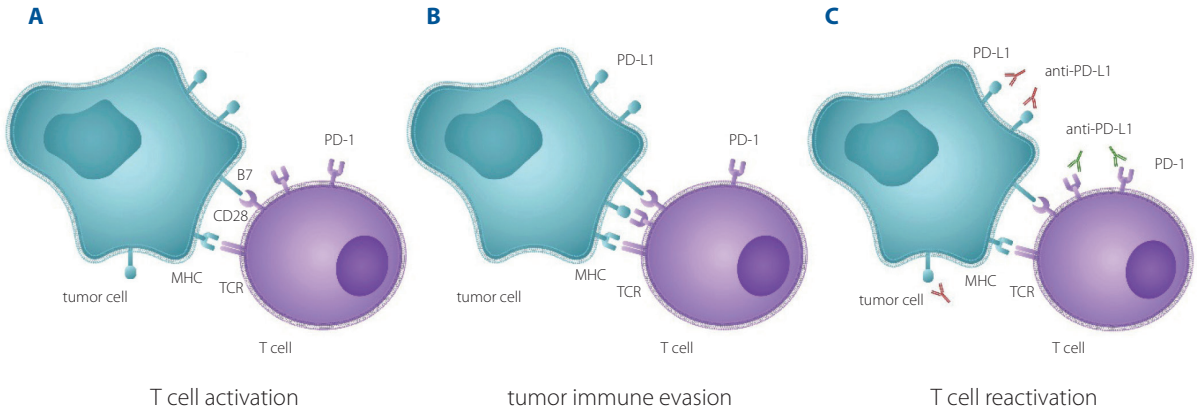


Figure 4. T cell activation after stimulation of TCR and costimulation from CD28 (A). Mechanism of the tumor immune evasion programmed death receptor (PD-1) and programmed death ligand 1 (PD-L1) (B). Introduction of PD-1 and PD-L1 monoclonal antibodies reactivates T cell (C)

infection [49]. Furthermore, higher expression of CD274 on macrophages was found in tumors with increased secretion of CXCL8 [50]. However, heterogeneity in PD-L1 expression is observed among different gastric cell lines which might be associated with different genomic mutations (e.g. TP53, SMAD4, KRAS) [51].

Pembrolizumab

Pembrolizumab (MK-3475) is an IgG4 monoclonal antibody which targets PD-1 and inhibits binding to PD-L1 and PD-L2 [52]. In phase II (KEYNOTE 059) trial, pembrolizumab was evaluated as monotherapy in post second line treatment. Therapeutic success of third line chemotherapy treatment is usually marginal. Thus, new agents are required to increase the benefits in case second line treatment fails. Pembrolizumab achieved promising results; 42.6% of enrolled patients experienced tumor size reduction [53]. In KEYNOTE-061, a randomized, phase III trial, pembrolizumab did not improve overall survival compared to pacilitaxel in patients with a PD-L1 combined positive score ≥1. However, it is suggested that pembrolizumab might achieve greater efficacy with patients with increased PD-L1 expression or with better performance status [54]. In 2022, an updated KEYNOTE-061 trial showed that pembrolizumab was associated with an increased 24-month survival rate but did not statistically increase OS compared to pacilitaxel. A benefit was also observed in patients with PD-L1 abundance [55]. In KEYNOTE 062, a phase III randomized controlled trial, pembrolizumab was used as monotherapy and compared to chemotherapy or added to chemotherapy. Results showed that pembrolizumab did not increase median overall survival, but it was non inferior compared to chemotherapy. On the other hand, fewer AE were observed. However, the survival benefit was significant in the case of CPS ≥10 and high microsatellite instability tumors [56]. Promising results were reached in KEYNOTE 659, a phase IIb trial, where pembrolizumab was combined with S-1 and oxaliplatin and used in first line treatment. The objective response rate was 73.9% in PD-L1 CPS >1 and <10 subgroups while 71% in CPS >10 [57]. Currently, KEYNOTE-811, a phase II, randomized, placebo-controlled trial is being performed. It will assess first line treatment efficacy of pembrolizumab, or placebo combined with trastuzumab and chemotherapy in HER2(+) GC [58]. A large phase III clinical trial with 1542 participants (KEYNOTE-859) will evaluate the efficacy of pembrolizumab combined with chemotherapy in HER2-negative GC as first line treatment [59].

Nivolumab

Nivolumab (ONO-4538) is IgG4 monoclonal antibody which targets PD-1. Consequently, PD-1/PD-L1 and PD-1/PD-L2 signaling pathways are blocked [60]. In ATTRACTION-2, a phase III randomized placebo-controlled trial, the efficacy and safety of nivolumab was compared to placebo in patients with at least two previous chemotherapy treatments. Results proved nivolumab prolongs progression-free survival and overall survival (HR 0.60; 0.49–0.75); $p < 0.0001$ and HR 0.63; 0.51–0.78; $p < 0.0001$, respectively) [61]. In ATTRACTION-3, a phase III trial, nivolumab was compared to chemotherapy in second line treatment. The addition of nivolumab was associated with a significant increase of OS (10.9 *vs.* 8.4 months; $p = 0.019$). Furthermore, survival enhancement was achieved regardless of PD-L1 expression [62]. Evaluating the efficacy of nivolumab as a first line treatment was also performed. ATTRACTION-4, a phase II clinical trial, showed high responsive rate in patients treated with nivolumab with S1 and oxaliplatin, as well as in patients with nivolumab, capecitabine, and oxaliplatin (66.7% and 70.6% respectively) [63]. A recent phase III clinical trial with 724 patients did not improve OS in HER negative GC compared to chemotherapy. On the other hand, an improvement in progression-free survival was identified [64].

Avelumab

Avelumab is an IgG1 antibody which binds to PD-L1 and removes the suppression of T cells. There are several ongoing clinical trials evaluating avelumab as a first, second or perioperative treatment agent [65]. In JAVELIN Gastric 300, a phase III, randomized trial (third line avelumab *vs.* chemotherapy), avelumab did not increase progression-free survival or overall survival. However, fewer AE were observed in the avelumab group compared to chemotherapy [66]. In JAVELIN Gastric 100, another phase III randomized clinical trial, avelumab did not show superiority in OS compared to chemotherapy in patients previously treated with chemotherapy. However, this treatment agent may be potentially successful in patients with higher expression of PD-L1. In addition, in this trial fewer grade 3 AE were observed as well (12.8% *vs.* 32.8% in the chemotherapy group) [67].

Durvalumab

Durvalumab is another anti-PD-L1 monoclonal antibody. Currently, monotherapy is used to treat unresectable stage III lung cancer. However, durvalumab has shown activity towards hepatocellular and GC as well [68]. In a phase Ib/IIb clinical trial, the efficacy of darvalumab was assessed as monotherapy or combined with tremelimumab (anti-CTLA-4). Response rates were low in all approaches. However, a combination of two treatment agents resulted in a 1-year survival rate [69]. Recently, PRODIGE 59-DURIGAST, a phase II study has begun. It will evaluate FOLFIRI with durvalumab and tremelimumab as a second line treatment in AGC [70]. MATTERHORN III is another study evaluating durvalumab compared to chemotherapy in resectable GC [71].

Chimeric antigen receptor

The application of chimeric antigen receptors (CAR) is a mechanism used to allow T cells to recognize tumor-specific antigens. Host's lymphocytes are modified using viral vectors and, after the introduction of CAR, are reinfused to the circulatory system.

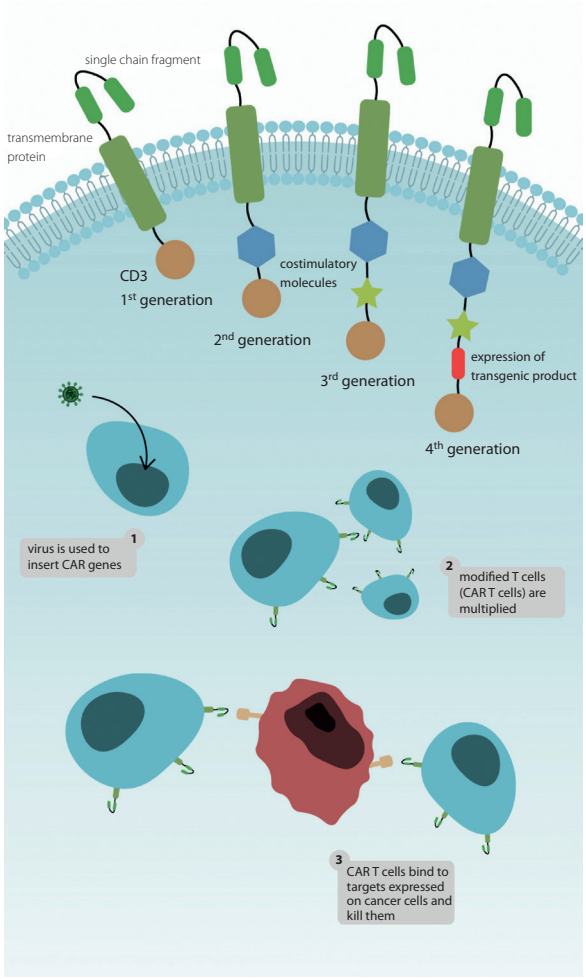


Figure 5. Chimeric antigen therapy (CAR) generations and antitumor mechanism

This would allow them to destroy cancer cells (fig. 5). The next generation of CARs have costimulatory domains or secrete cytokines that are able to remodel tumor environments, such as interleukin-12 (fourth generation – TRUCKs) [72]. Its presence in tumor tissue increases the activity of CD8+ cells, prolongs expansion of T cells, and suppresses exhaustion and apoptosis of immune cells. Additionally, IL-12 enhances NK cells and macrophages infiltration to targeted tissue [73]. CAR T cells treatment is associated with specific AE. Firstly, those might be associated with cells expressing certain antigens recognized by CARs – on-target effects. B cell aplasia is an example of AE which might develop after the introduction of CARs that recognize B cell antigens – CD19 or CD20. However, such AE can be reversed by suppressing the infusion of modified T cells or by eliminating target cells if the treatment is directed towards solid organ cancers [74]. One of the most frequent off-target AE is cytokine release syndrome (CRS). Cytokines from CAR T cells or the host's immune cells might induce CRS. Symptoms usually involve high fever, tachycardia, headache or malaise among others [75]. Several CAR T cells were developed to assess the potential treatment of GC. For instance, antitumor activity of CAR recognizing CLDN18.2, an isoform of claudin-18 which has been considered as potential target, was evaluated. *In vitro* and *in vivo* trials have proven that modified T cells could lyse GC cells that express CLDN18.2 [76].

Challenges and future directions

Ongoing clinical trials including the mentioned agents are listed in table I. Despite the extensive benefits of immunotherapy, resistance to HER2 and PD-1 inhibitors is a significant barrier which needs to be addressed. Mechanisms of resistance are unclear and not fully understood. Elimination of those obstacles would make GC cells more potent for therapy. A recent study by Sampera A. et al. found that HER2 resistance is associated with enhanced activity of two signal pathways (Pi3K/mTOR and MAPK/ERK) along with elevated expression of other members of the HER family. Pan-HER inhibitors effectively reversed trastuzumab resistance [77]. Normal epithelial cell--specific-1 (NES1) is one of the genes considered as responsible for inducing resistance to HER2 inhibitors. Overexpression of NES1 and activation of Pi3K/mTOR pathway has been found in resistant cells. Combining trastuzumab and PI3K/mTOR inhibitor could reduce resistance and block tumor growth [78]. The coiled-coin protein named GSE1 and human epidermal growth factor receptor-2 (ERBB2) have also been linked with trastuzumab resistance and greater risk of metastasis [79, 80]. Wang D.S. et al. suggest that noninvasive analysis of circulating tumor DNA (ctDNA) can demonstrate intrinsic or acquired resistance and offer personalized treatment [81]. Furthermore, anti-HER2 treatment agents induce expression of certain genes, such as HAS2 and SHB which could be used as predictive markers for trastuzumab response [82].

Microsatellites are repeated sequences of nucleotides which compose 3% of the human genome [83]. A mismatch repair system takes part in correcting errors which occurred during division of cell and DNA replication. Defects of this system can result in multiple mutations in microsatellites [84]. Microsatellite instability (MSI) has been linked with various neoplasms, including GC. The MSI phenotype is associated with expression of abundant neoantigens which stimulates an immunological response. Moreover, expression of PD-L1 has been identified in MSI tumor cells which makes it susceptible to ICI [85]. The clinical benefit of pembrolizumab has been demonstrated in metastatic MSI tumors [86]. The NCT04817826 clinical trial (INFINITY) will evaluate the efficacy of tremelimumab and durvalumab in the treatment of MSI GC. Wang Y.L. et al. have confirmed that MSI GC showed higher PD-1/PD-L1 expression compared to microsatellite stable (MSS) tumors [87]. GC can be additionally classified using the status of the Epstein-Barr virus (EBV). EBV is associated with the development of various neoplasms including GC, nasopharyngeal carcinoma or lymphomas. It is considered that 2–20% of all GC cases are EBV positive [88]. The Epstein-Barr virus(+) GC is associated with higher expression of PD-1L compared to EBV(–) cells [89]. Several clinical trials are being performed to evaluate

the efficacy of pembrolizumab in EBV(+) GC (NCT03257163, NCT05166577). Therefore, MSI and EBV(+) can be considered as beneficial markers in ICI treatment. MicroRNAs (miRNA) are other significant regulators of cancer genes which has been related to treatment resistance. Phosphatase and tensin homologue (PTEN) counteracts PI3K pathway. MiRNA-221/222 and miRNA-214 target PTEN and promote GC invasion [90]. Activity of miR-105-5 has been correlated with reduced expression of PD-L1 [91]. Circular RNA (circRNA) are covalently closed RNA fragments generated by back-splicing. Features of circRNA are not fully understood but they take part in gene transcription and interact with proteins. Furthermore, circRNA has been associated with cancer progression [92]. CircDLG1 has been identified in PD-1 resistant GC and enhanced invasion and immune evasion of cancer cells [93].

Despite recent advances in immunotherapy, multiple mechanisms of immune evasion remain unknown. Future studies should concentrate on overcoming resistance to known and tested treatment agents, such as trastuzumab or pembrolizumab. Trials with anti-HER2 agents combined with PI3K/mTOR inhibitors should be performed. Furthermore, it is necessary to identify potential targets in MSS and EBV(–) GC. Better understanding of miRNA and circRNA could reveal novel possibilities and treatment options. Additionally, novel potential targets are being evaluated: membrane mucin MUC17 (NCT04117958); methyl methanesulfonate and ultraviolet-sensitive gene 81 (MUS81) [94] or claudin 18.2 (CLDN18.2) [95].

Conclusions

Outcomes of many clinical trials are highly hopeful. The majority of the mentioned trials show the benefits of combination IA with chemotherapy compared to chemotherapy alone. Additionally, immunotherapy may constitute or support drugs in part of first, second or third line treatment. Adverse effects are related to treatment strategy and depend on whether they are in combination with chemotherapy. However, IA seem to be safer than chemotherapeutic agents. The achieved results from the clinical trials are promising enough to consider implementing immunotherapy in AGC management. Nevertheless, further studies toward evaluating the mechanisms of resistance to anti-HER2 antibodies and ICI are needed. In certain cases, a combination of treatment agents with various mechanisms of action may overcome resistance.

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Radiotherapy in the combined treatment

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Combined radiotherapy and chemotherapy

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Combined radiotherapy and chemotherapy is a standard procedure in radical treatment of many cancers. The objective of chemoradiotherapy is to increase loco-regional control, to reduce the risk of distant metastases and to prolong survival, and thus to improve treatment efficiency with less mutilating therapies. Concurrent chemoradiotherapy, however, is more toxic than chemotherapy and radiotherapy alone or sequential application of these methods. Optimalisation of combined treatment requires further research. New possibilities arise with inclusion of targeted treatment and immunotherapy in classical chemoradiotherapy.

Key words: radiotherapy, chemotherapy, combined treatment

Historically, the first method of treating neoplasms was surgery. Inclusion of radiation in neoplasm therapies allowed combination of those two methods. For several decades, radiotherapy supplementing surgery affected improvement of loco-regional control. Unfortunately, a range of factors specific for the tumour itself and for the patient limited efficiency of surgery alone, radiotherapy alone, and combination of the two methods as well. Among these factors, one should list impossibility to remove excessive tissue volumes and inability to deliver the high radiation dose to the target area due to the threat of permanent damage to healthy tissues. Inability of efficient anti-cancer therapy using only local treatment methods is also associated with infiltration of surrounding tissues beyond outside the primary tumour, metastases to distant organs and micro-metastases. The concept of multi-modal oncological treatment including systemic treatment created a chance to surpass the limitations involved in surgery and radiotherapy.

Currently, combination of radiotherapy and chemotherapy is a standard procedure in radical treatment of many cancers [1–3]. The objective of chemoradiotherapy is to increase loco-regional control, to reduce the risk of distant metastases and to prolong survival, and thus to improve treatment efficiency. It is assumed that combination of these methods makes the treatment less mutilating, allowing for preservation of organs and their functions [4, 5].

Chemoradiotherapy was applied for the first time in the early 1950s. The first cytostatic agent used in combination with radiotherapy was 5-fluorouracil [6]. Before the end of the 1950s, 5-fluorouracil was successfully implemented in combination with radiotherapy in treatment of gastrointestinal cancers, cervical cancers and head and neck cancers [7].

Originally, it was believed that radiotherapy and chemotherapy are interdependent in terms of efficiency and toxicity. The theoretical background for combining radiotherapy and chemotherapy was developed in 1979 by Steel and Peckham [8]. They described four potential ways how combined therapy might improve the therapeutic index, now known as Steel Paradigm:

- spatial cooperation,
- toxicity independence,
- better protection of normal tissues,
- enhancement of tumour response [4, 5, 8].

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Spatial cooperation

The concept of spatial cooperation assumes that radiotherapy and chemotherapy act entirely independently from each other. Radiotherapy acts loco-regionally, destroying the primary neoplastic tumour, while the systemic therapy is mainly focused on destroying micro-metastases. According to the concept of spatial cooperation, no interaction between chemotherapy and radiotherapy is needed – radiotherapy has local effect and chemotherapy acts on disease outside a radiation field and these effects accumulate. This approach to benefits of chemoradiotherapy can be illustrated with sequential chemotherapy and radiotherapy in breast cancer, as well as prophylactic brain radiation after completing chemotherapy in small-cell lung cancer.

Toxicity independence

Originally Steel and Peckham [8] assumed that as toxicity of cytostatic agents and radiation do not overlap, it would possible to kill cancer cells without enhancement of the toxic effect to healthy tissue. The concept of spatial cooperation provided exactly for independent toxicity of radiotherapy and chemotherapy, enabling relevant protection of healthy tissues and enhanced response to treatment with concurrent application of the two methods. However, this was not achieved in clinical practice. It was shown that concurrent introduction of chemotherapy and radiotherapy increases side effects of the anticancer therapy. In fakct toxicity adds up and moreover radiation can cause chemosensitisation or chemotherapy can cause radiosensitisation [4]. The standard of practice is to avoid direct overlap of toxicity of cytostatic agents and radiotherapy (e.g. methotrexate with radiation to the brain or bleomycin with radiation to lungs).

Protection of normal tissues

Another concept associated with combining chemotherapy and radiotherapy, as proposed by Steel and Peckham [8] involved a process targeted at protection of healthy tissues from adverse effects of radiation (radioprotective properties). However, no chemical substances have been identified that would protect normal tissues from adverse effects of radiotherapy, thus affecting the therapeutic index. A limited success was achieved with amifostine – it was only shown to reduce the risk of xerostomia after radiotherapy of the head and neck cancers [9].

Enhancement of tumour response

It seems that an important role in combination of chemotherapy and radiotherapy is radiation sensitisation effect of some cytostatic agents, which increases local efficiency of radiation. Better loco-regional control concurrent with systemic effect of cytostatic effects may also reduce the potential to metastasise. Radiosensitising effect of chemotherapy with respect to radiotherapy suggests enhanced efficiency in the case of concurrent application of the two methods as compared to their sequential use [4, 5].

Through the ionisation mechanism, radiotherapy causes directly or indirectly physical and chemical changes in the cell – mainly in its DNA. Theoretically, radiation sensitisation can be achieved by a range of interactions:

- direct increase of cell sensitivity to radiotherapy by damaging DNA,
- inhibiting accelerated repopulation,
- inhibiting cell repair,
- accumulation of cells in the radio-sensitive phase, or
- elimination of cells in the radio-resistant phase,
- improvement of cell oxidation [4, 5, 10–12].

Damaging DNA

Radiobiological principle of "radiosensitiser" provided that a drug would enhance post-radiation DNA damage. If a drug particle connects to DNA of a cancer cell or causes DNA damage itself, it increases DNA sensitivity to damage caused by radiation. Such drugs include 5-fluorouracil and cisplatin.

Inhibiting accelerated repopulation

When there is a partial cell loss caused by radiation, other cancer cells respond with accelerated repopulation. Cytotoxic or even cytostatic drugs have anti-proliferation effect and concurrently with radiation they may prevent accelerated repopulation of cancer cells between each radiotherapy fractions. This increases the tumour's sensitivity to radiation, and thus increasing chances for local recovery [13].

Inhibiting damage repair

Cancer cells which can effectively repair DNA damage display significant resistance to radiation. This is why compounds which interrupt transduction of the DNA damage repair signal may exacerbate the toxic effect of irradiation by inhibiting repair of sub-lethal and potentially lethal damages. Some chemotherapeutical agents disturb biosynthesis of nucleotides – for example 5-fluorouracil, gemcitabine, methotrexate, etoposide, cisplatin. Further, compounds which intervene in cell cycle may inhibit DNA repair indirectly.

Affecting cell distribution in the cell cycle

The highest sensitivity to radiation is recorded in cells in the G2 and M phases of the cell cycle and the lowest – in the S phase. A range of chemotherapeutical agents are phase-specific. Radiation efficiency is increased by compounds which may accumulate cells in radiation-sensitive phases and those which may eliminate cells from radiation-resistant phases. Taxanes and nucleoside analogues, as well as modified pyrimidines seem to have exactly this effect [14, 15].

Improvement of cell oxidation

Solid tumours contain areas of lower-oxidation cells. Hypoxia reduces efficiency of radiotherapy, as its effect relies mainly

on generating free radicals. This is why drugs which reduce hypoxia may increase efficiency of radiation. Through cytotoxic effect, chemotherapy may simply reduce tumour size, thus reducing parenchymal pressure and making oxygen flow into cells easier. Further, with the death of quickly proliferating cells, hypoxic cells get closer to vessels [16]. Additionaly, such drugs as nitroimidazole compounds may imitate / replace oxygen in hypoxic areas, reducing the negative effects of hypoxia [17].

Different sensitivity to treatment of different cell clones

A never concept explaining the benefits of chemoradiotherapy assumes that radiotherapy and chemotherapy kill various cell clones independently from each other [13]. With the heterogenous nature of cancers, some neoplastic cells are resistant to radiation, but they may prove to be sensitive toconcurrent administered chemical compound. An example of such cooperation may be found in application of hypoxic cytotoxins, e.g. tirapazamine in combined therapy of the head and neck cancers.

The cytotoxic agents improving effectiveness of radiotherapy

Antimetabolites

5-fluorouracil affects cell distribution in the cell cycle, influencing cells in the S phase of the cell cycle, which are radiation resistant. It also causes re-oxygenation of hypoxic cells [12, 15, 18]. Administration of 5-fluorouracil during radiotherapy by continous infusion or orally is more efficient than in bolus [19].

Alkylating drugs

Mitomycin C inhibits DNA and RNA synthesis by interrupting cross bonds, mainly at guanine and cytosine pairs. Although mitomycin C is not cell cycle-specific, it arrests cells in the G2/M phase of the cycle. In combination with radiation, mitomycin C acts as radiosensitiser for cells in hypoxia and prevents repopulation [20–23].

Temozolomide damages DNA by DNA methylation in the position of 0-6 guanine. The methylation triggers the abnormal DNA repair pathvay, leading to increased cell sensitivity to irradiotion and leads them to the apoptosis [24, 25]. Additionaly temozolomide inhibits repopulation of cancer cells [12, 18].

Platinum-base drugs

Cisplatin consolidates DNA damages induced by irradiation – potentially repairable changes (e.g. interruption of the DNA strand) become lethal damage. It inhibits DNA synthesis and transcription, inhibiting repair of post-radiation damage to DNA [12, 26–28]. Cisplatin acts both in well oxidated and hypoxic cells [29]. Meanwhile, radiation facilitates cisplatin penetration into cancer cells and formation of its active metabolites [30–32].

Drugs affecting microtubules of the spindle apparatus

Vinca alkaloids affect the cell cycle itself – they cause depolymerisation of microtubules and interrupt functioning of the mitotic spindle. This results in arresting cells in the radiotherapy-sensitive M phase. They also inhibit repair of radiotherapy-induced DNA damage [33].

Taxanes stabilise microtubules, thus inhibiting centrosomes, which leads to deceleration of mitosis and cumulation of cells in G2 and M phases of the cell cycle [12, 33–35]. Taxanes reduce parenchymal pressure and thus allow better oxidation of cancer cells, making them more sensitive to irradiation [12, 16, 34]. Taxanes induce apoptosis [12, 35].

Topoisomerase inhibitors

Etoposide and topotecan inhibit repair of post-radiation DNA damage, they arrest cells in G2 phase, process single breaks of DNA strands into double ones [12, 36, 37].

Examples of application of chemoradiotherapy

There are various ways to combine chemotherapy with radiotherapy. Chemotherapy can be applied as neoadjuvant or adjuvant therapy, as sequential / alternating with radiotherapy or concurrent with radioteherapy.

Anal cancer

In the 1970s for the first time it was showed that anal cancer can be cured effectively with chemoradiotherapy applying 5-fluorouracil and mitomycin C without a surgical treatment [38]. Two out of three patients treated with 5-fluorouracil, mitomycin C and radiation achieved full pathologic response and progression-free survival was 14 months [38]. These results were confirmed in further studies [39–42]. The EORTC phase III study showed that chemoradiotherapy with 5-fluorouracil and mitomycin C provides better local control and longer colostomy-free survival as compared to radiotherapy alone [40]. The reduction of risk of death related to the anal cancer and prolongation of overall survival (7.6 *vs.* 5.4 years) was observed [43]. Patients who received 5-fluorouracil and mitomycin C significantly less frequently underwent colostomy, and 4-year progression-free survival in this group is higher as compared to patients treated with 5-fluorouracil only (73% and 51%, respectively) [44]. Concurrent chemoradiotherapy based on 5-fluorouracil and mitomycin C is currently considered standard management of the anal cancer. Modern radiotherapy techniques allow reduction of toxicity, but they do not contribute to improvement of overall survival [45].

Rectal cancer

Four big trials indicated that addition of chemotherapy to the preoperative radiotherapy in the rectal cancer in stage II and III, increases the rate of complete responses and improve

local control [46–50]. Preoperative chemoradiotherapy was shown to be more effective than post-operative chemoradiotherapy with respect to local control and sphincter preservation. This aproche was less toxic than adjuvant treatment [51]. Neoadjuvant chemoradiotherapy is nowadays a standard in treatment of locally advanced rectal cancer.

Oesophageal cancer

The RTOG study (85–01) showed that radiotherapy combined with chemotherapy (5-fluorouracil and cisplatin) improved significantly the five-year overall survival (26% *vs.* 0%) [52, 53]. This was also confirmed by newer studies [54, 55] and a meta-analysis [56]. Preoperative chemoradiotherapy affects improved results of the surgical treatment. The CALGB 9781 study showed that patients treated with neoadjuvant chemoradiotherapy had significantly better prognosis (median overall survival of 54 *vs.* 21.6 months; 5-year overall survival of 39% *vs.* 16%) [57]. Similar findings were recorded in the study published by van Hagen et al. (median overall survival of 49.4 *vs.* 24 months; 5-year overall survival of 47% *vs.* 34%) [58]. Preoperative chemoradiotherapy contributed to significant reduction of the locoregional recurrence as compared to surgery only (from 34% to 14%) [59]. The current standard of treatment of the locally advanced oesophageal cancer is surgery preceded by chemoradiotherapy or chemoradiotherapy alone(cisplatin with docetaxel or paclitaxel).

Cervical cancer

A large randomised trial found that cisplatin-based chemoradiotherapy improved disease-free survival as compared to neoadjuvant chemotherapy followed by a radical surgery (77% *vs.* 69%) [60]. Many randomised studies showed better rate of disease-free survival and overall survival with chemoradiotherapy as compared to radiotherapy alone in locally advanced cervical cancer [61–64]. For the locally advanced cervical cancer chemoradiotherapy has become a standard treatment. Currently, the following is seen as the most promising scheme: neoadjuvant chemotherapy (carboplatin / paclitaxel) and then chemoradiotherapy [65, 66]. Although it has been found that chemoradiotherapy is associated with significantly higher risk of toxicity to the rectum, urinary bladder and vagina three months after the treatment, after two years the risk was not higer (with the exception of vaginal toxicity) [60].

Non-small cell lung cancer

Three big randomised trials published in the 1990s showed improvement in treatment results of locally advanced non-small cell lung cancer with application of sequential chemotherapy and radiotherapy [67–69]. With sequential chemoradiotherapy, an increase of five-year overall survival was recorded from 5% to 10% [67, 70, 71]. Auperin et al. showed in 2010 [72] that five-year overall survival of patients with non-small cell lung cancer treated with concurrent chemoradiotherapy is almost 5% higher that with sequential treatment, reaching 15%. Concurrent therapy is associated with a high risk of oesophageal toxicity and pneumonia. Currently, standard treatment of the locally advanced inoperable non-small cell lung cancer involves concurrent platin-based chemotherapy and radiotherapy.

Urinary bladder cancer

Concurrent chemoradiotherapy was shown to ensure better survival as compared to radiotherapy alone in the case of invasive urinary bladder cancer [73]. However, compared to radical cystectomy, chemoradiotherapy is associated with lower median of overall survival (32.8 *vs.* 36.1 months) [74, 75].

Head and neck cancers

The first study which showed significant advantage of the combined treatment with 5-fluorouracil and cisplatin as compared to radiotherapy alone was done for nasopharyngeal cancers (five-year overall survival of 67% and 37% respectively) [76]. There were over 100 randomised studies concerning chemoradiotherapy of head and neck cancers, showing absolute increase of five-year overall survival by 6.5%, prolonged time to progression, improved local control and increased chance of organ preservation [77]. Better results were achieved with concurrent than sequential chemoradiotherapy – both as the radical therapy and as post-operative treatment [78–80]. Currently a standard method of treating patients with locally advanced head and neck cancers is concurrent cisplatin-based chemoradiotherapy. However, this management is associated with intensified early and late adverse effects.

Conclusions

It has been demonstrated that chemoradiotherapy brings significant benefits in local control of the disease, organ preservation and overall survival of patients with some cancers.

However, concurrent chemoradiotherapy is more toxic than chemotherapy alone and radiotherapy alone or sequential application of these methods. This concerns both early and late complications and it may have negative impact on the patients' quality of life. Further studies are needed to optimise combined treatment. Nowadays, addition of targeted treatment and immunotherapy to chemoradiotherapy is already changing standardsof cancer treatments There are many trials underway to assess effectiveness and potential toxicity of particular scheme combinations.

The basic prerequisite for good combined treatment of cancer is proper diagnosis and its comprehensive organization, giving the opportunity to make the right clinical decisions by multidisciplinary teams.

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SDH-deficient gastrointestinal stromal tumours

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Gastrointestinal stromal tumours (GIST) comprise a heterogeneous group of the most common mesenchymal neoplasms of the gastrointestinal tract. The majority of GIST are induced by activating, mutually exclusive mutations of two genes – *KIT* and *PDGFRA* (platelet-derived growth factor receptor-alpha). However, approximately 10–15% of GISTs lack oncogenic *KIT* or *PDGFRA* mutations and these tumours are often called "wild type" (WT) GISTs. The SDH-deficient GISTs form a distinctive subset of tumours accounting for 20–40% of *KIT/PDGFRA* WT GIST, which results from the loss of function mutations in the genes encoding the SDH enzyme complex. The true frequency of SDH-deficient GISTs was reported to be approximately 7.4 to 7.7%. These tumours usually occur in the stomach (most commonly in the antrum) and have a spectrum of behaviour from indolent to progressive. In most cases the molecular mechanism behind the SDH-deficient GISTs is connected to germline mutations. *SDHA* germline mutations occur in approximately 30% of the SDH-deficient GIST, those in *SDHB*, *SDHC*, and *SDHD* appear in 20–30% of patients.

The SDH-mutated GISTs do not respond well to the commonly used targeted therapy, with no objective tumour response to imatinib. Taking into account the biological features of SDH-deficient GIST, new therapies of potential interest comprise PI3K/AKT/mTOR inhibitors, heat-shock protein inhibitors, HIF1-α targeting agents, epigenetic modifiers and demethylating agents. However, further research is necessary in these fields.

Key words: gastrointestinal stromal tumour, SDH-deficient GIST, Carney Triad, Carney-Stratakis syndrome, TKI, *SDHA/SDHB/SDHC/SDHD* mutations, targeted therapy, imatinib, regorafenib

Introduction

Gastrointestinal stromal tumours (GIST) comprise a heterogeneous group of the most common mesenchymal neoplasms of the gastrointestinal tract. Most GIST are related to activating, somatic, mutually exclusive mutations of two genes – *KIT* and *PDGFRA* (platelet-derived factor receptor-alpha), which are early oncogenic events during GIST development [1–3]. Advances in the understanding of molecular events underlying GIST tumorigenesis have led to an awareness of the essential role of KIT and PDGFRA oncoproteins as diagnostic and therapeutic targets, and to the paradigm for molecularly targeted therapy. However, approximately 10–15% of GISTs lack oncogenic *KIT* or *PDGFRA* mutations and these tumours are often called "wild type" (WT) GISTs (fig. 1) [4–5]. They are indistinct from *KIT/PDGFRA*-mutated tumours in terms of morphology, anatomic localization and the expression of two diagnostic immunohistochemical markers (KIT and DOG-1). Importantly, from a molecular point of view and based on their succinate dehydrogenase (SDH) immunohistochemical status, WT GISTs are heterogeneous group of tumours that can be classified

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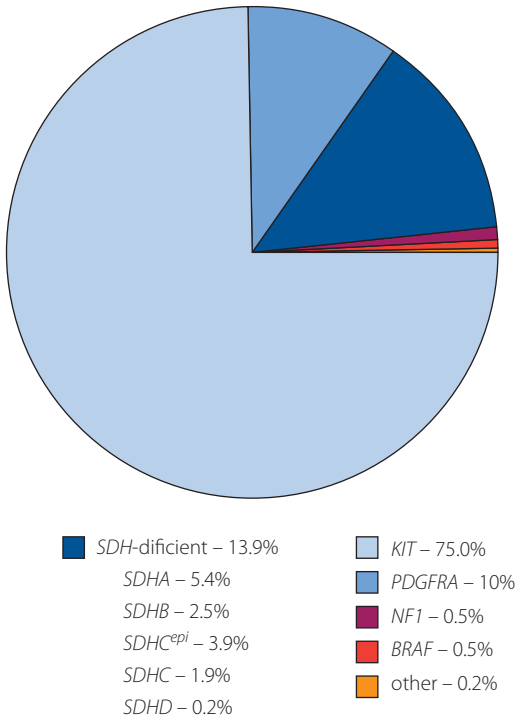
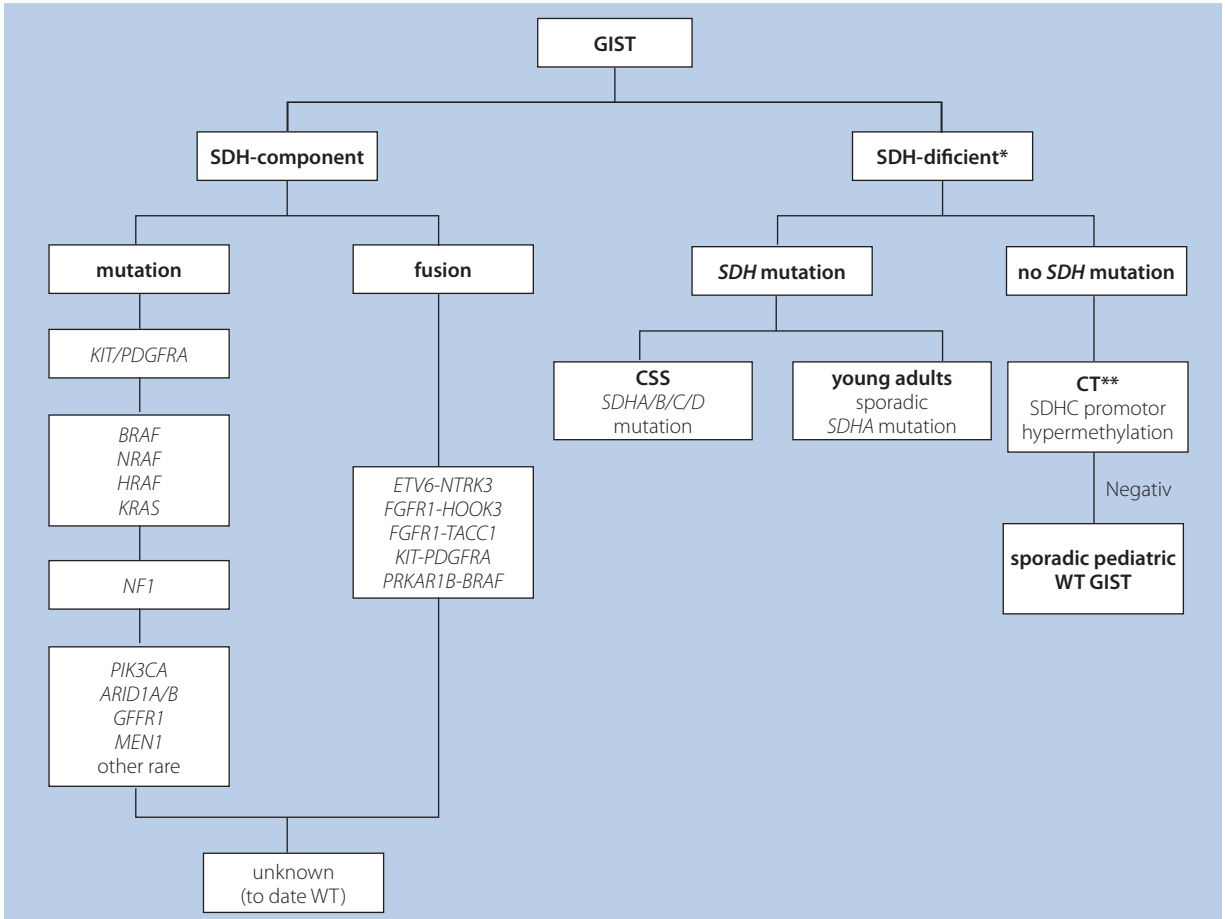


Figure 1. Molecular subtypes in GIST. Based upon Schaefer et al. [6]

into two main subtypes: SDH-competent and SDH-deficient tumours (fig. 2) [6–8]. The SDH-competent group constitutes mainly GIST related to neurofibromatosis type 1 (von Recklinghausen disease) [9, 10], but also includes rare tumours that carry oncogenic fusions of neurotrophic tyrosine kinase (*NTRK*), *BRAF* and fibroblast growth factor receptor (*FGFR*) genes [12, 13], as well as more aggressive and occurring in older patients WT GISTs harbouring somatic mutations in *NF-1, BRAF, NRAS, HRAS, KRAS, EGFR1, MAX, MEN1*and *PIK3CA* genes [10, 14, 15]. In some of these WT cases (especially paediatric), overexpression of the insulin-like growth factor 1 receptor (IGF1R) has been observed [16].

Clinical and molecular features of SDH-deficient GISTs

SDH-deficient GISTs form a distinctive subset of tumours accounting for 20–40% of *KIT/PDGFRA* WT GIST, which results from the loss of function mutations in the genes encoding the SDH enzyme complex. The true frequency of SDH-deficient GISTs was reported to be approximately 7.4 to 7.7% [17, 18]. These tumors comprise the majority of pediatric GISTs, a low percentage of sporadic cases, and two classes of syndromic GISTs – Carney triad and Carney-Striatakis syndrome [5, 7, 8,



CT – Carney traid; CSS – Carney-Stratakis syndrome; SDH-defiecient* – screening by immunohistochemistry; CT** – in some cases mutation described; SDH – succinate dehydrogenase; GIST – gastrointestinal stromal tumours

Figure 2. SDH-component and SDH-deficient sub-classification of GISTs [4, 9]

19, 20]. They are characterized by a predominant location in the stomach, multifocality, propensity for lymphatic spread and often indolent clinical behaviour even in metastatic disease [21, 22].

SDH-deficient GISTs usually develop early in childhood and in adolescents/young adults [2]. However, patients in their forties or fifties may also emerge with an initial diagnosis of SDH-deficient GIST. Females are reported to be disproportionately affected. SDH-deficient GISTs usually occur in the stomach (most commonly the antrum) and have a spectrum of behaviour from indolent to progressive. The summary of the main characteristics of SDH-deficient GIST is presented in table I and II. Over 80% of pediatric GIST has inactivating mutations in SDH subunits [23, 24].

Succinate dehydrogenase (SDH, also known as mitochondrial complex II or succinate-ubiquinone oxydoreductase) is a highly conserved heterotetrameric enzyme complex (composed of four protein subunits – SDHA, SDHB, SDHC, and SDHD, encoded by nuclear genes, mapped to 5p15.22, 1p36.13, 1q23.3 and 11q23.1, respectively), which acts at the interphase of the tricarboxylic acid cycle and electron transport chain. SDH is the only enzyme that is concurrently both a functional member of both the Krebs cycle and the electron transport chain (ETC), where it provides electrons for oxidative phosphorylation [24].

The SDH-complex takes part in the Krebs cycle with subunit A (SDHA), a flavoprotein, which is the catalytic unit responsible for the conversion of succinate to fumarate, and Subunit B (SDHB), which is an iron-sulfur- protein participating in the electron transport chain for the oxidation of ubiquinone to ubiquinol. Together SDHA and SDHB make up the main catalytic component of the complex, while the other two subunits (SDHC and SDHD) are two integral membrane proteins, anchoring the complex to the inner mitochondrial membrane [25]. Additionally, the succinate dehydrogenase assembly factor 2 (SDHAF2) is required for the flavination and thus normal function of SDHA [26].

Genetic or epigenetic alterations in any of the subunits lead to an accumulation of succinate, which is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases (including the TET family of 5-methylcytosine hydroxylases). Members of the TET family are active DNA demethylases that convert 5-methylcytosine to 5-hydroxymethylcytosine, and inhibition of their activities can lead to aberrant DNA methylation observed in GISTs [27]. A genome-wide DNA methylation analysis of SDH-deficient GISTs revealed higher DNA hypermethylation than in GISTs with *KIT* mutation [28].

Carney triad (CT) is a very rare disease characterized by the synchronous or metachronous occurrence of at least three different tumour entities, i.e GIST, paraganglioma and pulmonary chondroma [29]. Carney triad is never inherited, affects mostly females and the symptoms occur in young adults. Most cases of CT show down-regulation of SDH through site-specific hypermethylation (epigenetic downregulation) of the SDHC gene [27], which leads to downstream activation of the HIF signalling pathway by accumulation of succinate, causing stabilization of HIF1-α that controls oncogene transcription. Activated cellular pathways leading to increased angiogenesis and cellular proliferation are activated [31].

Table I. Summary of the main characteristics of SDH-deficient GIST

Characteristics	
clinical	• rare • more often developing in young patients and women • commonly developing in the stomach and small intestine • more often diagnosed in emergency settingsprimary resistance to imatinib is common • GIST with *SDH* mutations tend to metastasize, including to the lymph nodes and less frequently to the liver, usually growing slowly • indolent growth causes that standard risk classifications do not apply to SDH-deficient GIST • many are related to hereditary syndromes, i.e. Carney triad or Carney-Stratakis syndrome
pathological	• frequently epithelioid/mixed morphology, SDHB loss detected by immunohistochemistry, regularly express KIT and its pathway is activated, insulin-like growth factor 1 receptor (IGF1R) is overexpressed
molecular	• *KIT/PDGFRA* wild type, loss of function mutations in *SDHA*, *SDHB*, *SDHC* or *SDHD* in approximately 80% of cases

Table II. Anatomic distribution, frequency and treatment response of the SDHB-immunonegative/SDH-deficient GISTs

Genetics	Frequency	The most frequent anatomic location	Systemic treatment
SDHB IHC(–)/SDH-deficient *SDHA/B/C/D* mutations (CSS)	2%	stomach	• limited responses to imatinib • possible response to other TKIs (limited data)
part of the CT *	1%	stomach	
SDHA mutation (young adults)		stomach	
sporadic paediatric WT GIST	1%	stomach	

CSS – Carney-Stratakis Syndrome; CT – Carney triad; * – most cases show promotor hypermethylation

Carney-Stratakis syndrome (CSS) is characterized by gastric multifocal GISTs and paragangliomas [19], showing an autosomal dominant inheritance pattern with incomplete penetrance. It affects both males and females during childhood and adolescence. Succinate dehydrogenase deficiency is caused by inactivating germline mutations or large deletions in the *SDHB*, *SDHC* or *SDHD* (rarely *SDHA*) genes encoding the corresponding subunits B, C or D of the SDH enzyme [29, 32, 33].

In contrast to CT, in patients with CSS, DNA methylation patterns were identified only at a few of the CpGs located close to the *SDHB* gene [27]. In these patients, the *SDHC* gene promoter was completely unmethylated in all screened CpG sites, supporting the hypothesis that the CSS is in fact a different entity from CT [28].

The most practical way to identify the loss of SDHB is to find SDH-deficient tumours with the use of immunohistochemistry (IHC) [17]. Immunohistochemical expression of SDHB becomes negative whenever there is bi-allelic inactivation of any component of SDH, which is very rare in the absence of syndromic disease[35]. Unfortunately, only approximately 30% of SDH-deficient GISTs demonstrate loss of expression for SDHB and SDHA by IHC. Furthermore, tumours with loss of SDHB expression by IHC can be subdivided into 2 groups: tumours with *SDH* gene mutations and those with a loss of SDHB by immunostaining but without *SDH* mutations. Those with *SDH* mutations occurring in young adults are gastric in location, and have a female preponderance [8].

Loss of function of the succinate dehydrogenase complex characterizes other rare human tumours including some paragangliomas, renal carcinomas and pituitary adenomas. Along with GISTs, they can all be characterized as SDH-deficient tumours [36]. From a histopathological perspective, SDH-deficient GISTs show characteristic morphologic features including a multinodular growth pattern, the occurrence of multiple tumours, lymphovascular involvement and lymph node metastasis [37].

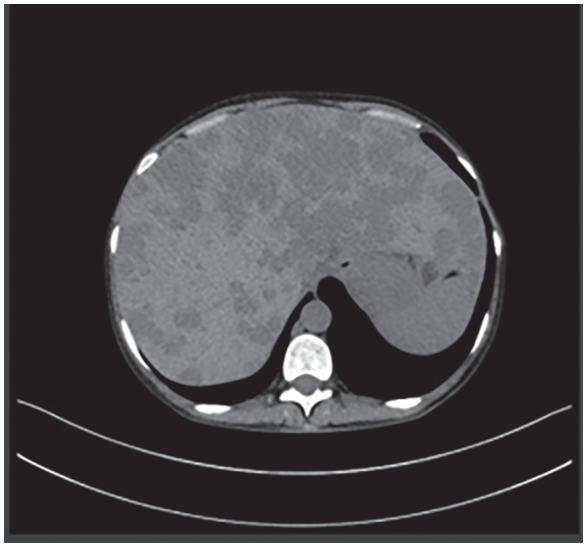


Figure 3. Computed tomography imaging demonstrating SDH-deficient gastric GIST with extensive liver metastases

Liver metastases are common (fig. 3). Morphologically, these tumours are epithelioid or mixed epithelioid/spindled [34].

The molecular mechanism behind the SDH-deficient GISTs is connected to germline mutations. Germline mutations in *SDHA* occur in approximately 30% of the SDH-deficient GIST, those in *SDHB*, *SDHC* and *SDHD* occur in 20–30% of cases (tab. III) [34, 36–38].

The most common *SDHA* mutation detected in SDH-deficient GISTs patients is the c.91C>T (p.Arg31Ter) substitution. Simultaneous allelic loss at the *SDHA* locus at 5p15 has been described; in this scenario the tumour follows a classic 2-hit hypothesis, with SDHA acting as tumour suppressor [8, 41, 42]. The loss of SDHA protein expression may result

Table III. *SDHA/B/C/D* mutations detected in SDH-deficient GISTs [5, 32, 33, 39, 41, 42]

Gene	Exon	Mutation
SDHA	2	c.113A>T c.91C>T
	4	c.356G>A
	5	c.457-2_457del c.512G>A
	6	c.628C>T c.698G>T c.770G>C
	9	c.1151C>G
	12	c.1663+3G>C
	13	c.1754G>A c.1766G>A
	14	c.1799G>A
SDHB	1	c.17 42dup
	2	c.137G>A
	3	c.274T>A
	4	c.380T>G c.423+1G>A c.423+20T>A
	6	c.600G>T
	7	c.725G>A
SDHC	1	c.1A>G c.6delT
	4	c.380A>G c.301delT c.224G>A
	5	c.397C>T c.405+1G>A
	6	c.455G>C
SDHD	1	c.34G>A polymorphism
	4	c.416T>C c.352delG

from both truncating and missense germline mutations. *SDHA*-mutation associated GISTs occur at an older age than other SDH-deficient GISTs, with a median age of 34 years at presentation [39, 40].

SDHB-, *SDHC*-, and *SDHD*-mutation associated tumours occur in a minority of cases (20–30%). Most of these *SDH* mutations are germline. Approximately 20% of patients with these SDH subunit mutations also develop paragangliomas [5, 41]. The remaining 50% of the SDH-deficient GIST (without a germline *SDHA/B/C/D* variants) are caused by CpG island hypermethylation in the promoter region of the *SDHC* gene, which is also referred to as a "*SDHC* epimutation" [28, 40]. *SDHC* epimutations can be associated with Carney's triad as previously described [43]. The lifetime penetrance of GIST in asymptomatic *SDH* genes mutation carriers is not known [36].

Therapy

SDH-deficient GISTs behave as an indolent disease and most patients survive with disease progression with a median survival time of 10 years[44]. Studies have found that current risk stratification criteria might not be appropriate for use on this type of GIST [22]. Despite low overall mortality, disease progression and recurrence occur frequently. The results of a retrospective analysis from the NIH Pediatric and Wild-type GIST clinic reported in 2017 revealed that 76 WT GIST patients, who underwent surgery, had a median event-free survival (EFS) of 2.5 years, with 71% of patients experiencing tumour recurrence or disease progression [44]. The EFS was negatively impacted by an elevated mitotic index and the presence of metastases. Noteworthy, negative resection margins and neoadjuvant or adjuvant treatment did not appear to affect EFS. The localized cases of SDH-deficient GIST should be treated with surgery as it is the essential and only potentially curative modality. All surgical decisions should be individualized and morbidities weighed against the benefits of resection. Generally, in SDH-deficient GIST with pathologically enlarged nodes, lymphadenectomy must be considered, but in cases of multifocal disease, extensive surgery (as total gastrectomy) related to significant morbidities is not recommended to reduce the risk of recurrence in the stomach [45]. In GIST patients with SDH-deficiency, the risk of paraganglioma is increased and diagnostic tests should be considered prior to surgery.

The role of adjuvant therapy with imatinib in even the theoretically higher risk group of this GIST subtype is not established, as WT GIST have no confirmed benefit from postoperative imatinib therapy.

The introduction of imatinib mesylate, a small-molecule selective inhibitor of receptor tyrosine kinase, has revolutionized the therapy of advanced (inoperable and/or metastatic) GIST [46, 75], and subsequently imatinib was applied in adjuvant therapy after resection of high risk GIST [47]. In cases of GIST progression on imatinib therapy, the commonly used strategy is to introduce alternative molecular targeted agents such as sunitinib, regorafenib and ripretinib [48–50]. Nevertheless, *KIT* and *PDGFRA* mutational status strongly correlates with the response and progression-free survival (PFS) in GIST patients treated with imatinib. It has been observed that systemic treatment in metastatic WT GIST showed no objective tumour response to imatinib, and superior response to sunitinib, especially in the pediatric GIST group [51]. That said, there was still an inferior response to all tyrosine kinase inhibitors when compared to KIT-mutated GIST [40]. Specifically, SDH-deficient tumours are not well recognized in terms of sensitivity to tyrosine kinase inhibitors in large phase II and III clinical trials. As mentioned previously, it is implied that SDH-mutated GISTs do not respond well to the commonly used targeted therapy, with no objective tumour response to imatinib [8]. Reliable clinical research on pure populations of SDH-deficient GIST is uncommon because these tumours are rare, and they are well identified relatively recently. These factors, together with the commonly observed slow growth of these tumours, make collection of reliable data concerning their natural clinical course and biology, as well as their response to drugs, very difficult, as time lapses of apparent disease stability could be independent of the drug activity [52, 53].Interestingly, a subgroup analysis in the EORTC phase III trial 62005 with the use of imatinib has demonstrated that *KIT/PDGFRA* wild-type GIST patients had a 76% greater risk of death compared with *KIT* exon 11 mutants [54]. In phase I/II study in 97 patients with metastatic imatinib-resistant GISTs (including nine WT GIST patients), sunitinib was shown to be more active in *KIT* exon 9 mutations and WT GISTs compared with *KIT* exon 11 mutations. In another study, a potential response to pazopanib (an inhibitor of KIT, PDGFRA, VEGFR) was demonstrated in heavily pretreated patients, although only five WT GIST patients were recruited in this phase II study [55]. In studies using imatinib in the adjuvant setting, subanalyses of WT GISTs in both the ACOSOG Z9001 trial (32 patients) [56] and the SSGXVIII (19 patients) [57] did not detect any benefit.

A recent report from the NIH Pediatric and Wildtype GIST Clinic demonstrated that the vast majority of the patients gained no clinical benefit from imatinib; only one out of 49 patients treated with imatinib mesylate had partial remission [4]. On the other hand, in the same study, seven out of 38 patients with SDH-deficient GISTs showed responses to sunitinib (one complete, three partial, three mixed). Our multicentre series of paediatric/young adult patients with advanced KIT/PDGFRA WT GISTs confirmed some clinical benefits of sunitinib (strong antiangiogenic inhibitor) in this population [58]. These data were similar to a series of Janeway et al. in paediatric GIST patients, in which longer time to progression on sunitinib as compared to prior imatinib therapy was observed [59]. Similarly, Murray noticed that sunitinib therapy had better outcomes in this type of GIST than imatinib. In a single institution study on SDH-deficient GIST, Liu et al. [18] reported four patients with disease progression during imatinib treat-

ment after initial resection, who all achieved disease control after changing therapy to sunitinib. It is suggested that the absence of functional SDH complex drives increased the vascular endothelial growth factor receptor (VEGFR) and insulin growth factor receptor (IGF1R) signalling *via* hypoxia-inducible factor HIF1-α transcriptional activity. This mechanism may be related to the efficacy of sunitinib, which inhibits both VEGFR and IGF1R, targeting these receptors and HIF2α, or their downstream effectors, making rationale for the use of antiangiogenic drugs. In another study, six patients with SDH-deficient GIST experienced clinical benefit from regorafenib, with tumour response (33.3%) or stable disease for at least 16 weeks [60]. This study, reported by Ben-Ami and co-workers, found potential improvement of PFS with regorafenib in patients with unresectable SDH-deficient GIST after failure of prior therapy with a tyrosine kinase inhibitor.

Overexpression of insulin-like growth factor receptor type 1 (IGFR1) at the protein level has also been observed in the majority of SDH deficient GISTs, with the exact molecular mechanism remaining unknown [16, 61, 62]. Since WT GIST frequently overexpress IGF1R, the SARC 022 phase II trial tested a new kinase inhibitor, linsitinib, with properties of potent inhibition of IGF1R [63]. Unfortunately, preliminary findings were not promising, with no objective response observed. PFS at 9 months was only 52%. Succinate dehydrogenase deficiency is related to hypermethylation of the genes involved in chromatin cell differentiation, thus the use of DNA hypomethylating agents is under investigation for these tumours [64]. There is currently a recruiting phase II clinical trial with the use of a new-generation DNA methyltransferase inhibitor, guadecitabine (SGI-110), in non-KIT/PDGFRA-mutated GIST and SDH-deficient paragangliomas and pheochromocytomas (NCT03165721). There are also other clinical trials operating specifically for SDH-deficient tumours, one using the glutaminase inhibitor CB-839 (NCT02071862) and one using a new-generation DNA methyltransferase inhibitor [65]. These trials are ongoing, and the results have not been yet disclosed. The hypermethylation status correlates with aberrant expression of FGF4, disrupting the binding of CTCF at DNA regions located on the boundaries of the FGF3/FGF4 locus; it was also recently discovered that FGFR1/FGFR2 receptors, and FGF4, FGF2, FGF7, and FGF10 ligands are highly expressed in SDH-deficient GIST [66, 67]. These may lead to novel potential treatment strategies using selective FGF/FGFR inhibitors, which is being currently tested in the frame of a clinical trial (NCT04595747).

Taking into account the biological features of SDH-deficient GIST, the new therapies of potential interest comprise PI3K/AKT/mTOR inhibitors, heat-shock protein inhibitors, HIF1-α targeting agents, epigenetic modifiers and demethylating agents. However, further researches are necessary in this fields.

The next possible target is related to the fact that SDH-deficient GIST typically feature widespread DNA methylation [68]. The actual occurrence of MGMT methylation in these tumours potentially predispose them to respond to alkylating drugs [69]. Recent and very interesting molecular data indicate that O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is markedly prevalent in SDH-deficient GIST, suggesting sensitivity to alkylating agents. One of the examples is temozolomide, an alkylating agent, which is ineffective in unselected GIST patient populations [70–72]. However, the study on 15 patients with paraganglioma and pheochromocytoma showed that 50% of SDHB-mutated patients had a partial response to temozolomide [73], while none of the SDHB wildtype patients had partial responses. These data suggest that SDHB mutations may be a kind of biomarker for sensitivity to temozolomide in paraganglioma and pheochromocytoma, which share genomic mutations and inheritance patterns to SDH-deficient GIST. Similarly, the report of Yebra et al., presented during the 2019 Annual Meeting of the Connective Tissue Oncology Society, demonstrated therapeutic vulnerability of SDH-deficient GISTs to temozolomide, with a 40% rate of objective responses among five patients treated with this drug [70]. Phase II study (NCT03556384) is ongoing [74]. Further preclinical and clinical research on SDH-deficient GISTs is needed.

Conclusions

To summarize the possible options of systemic therapy in SDH-deficient GIST, they have a high rate of primary resistance to various TKI. That said, even though related often to the indolent course of the disease, these tumours demonstrate some responsiveness to regorafenib and sunitinib. Further research with agents directed against other possible targets in SDH-deficient GIST are necessary.

Conflict of interest: none declared

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Guidelines and recommendations

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Polish consensus on gastric cancer diagnosis and treatment – update 2022

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This document – "Polish consensus on gastric cancer diagnosis and treatment – update 2022" – represents an expert consensus following a year's worth of dedicated effort by a team of specialists throughout 2021, put forward in a conference in December 2021 in Krakow, and finalized below for publication in 2022. The effective date of this document is June 14th 2022. The work that went into updating this consensus was made under auspices of the Polish Society of Surgical Oncology and the Association of Polish Surgeons.

Key words: chemotherapy, early gastric cancer, endoscopic treatment, gastric cancer, guidelines, surgical treatment

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History

Specific interest regarding issues related to gastric cancer management in Poland dates back to the 1970s. A project, "Polish Research in Gastric Cancer" was launched in 1977 at the initiative of Prof. Tadeusz Popiela and Prof. Tadeusz Koszarowski. The first edition of the Polish Consensus – Principles of Gastric Cancer Management – was published in the Polish Journal of Surgery at a conference memorializing the 20th anniversary of this project in 1997 [1]. Subsequent consensus updates followed in 2013 and 2017 [2, 3].

Consensus update methods

The Delphi consensus method was used for the purposes of this update [4]. As this current consensus is an update to the previous version, the first stage was modified to limit the group of specialists selecting points for discussion to 30 people. Special attention was paid to issues that may have changed over the past 5 years of evidence-based medicine. This stage produced a list of questions that were linked via email, along with a letter outlining the purpose and principles behind the consensus, to a panel of 92 experts in general and oncological surgery, clinical oncology, pathomorphology, oncological radiotherapy, and gastroenterology. Each question was answered using a seven-point Likert scale. Respondents to this questionnaire (N = 66) received the same questions again along with additional information regarding the voting distribution of all respondents. With this supplemental information, each individual could choose to either keep or change their initial vote. Forty-five specialists responded to this second questionnaire. Questions with 75% concordance to "yes", "definitely yes", "no", or "definitely no" were considered a definitive consensus. Questions with convergent, yet sub – 75%, responses were discussed and voted on during a conference of specialists in Krakow on December 10, 2021. If the final vote was conclusive, the question was determined to have reached a definitive consensus. It should be noted that consensus does not constitute a formal guideline, the methodology and form of which must adhere to appropriate conditions [5], but it is an objective representation of expert clinical opinions nonetheless.

Some points below include comments meant to clarify or refine the consensus recommendations.

Requirements for gastric cancer treatment centers

1. It is recommended that patients with gastric cancer be treated in centers that have adequate experience and a multidisciplinary team of specialists on site.
2. In centers treating gastric cancer, it is recommended to create and maintain a prospective patient registry.
3. Treatment of gastric cancer must be led by a multidisciplinary team (MDT) of experienced specialists.
4. The MDT must include at least the following specialties: general/ oncological surgery, clinical oncology, and radiotherapy.
5. Representatives of all specialties related to the treatment of gastric cancer should be involved in the MDT, namely: radiology, gastroenterology, pathomorphology, palliative medicine, and psychology.

Comment

We acknowledge that creating such a large team may not be feasible in many centers, but it is the consensus opinion that a diverse MDT would improve the quality of care and patient outcomes.

6. It is recommended that the MDT meet regularly to monitor the treatment progress as well as the percentage of patients who completed each planned stage of treatment, i.e., neoadjuvant, adjuvant, and surgical.

Comment

This recommendation goes beyond the scope of an oncological concilium within the "national fast oncological track in Poland", where management of a given patient is mandatory discussed once.

7. Gastric cancer treatment centers must ensure access to the following equipment and medical personnel:
   - 24/7 access to operating rooms,
   - 24-hour intensive care units,
   - 24-hour endoscopic suites, especially the upper gastrointestinal tract,
   - intraoperative endoscopic examination,
   - intraoperative histopathological examination,
   - intraoperative ultrasound.
8. Combination or multimodal therapy (chemotherapy and radiotherapy) on site or via dependable contractual agreements with a third party.
9. It is recommended that elective surgeries take place at specialized centers or units with extensive clinical experience, where at least 30 gastric cancer resections are performed annually.

Comment

According to the consensus, this number represents an adequate level of expertise considering the total number of gastric cancer resections performed in Poland each year.

10. It is likewise recommended that treatment centers monitor at least the following outcome measures:
    - inpatient mortality,
    - prevalence of anastomosis leakage or fistula formation,

- percentage of complications ranked on severity per the Clavien-Dindo scale,
- total hospitalization time,
- classification of radical resections,
- patients' survival rate,
- stage on presentation.

11. Centers providing surgical treatment of gastric cancer should be subject to periodic external audits.

Comment

Given the current state of gastrointestinal neoplasm management, including gastric cancer, there is no independent governing entity to access centers for compliance with the above standards.

Consensus regarding preoperative diagnostics

1. Thorough and comprehensive medical evaluation, specifically the endoscopic examination of the upper gastrointestinal tract, of every patient with suspected gastric cancer is critical.
2. Endoscopic examination must be performed in accordance with guidelines described by the Polish Society of Gastroenterology, paying special consideration to the quality indicators established for gastrointestinal endoscopy: http://www.ptg-e.org.pl/Wysznejakosci--endoskopii-2014-,140.html.

Comment

The consensus does not discuss individual guidelines regarding the endoscopic examination, relying instead on the above-mentioned resource for guidance.

3. It is recommended to collect multiple samples [6–8] during endoscopic examinations for histopathological analysis.

Comment

In the case of unresectable or disseminated tumors, additional assessment of HER2 expression should be performed on these samples.

4. Computed Tomography (CT) with intravenous and oral contrast of the abdominal, thoracic, and pelvic cavities is necessary in all patients with gastric cancer.

Comment

The inclusion of all three regions for CT examination was approved separately.

5. Routine PET-CT is not recommended. PET-CT can be performed when the presence of distant metastases is clinically suspected but inadequately visualized through other imaging studies.

Comment

The use of PET-CT in gastric cancer is not currently reimbursed. Voting members of the consensus however acknowledge expanding the indications for PET-CT in certain cases of gastric cancer.

6. Routine endoscopic ultrasonography (EUS) is not recommended. However, EUS is required for every patient with gastric cancer and planned endoscopic treatment.
7. It is recommended to perform a diagnostic laparoscopy with peritoneal lavage to best assess the stage of advance of gastric cancer before initiating treatment, if possible.

Comment

The voters rejected the absolute requirement to perform a diagnostic laparoscopy due to the possibility it will delay treatment due to additional inpatient stay. However, there is no doubt as to the clinical validity of diagnostic laparoscopy, especially in patients with advanced gastric cancer without clinically evident peritoneal dissemination [8].

8. A thorough and comprehensive medical examination is recommended for all patients to determine their overall state of health, taking special consideration for comorbid or chronic illnesses, prior to beginning treatment.
9. It is necessary to assess a patient's overall nutritional status, and take steps to optimize their nutritional status when indicated, before beginning treatment.

Comment

Early nutritional intervention should take place during the diagnostic and therapeutic process. Nutritional supplementation is mandatory in patients with confirmed malnutrition.

10. For patients with adenocarcinoma of the esophageal-gastric junction (EGJ), it is necessary to determine the type of tumor according to the Siewert classification. Type I and II tumors should be treated according to guidelines for esophageal cancer, while type III tumors according to guidelines for gastric cancer.

Comment

Apart from the above statements, the consensus does not address the particular standards of EGJ cancer management.

Consensus regarding pathomorphological diagnostics

1. It is recommended that pathomorphological evaluations be performed according to guidelines formulated by the Gastrointestinal Tract Group of the Polish Society of Pathologists (with appropriate modifications given changes to the classifications updates) http://pol-pat.pl/index.php/standardy/.

Table I. Assessment of the response to preoperative treatment

Category	Code	Description
complete response	R0	no evidence of live cancer cells
near complete response	R1	individual live cancer cells
partial response	R2	evidence of tumor regression occurring in larger clusters, not individual cells or limited to small groups
poor or no response	R3	no or very little cancer regression

2. The gold standard methodology for staging gastric cancer is the current AJCC/UICC TNM classification (VIII edition, 2017).
3. Microscopic examination of the sample after gastrectomy should include an assessment of responsiveness to any preoperative treatment, where appropriate. The consensus recommends using the classification established by the College of American Pathologists and International Collaboration on Cancer Reporting (tab. I).
4. Determining HER2 receptor expression is necessary in patients with advanced gastric cancer. This also applies to samples taken during endoscopic examination in patients where gastric resection is not planned.
5. Microscopic analysis following gastric resection should include microsatellite instability (MSI) testing.

Comment

According to current data [6, 7], tumors showing MSI probably do not benefit from adjuvant chemotherapy and have a better prognosis as compared to patients with tumors showing microsatellite stability. They may, however, benefit from immunotherapy, but that is currently being investigated.

There was no consensus regarding the statement

Microscopic examination following gastrectomy should include the evaluation of PD-L1 expression (programmed death ligand 1). The discussion raised limited scientific data regarding the introduction of PD-L1 testing into routine practice.

Consensus regarding surgical treatment

1. The goal of surgical gastric cancer treatment is to achieve a complete R0 resection of the tumor.
2. A partial gastrectomy is recommended in the case of distal gastric cancer if doing so can achieve an adequate proximal margin.
3. The optimal proximal margin of the resected specimen following distal gastrectomy when assessed macroscopically is at least 5 cm.

Comment

As in the previous version of the consensus, there is no distinction between the histological types of the tumor.

4. A proximal gastrectomy is allowed in the case of gastric cancer located in the upper part of the stomach.
5. The extent of lymphadenectomy is to be classified by the D-level criteria per the Japanese Gastric Cancer Association (JGCA) classification (tab. II, III).
6. In cases of patients with advanced gastric cancer (>cT1b) and those with planned curative gastrectomies, it is recommended to perform routine D2 lymphadenectomy.
7. D1/D1+ lymphadenectomy is allowed for patients with stage cT1a gastric cancer.
8. D1/D1+ lymphadenectomy is allowed for patients with stage cT1bN0 gastric cancer if the tumor is <1.5 cm and shows a high degree of differentiation.
9. Lymphadenectomy beyond D1 is not recommended in cases of palliative resections.
10. Routine splenectomy is not recommended except in cases where direct neoplastic infiltration of the spleen is observed or where there is suspicion of metastasis to the splenic hilum lymph nodes.
11. In cases of stage cT4b tumors, it is necessary to evaluate the feasibility of multiorgan resection to achieve an R0 resection.
12. A palliative, non-radical gastrectomy is allowed to reduce the severity of symptoms or complications related to the tumor, i.e., bleeding, obstruction, perforation.
13. It is not recommended to perform a gastrectomy with the intent of cytoreduction in patients lacking indications for palliative surgical intervention in order to mitigate complications associated with the tumor, i.e., bleeding, obstruction, perforation.
14. In patients with an isolated distant metastasis (oligometastatic disease), surgery is possible as long as it achieves an R0 residual margin for both the primary and metastatic tumors.
15. In the case of early gastric cancer, laparoscopic distal gastrectomy is considered to be equivalent to laparotomy if performed in centers with adequate experience. Laparoscopic total gastrectomy is also considered equivalent for early gastric cancer.
16. In the case of advanced gastric cancer, laparoscopic distal gastrectomy is considered to be equivalent to laparotomy if performed in centers with adequate experience. Laparoscopic total gastrectomy however is not considered equivalent for advanced gastric cancer
17. In the case of clinical symptoms of stenosis in patients where a radical or palliative gastrectomy is not possible, it is necessary to consider a bypass anastomosis or endoscopic stenting of the stenotic region

Table II. Anatomical definition of lymph node (LNs) station in gastric cancer

LNs station	Definition
1	right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery
2	left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery
3a	lesser curvature LNs along the branches of the left gastric artery
3b	lesser curvature LNs along the 2nd branch and distal part of the right gastric artery
4sa	left greater curvature LNs along the short gastric arteries (perigastric area)
4sb	left greater curvature LNs along the left gastroepiploic artery (perigastric area)
5	suprapyloric LNs along the 1st branch and proximal part of the right gastric artery
6	infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein
7	LNs along the trunk of the left gastric artery between its root and the origin of its ascending branch
8a	anterosuperior LNs along the common hepatic artery
8b	posterior LNs along the common hepatic artery
9	celiac artery LNs
10	splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries, and those along the left gastroepiploic artery proximal to its 1st gastric branch
11	proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end; distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail
12a	hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
12b	hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas; hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
13	LNs on the posterior surface of the pancreatic head proximal to the ampulla of Vater
14	LNs along the superior mesenteric vein
15	LNs along the middle colic vessels
16a1	paraaortic LNs in the diaphragmatic aortic hiatus
16a2	paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein
16b1	paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery
16b2	paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	LNs along the inferior border of the pancreatic body
19	infradiaphragmatic LNs predominantly along the subphrenic artery
20	paraesophageal LNs in the diaphragmatic esophageal hiatus

18. In the case of clinical symptoms of stenosis in the cardia, where a radical or palliative gastrectomy is not possible, it is necessary to consider either endoscopic stenting or the creation of a feeding jejunostomy.

Consensus regarding endoscopic treatment

1. Curative endoscopic treatment is allowed in select patients with early gastric cancer.
2. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) should be performed exclusively in centers with adequate experience using these techniques.
3. The standard indications for EMR in the case of early gastric cancer are the following:
   - a high degree of histological differentiation (G1),
   - no ulceration (UL0),

Table III. The type of lymphadenectomy based on the extent of resection

Type of resection	Lymphadenectomy	LNs station
total gastrectomy	D0	lymphadenectomy less than D1
	D1	excision of LNs of stations 1 to 7
	D1+	excision of LNs in the D1 range and stations No. 8a, 9, 11p
	D2	excision of LNs in D1 and stations No. 8a, 9, 11, 12a; additionally, in the case of tumors infiltrating the esophagus, LNs should be removed from stations No. 19, 20, 110 and 111
distal gastrectomy	D0	lymphadenectomy less than D1
	D1	excision of LNs in stations No. 1, 3, 4sb, 4d, 5, 6, 7
	D1+	excision of LNs in D1 and stations No. 8a, 9
	D2	excision of LNs in D1 and stations No. 8a, 9, 11, 12a
proximal gastrectomy	D0	lymphadenectomy less than D1
	D1	excision of LNs in stations No.1, 2, 3a, 4sa, 4sb, 7
	D1+	excision of LNs in D1 and stations No. 8a, 9, 11

- infiltration limited to the mucosa (cT1a),
- tumor diameter less than 2 cm.

4. The indications for ESD in the case of early gastric cancer are the following:
   - a high degree of histological differentiation (G1),
   - no ulceration (UL0),
   - infiltration limited to the mucosa (cT1a),
   - tumor diameter greater than 2 cm.

Comment

Additional, extended criteria indicated by JGCA recommendations were not agreed upon by the consensus (tab. IV).

5. The radicality of endoscopic resection should be assessed in accordance with the JGCA classification in every case of EMR /ESD (tab. V).
6. In the case of confirmed Grade A and B resections (eCura A, eCura B) according to the JGCA, it is sufficient to perform appropriate post-operative follow-up examinations.
7. In the case of confirmed Grade C resection (eCura C) according to the JGCA, it is necessary to consider surgical intervention.
8. In the case of recurrence that is isolated to the mucosa following endoscopic surgery, performed in accordance with initial indications, a one-time repeat submucosal dissection procedure is acceptable.

Consensus regarding multimodal therapy

1. Combination therapy utilizing an MDT should be considered in the case of advanced gastric cancer (>cT1b).
2. Perioperative chemotherapy should be considered in each case of potentially resectable gastric cancer stage cT2, any

Table IV. Indications for the endoscopic treatment of gastric cancer according to JGCA

	Basic indications	Extended indications
EMR/ESD	highly differentiated adenocarcinoma: • no ulceration (UL0) • stage cT1a • tumor size ≤2 cm	
ESD	highly differentiated adenocarcinoma without ulceration (UL0): • stage cT1a, • tumor size >2 cm	**low-differentiated adenocarcinoma without ulceration (UL0):** • **CT1a advancement,** • **tumor size ≤2 cm**
	highly differentiated adenocarcinoma with ulceration (UL1): • **stage cT1a,** • **tumor size ≤3 cm**	

*Bold areas were not included into consensus

Table V. Endoscopic curability classification

Category	Description
eCura A	neoplasm without ulceration (UL0) meeting all of the following conditions: • complete resection (*en bloc*), • any neoplasm size, • predominantly a highly differentiated neoplasm, • pT1a, • negative horizontal and vertical margins, • no vascular infiltration (L0V0)
	ulcerative neoplasm (UL1) meeting all the following conditions: • complete resection (*en bloc*), • neoplasm size ≤3 cm, • predominantly highly differentiated neoplasm, • pT1a, • negative horizontal and vertical margins, • no vascular infiltration (L0V0)
eCura B	predominantly poorly differentiated neoplasm meeting all of the following conditions: • no ulceration (UL0), • complete resection (*en bloc*), • neoplasm size ≤2 cm, • pT1a, • negative horizontal and vertical margins, • no vascular infiltration (L0V0)
	for pT1b cancer meeting all of the following conditions: • complete resection of neoplasm (*en bloc*), • predominantly highly differentiated neoplasm, • neoplasm size ≤3 cm, • SM1 – submucosa infiltration <500 µm from muscularis mucosae, • • negative horizontal and vertical margins, • • no vascular infiltration (L0V0)
eCura C	endoscopic resections that do not meet the criteria for eCura A or eCura B
	eCura C1: • highly differentiated tumor meeting eCura A or eCura B criteria but not completely removed (*en bloc*) or removed with a positive horizontal margin eCura C2: • all other eCura C resections

N, M0, where an R0 resection margin is deemed possible, and there are no indications for urgent gastrectomy.

3. Perioperative FLOT chemotherapy should be considered in patients determined to be in very good general health following an extensive clinical evaluation.

Comment

The assumption is a 4+4 regimen, however in some patients, it may not be possible to complete all cycles before or after surgery.

4. Perioperative FOLFOX/XELOX chemotherapy should be considered in patients determined to be in good to moderate overall health.

Comment

This statement is supported by moderate evidence; however, this strategy increases the group of patients receiving perioperative chemotherapy.

5. Postoperative radiotherapy has not been shown to provide additional benefits in patients who received perioperative chemotherapy.
6. In patients with stage 1B or higher gastric cancer who did not receive perioperative chemotherapy, adjuvant radiochemotherapy, or less commonly, self-administered chemotherapy, is recommended.
7. In patients with stage 1B or higher gastric cancer where a D2 lymphadenectomy was not performed, adjuvant radiochemotherapy is recommended.
8. In patients with gastric cancer not exceeding stage pT2N0 where a D2 lymphadenectomy was performed, adjuvant chemotherapy may be considered, although observation is also possible.

Comment

This provision applies to patients who did not receive perioperative chemotherapy.

9. In patients with advanced, locally unresectable tumors and no evidence of distant metastasis (T4b, any N, M0), inductive chemotherapy should be considered. After its completion, it is recommended to reassess the feasibility of surgical resection.
10. In patients with advanced, unresectable gastric cancer, chemotherapy regimens should consist of a combination of two or three agents, including platinum and fluoropyrimidine derivatives.
11. Hyperthermic intraperitoneal chemotherapy (HIPEC) is acceptable in select cases of stage IV gastric cancer, preferably as part of clinical trials.
12. In patients with advanced, unresectable gastric cancer with positive HER2 expression, systemic therapy including trastuzumab in combination with a platinum derivative and a fluoropyrimidine is recommended.

Abbreviations

CT – computed tomography
EGJ – esophageal-gastric junction
EMR – endoscopic mucosal resection
ESD – endoscopic submucosal dissection
EUS – endoscopic ultrasonography
HIPEC – hyperthermic intraperitoneal chemotherapy
JGCA – Japanese Gastric Cancer Association
MDT – multidisciplinary team
MSI – microsatellite instability
PD-L1 – programmed death ligand 1
PET-CT – positron emission tomography
UL0 – no ulceration

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Guidelines and recommendations

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Diagnostic and therapeutic management of patients with ocular melanomas – recommendations of the Polish Society of Oncology

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Uveal melanoma is the most common malignant neoplasm of the eyeball, developing from melanocytes of the uveal membrane of the eye, which is significantly different from melanoma of the conjunctiva, mucous membranes and skin. The management of this disease is therefore different from that of other forms of melanoma. The disease is most often confined to the eye and its local treatment includes radiation therapy and surgery. Some patients, despite successful local treatment, develop distant metastases, most often located in the liver. The guidelines presented here cover the principles of diagnosis, prognostic evaluation and treatment of both the disease confined to the eyeball and the disease at the metastatic stage. The principles of management of conjunctival melanoma are also discussed. The recommendations are based on a review of the literature and expert opinion, and are accompanied by an assessment of their strength and reliability.

Key words: ocular melanoma, conjunctival melanoma

Introduction

According to the authors and editors, recommendations contain the most reasonable principles of diagnostic and therapeutic management. They were prepared by taking into account the value of scientific evidence and categories of recommendations. The management principles should always be interpreted in the context of the individual clinical situation. The recommendations do not always correspond to the current reimbursement rules that apply in Poland, and this is described in the text. When in doubt, current reimbursement options for particular procedures should be determined.

The quality of scientific evidence and recommendation categories were determined according to the following criteria.

1. Quality of scientific evidence:
   - I. Evidence from at least one large randomized controlled trial (RCT) of high methodological quality (low risk of bias) or meta-analysis of correctly designed RCTs without significant heterogeneity.
   - II. Small RCTs or large RCTs with risk of bias (lower methodological quality) or meta-analyses of such studies or RCTs with significant heterogeneity.
   - III. Prospective cohort studies.

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IV. Retrospective cohort studies or case-control studies.
V. Studies without a control group, case reports, expert opinions

2. Strength of recommendations:
   1. Recommendation based on high-quality evidence for which the expert panel has reached unanimity or a high level of consensus.
   2A. Recommendation based on lower-quality evidence for which the expert panel has reached unanimity or a high level of consensus.
   2B. Recommendation based on lower-quality evidence for which the expert panel reached a moderate level of consensus.
   3. Recommendation based on evidence at any level of quality, for which the expert team did not reach consensus.

Scope and purpose of the guidelines

The guidelines provide recommendations for the prevention, diagnosis and treatment of uveal melanomas and melanomas of the conjunctiva. They are addressed to those responsible for organizing and providing care for melanoma patients at all levels of health care, including physicians, nurses and pharmacists. The guidelines were created – based on available scientific evidence – to systematize and standardize clinical practice, and thus provide patients with the best possible care.

The document presents a range of diagnostic and therapeutic options that allow clinicians to choose the most appropriate management for each patient. The guidelines outline interventions that may be preferred due to their efficacy and safety profile compared to other medical technologies. In addition, the guidelines identify publicly funded methods in the Polish health care system and include an analysis of the effectiveness of alternative treatment options (including those that are not reimbursed).

Methodology

To find relevant scientific evidence, a non-systematic search of clinical practice guidelines was conducted and medical information databases were searched. The search for clinical practice guidelines included recommendations for the diagnostic and therapeutic management of uveal and conjunctival melanoma published in Polish, English and German between 2016 and 2021. Recommendations from the European Society of Medical Oncology (ESMO), American Society of Surgical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), American Academy of Dermatology (AAD) were included in the review, European Association of Dermato-Oncology (EADO), Scottish Intercollegiate Guidelines Network (SIGN), Cancer Council Australia (CCA), Japanese Dermatological Association (JDA), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) and Polish Society of Clinical Oncology (PTOK).

A non-systematic search of medical information databases (PubMed) was also conducted to obtain key literature. The review included all phase II and III clinical trials published between 1990 and 2021, which included the keywords ocular melanoma, uveal melanoma and conjunctival melanoma. The recommendations in the guidelines are derived from a critical appraisal of the evidence, combined with the clinical expertise and consensus of a multidisciplinary panel of specialists. They were written in accordance with the principles for formulating and adopting recommendations described in the document Consensus on Methodology for Developing Clinical Practice Guidelines in Oncology under the auspices of the National Cancer Institute and the Agency for Health Technology Assessment and Tarification [1]. The panel of specialists worked together on the final document in the form of consensus (no dissenting opinions were submitted), and the document was available to all panel members at all times. All panelists completed conflict of interest disclosure statements, and potential conflicts of interest were presented.

Ocular melanoma

Uveal melanoma

Epidemiology and etiology

Uveal melanoma is the most common malignant primary intraocular neoplasm in adults [2–6]. It is significantly different from melanoma of the conjunctiva, mucous membranes, and skin [7]. According to 2018 data from the National Cancer Registry (KRN – Krajowy Rejestr Nowotworów), ocular malignancies (C69) account for 0.3% of all cancers in Poland (523 cases), most of which are uveal melanoma. The mortality for this was 0.1% (121 deaths) [8]. Its incidence varies by race and latitude. The incidence is highest among Caucasians (98% of all patients) and at higher latitudes. In Mediterranean countries it is 2 new cases per 1 million inhabitants per year, while in Scandinavian countries it is 8–11/1 million inhabitants. In the United States, there is an average of 4.3 new cases per year per 1 million people [4, 6, 9, 10].

Children rarely develop this type of cancer, and their prognosis is significantly better (5- and 10-year survival rates are 97% and 92%) [11, 12].

Uveal melanoma develops from melanocytes of the uveal membrane, occupying different parts of it with varying frequencies. It is found in the iris in about 4–6%, in the ciliary body in 6–9%, and most often in the choroid in 85–90% [2, 13, 14].

Staging and prognostic factors

The prognosis of uveal melanoma depends on many factors. One of them is the size of the primary tumor (largest base diameter and height). Larger tumors offer a lower chance of survival. Increasing the height of the tumor by 1 mm increases the risk of metastasis by 5% over 10 years [3, 15]. Based on the assessment of thickness (height), tumors were divided into small (small; 0–3 mm), medium (medium; 3.1–8.0 mm)

and large (large; >8 mm). The 5-, 10- and 20-year mortality rates were 6%, 12% and 20% in each group, followed by 14%, 26% and 37%, and 35%, 49% and 67% in the last group, respectively [3, 15]. Another factor that negatively affects prognosis is tumor involvement of the ciliary body. In this case, 33% of patients develop metastases within 10 years of follow-up. When the tumor involves the iris, metastasis occurs in 7% of patients, and when it involves the choroid – in 25%.

Other factors that worsen the prognosis and are associated with a higher propensity for metastasis are the following histopathological features:

- epithelioid type of melanoma,
- deep infiltration of the eyeball wall (sclera),
- presence of extraocular infiltration,
- high mitotic index,
- infiltration of the optic nerve,
- intrinsic vascularization of the tumor with a tendency to form arches, branches, closed loops and vascular networks,
- inflammatory infiltration in the tumor mass (especially T lymphocytes and macrophages) [2, 16, 17].

Genetic disorders such as monosomy of chromosome 3, multiple copies of 1q, 6p and 8q, loss of 1p, 6q and 8p, and mutations of the BAP1, GNAQ and GNA11 genes are associated with a high risk of metastasis [2, 18]. In contrast, mutation in the EIF1AX gene is associated with a good prognosis [2, 18]. Genetic testing is not recommended for routine use, although it may influence the pattern of follow-up testing after local treatment (IV, 2B).

Local control after treatment of ocular choroidal melanoma is very high (86–98%) and is achieved by various conservative treatments, such as brachytherapy, proton therapy, transpupillary thermotherapy (TTT), endo- or exoresection of the tumor, and various combinations of these (II, 2A) [2, 19]. In very large tumors, i.e., those with a base diameter greater than 20 mm or a height greater than 12 mm, and if the neoplasm substantially occupies the optic nerve disc, the best treatment is still surgery to remove the eyeball [20] (III, 2A). A big problem in this condition is still the approximately 50% mortality rate due to generalized dissemination, for which treatment options are still limited [2, 21]. In more than 90% of cases, metastasis localizes to the liver, despite good local treatment [2, 21]. This is due to the propensity of uveal melanoma to form micro-metastases in the early stages and the presence of tumor cells in the vascular bed before treatment [2, 21].

The AJCC TNM classification developed by the American Joint Committee on Cancer is used in the staging and prognosis of uveal melanoma, which takes into account the size of the largest tumor base, its thickness (height), involvement of the ciliary body, the presence and size of extraocular infiltration, and the presence of metastases [22]. Regional lymph node involvement in uveal melanoma is extremely rare [23] (tab. I). To assess the risk of metastasis, the genetic analyses mentioned above should also be considered, with chromosome 3 monosomy and BAP1 mutations [2] being the first consideration (III, 2B).

Symptoms

About $^{1}/_{3}$ of patients with uveal melanoma report no symptoms, or if any occur, they are uncharacteristic [24]. Among the most common are decreased visual acuity and visual field abnormalities. There may also be pain due to elevated intraocular pressure values, and there may be a "veil" in front of the eye or distorted vision [24].

Diagnostic examinations

1. Anterior ophthalmoscopic examination under a slit lamp (III, 2A).
2. Fundus examination after pupil dilation (indirect ophthalmoscopy preferred) (III, 2A).
3. Ultrasound examination (III, 2A):
   a) ultrabiomicroscopy – ultrasonography of the anterior segment of the eyeball, ciliary body and anterior choroid,
   b) ultrasonography of the posterior segment of the eyeball (finding a mycotic tumor shape is a typical feature of uveal melanoma).
4. Optical coherence tomography (OCT) (III, 2A).
5. Photography of the observed lesion to determine possible progression (III, 2A).
6. Gonioscopy – when a lesion is suspected to occupy or reach the iridocorneal angle (III, 2A).
7. Diaphanoscopy, or transillumination (makes the base of the tumor visible) (III, 2A).
8. Additional examinations (performed when there is diagnostic doubt) (III, 2B):
   a) fluorescein angiography,
   b) indocyanine angiography,
   c) computed tomography of the orbits,
   d) magnetic resonance imaging of the orbits,
   e) autofluorescence [19].
9. Tumor biopsy, is still controversial due to the increased risk of tumor dissemination and the high rate of false negative results [25] (III, 2A) [26] (NCCN Guidelines. Uveal Melanoma. Version 3.2020).

Differential diagnosis

Uveal melanoma needs to be differentiated from metastatic tumors of other locations and from pigmented nevi [19, 27]. It is very important to distinguish an atypical pigmented nevus from a small melanoma (TFSOM rule developed by Shields et al.) [28] (III, A). Less commonly considered in the differential diagnosis are:

- choroidal hemangioma (limited or diffuse),
- intraocular lymphoma,
- retinal hemangiomas,
- osteoma,

Table I. Primary tumors – T feature

T (primary tumor)	Disease staging
all uveal membrane melanomas of the eyeball	
TX	primary tumor cannot be evaluated
T0	no primary tumor is found
iris	
T1	tumor limited to the iris
T1a	tumor limited to the iris, not more than 3 clock hours in size
T1b	tumor limited to the iris more than 3 clock hours in size
T1c	tumor limited to the iris with secondary glaucoma
T2	tumor confluent with or extending into the ciliary body, choroid or both
T2a	tumor of the iris involving the ciliary body, without secondary glaucoma
T2b	iris tumor involving the choroid, without secondary glaucoma
T2c	iris tumor involving the ciliary body and/or choroid, with secondary glaucoma
T3	iris tumor involving the ciliary body and/or choroid with scleral infiltration
T3a	iris tumor involving the ciliary body and/or choroid with infiltration of the sclera and secondary glaucoma
T4	melanoma with extrascleral extension
T4a	tumor with extrascleral extension less than or equal to 5 mm in diameter
T4b	tumor with extrascleral extension more than 5 mm in diameter
ciliary body and choroid	
T1	tumor size category 1
T1a	tumor size category 1 without ciliary body involvement and extraocular extension
T1b	tumor size category 1 with ciliary body involvement
T1c	tumor size category 1 without ciliary body involvement, and with extraocular extension less than or equal to 5 mm in diameter
T1d	tumor size category 1 with involvement of the ciliary body and with extraocular extension less than or equal to 5 mm in diameter
T2	tumor size category 2
T2a	tumor size category 2 without ciliary body involvement and extraocular extension
T2b	tumor size category 2 with ciliary body involvement
T2c	tumor size category 2 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T2d	tumor size category 2 with involvement of the ciliary body and with extraocular extension less than or equal to 5 mm in diameter
T3	tumor size category 3
T3a	tumor size category 3 without ciliary body involvement and extraocular extension
T3b	tumor size category 3 with ciliary body involvement
T3c	tumor size category 3 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T3d	tumor size category 3 with ciliary body involvement and with extraocular extension less than or equal to 5 mm in diameter
T4	tumor size category 4
T4a	tumor size category 4 without ciliary body involvement and extraocular extension
T4b	tumor size category 4 with ciliary body involvement
T4c	tumor size category 4 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T4d	tumor size category 4 with ciliary body involvement and with extraocular extension less than or equal to 5 mm in diameter
T4e	any tumor size category with extraocular extension more than 5 mm in diameter

To determine the T-feature for ciliary body and choroidal melanoma, it is necessary to first classify the tumor into the appropriate size category based on the height and largest diameter of the tumor base (fig. 1)

- retinal-vascular calcifications,
- staphyloma (astrocytoma),
- age-related macular degeneration (AMD), especially the exudative form [19, 27].

The TNM staging classification according to AJCC revision 8 is shown in tables I–IV. Table V shows the histological grade [22].

Tumor features such as largest diameter and thickness (height) are used to determine the size category (tab. I, fig. 1 – T-feature). Determination of pT is required for the ciliary body and choroidal melanomas, but is only feasible if the primary treatment was ocular excision (enucleation). In these situations, proper technique is essential to visualize the greatest base diameter and thickness (height) of the tumor in the removed eyeballs. To achieve this, the eyeball should be illuminated with a strong light source to map the tumor's shadow on the sclera and determine its position in relation to the optic nerve. The eyeball should be cut so that the plane of the section contains the largest diameter of the tumor base, rests on the shadow, and passes through the center of the disc as well as the optic nerve.

Table II. Regional lymph nodes – N feature

N (regional lymph nodes)	Disease staging
Nx	regional lymph nodes cannot be assessed*
N0	no regional lymph node metastasis
N1	metastasis in regional lymph nodes or separate tumor infiltration in the orbit is found
N1a	metastasis in one or more regional lymph nodes
N1b	separate tumor infiltration in the orbit without continuity with the eyeball, without metastasis to regional lymph nodes

*Regional lymph nodes include the preauricular, submandibular and cervical lymph nodes

Table III. Distant metastasis – M feature

M (distant metastasis)	Disease staging
M0	no distant metastasis
M1	distant metastasis
M1a	diameter of the largest distant metastasis ≤3 cm
M1b	diameter of the largest metastasis is between 3.1–8.0 cm
M1c	diameter of the largest metastasis >8 cm

Table IV. Tumor stage

Stage	T	N	M
I	T1a	N0	M0
IIA	T1b–d	N0	M0
	T2a	N0	M0
IIB	T2b	N0	M0
	T3a	N0	M0
IIIA	T2c–d	N0	M0
	T3b–c	N0	M0
	T4a	N0	M0
IIIB	T3d	N0	M0
	T4b–c	N0	M0
IIIC	T4d–e	N0	M0
IV	any T	N1	M0
	any T	any N	M1 a–c

Table V. Evaluation of histological structure (grading) – G feature

G (histological grade)	Histological structure of melanoma
GX	histologic type cannot be assessed
G1	spindle cell melanoma (>90% spindle cells)
G2	mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
G3	epithelioid cell melanoma (>90% epithelioid cells)

Primary tumor thickness	Size (mm)						
>15	4	4	4	4	4	4	4
12.1–15.0	3	3	3	3	3	4	4
9.1–12	3	3	3	3	3	3	4
6.1–9.0	2	2	2	2	3	3	4
3.1–6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	≤3.0	3.1–6.0	6.1–9.0	9.1–12	12.1–15.0	15.1–18.0	>18.0
	Largest dimension of the tumor base (mm)						

Figure 1. Classification of ciliary body and uveal melanoma based on the thickness and size of the primary tumor

In the past, in the clinical evaluation of tumor dimensions, the largest base diameter was expressed in multiples of the optic disc diameter (DD) (average 1 DD = 1.5 mm), and the thickness (height) of the tumor in diopters (average 3 diopters = 1 mm). Nowadays, the standard is to determine the size of intraocular tumor parameters in millimeters based on ultrasound measurements (T-feature determination) [22]. As the majority of patients with uveal melanoma are treated conservatively, so ultrasonography remains the only method to assess tumor size.

Treatment

Local treatment of uveal melanoma can be divided into two main types.

1. Eye-sparing treatment, which preserves the eyeball and even useful visual acuity in some cases

Radiation therapy (II, 2A):

- Brachytherapy (used most often) with various radioactive elements, which allows very good local tumor control of 95–98% [29, 30]. Commonly used are the isotopes ruthenium-106 (Ru-106) and iodine-125 (I-125). Palladium (Pd-103) and iridium (Ir-192) are used much less frequently due to their short half-life and the associated high cost of therapy. Ru-106 is effective in treating tumors up to 5 mm in height, or up to 6 mm, but in combination with transpupillary thermotherapy (TTT). I-125 is used to treat tumors that are 5 mm and above, but not more than 10–12 mm. The base of the tumor is also an important determinant in the use of applicators, which should not exceed the diameter of the applicator and can be no more than 18 mm to maintain a safe margin [31]. The dose to the top of the tumor should not be less than 70 Gy, and ideally for I-125 it should be around 82.5 Gy [31–35].
- Proton beam therapy – a positive local result is achieved in 95-98% of cases. The therapy uses a collimated beam of protons or helium nuclei. Irradiation is performed for 4 consecutive days with a total dose to the tumor apex of 60 Gy (4 × 15 Gy) [36].
- Stereotactic radiotherapy.

Local sparing surgical treatment (II, 2A):

- Exoresection – this is used to treat lesions located in the iris, ciliary body, or anterior choroid [2]. The tumor is removed under the scleral flap, in combination with brachytherapy [2].
- Endoresection – can be performed after prior radiation therapy. The tumor is removed during pars plana vitrectomy [37–39].

Laser treatment:

- Transpuppilary thermal therapy (TTT) is designed to treat small melanomas. It is most commonly used with brachytherapy, especially in the parathyroid localization of the tumor, the so-called sandwich therapy method (III, 2B).
- Photodynamic therapy – an experimental and controversial therapy, using a photosensitizing dye (verteporfin), for the treatment of amelanotic small melanomas [40, 41] (IV, C) – this type of therapy is currently not reimbursed in Poland.

2. Radical surgical treatment

Enucleation, or removal (excision) of the eyeball. Recommended when the tumor is more than 12 mm thick and more than 20 mm in base, and when the tumor infiltrates the optic nerve or secondary glaucoma is present [20] (III, 2A). It is recommended that an orbital implant be placed at the same time, after removal of the eyeball – provided there are no features of extraocular infiltration, and and orbital prosthesis up to 14 days after the procedure.

Exenteration, or evisceration of the orbit, is indicated when there is massive extraocular infiltration.

Both diagnosis and qualification for treatment, as well as treatment of uveal melanoma, should be carried out in ophthalmic oncology centers by specialists experienced in the subject.

Treatment at the generalized stage

Treatment of generalized uveal melanoma of the eyeball makes it possible to prolong survival by several months, especially if local treatment of liver metastases is possible.

The key element determining the length of survival of patients with uveal membrane melanoma is the presence of liver metastases. The liver is the most common site of metastasis – 70-90% of cases, with the liver being the only site of metastasis in about 50%. Metastases of ocular choroidal melanoma spread via the bloodstream. Survival after finding metastatic lesions in the liver is usually short, with a median of 2–3 months. Metastases of this cancer to the liver are classified as:

- stage 1: ≤50 μm in diameter,
- stage 2: 51–500 μm,
- stage 3: >500 μm,

In the latter stage, two types of metastatic growth occur:

- infiltration and replacement of hepatic lobules with peri--lobular fibrous septa,
- formation of large islands of tumor cells adjacent to small portal veins.

During progression, the tumor becomes vascularized and mitotically active [42, 43].

To date, there are no established, agreed-upon methods for the management of such patients. Various methods of surgical treatment are described in the literature, including:

- liver resection,
- isolated liver perfusion,
- intraarterial chemoinfusion,
- transarterial chemoembolization,
- immunoembolization,
- selective radiotherapy,
- thermoablative methods (radiofrequency ablation – RFA, microwave ablation – MWA).

There are more than a dozen publications in the literature, most of them retrospective, that analyze the outcomes of patients undergoing liver resection. A significant number of publications either do not include a comparison group or compare with a historical group of patients undergoing surgery, or with patients treated conservatively. A systematic review published in 2020 includes a group of nearly 800 operated patients with an overall survival of 10 to 35 months, compared with a survival of 9 to 15 months in the group treated with systemic chemotherapy [44]. In the largest group in the retrospective analysis – 255 patients undergoing resection – median survival was 14 months, compared to 8 months in the group treated conservatively.

Surgical treatment usually consisted of classical resection of the liver parenchyma along with the focal lesion. Sometimes the resection was supplemented by intraarterial chemotherapy, chemoembolization or thermoablation.

There are reports of the successful use of laparoscopic techniques for resection and/or complementary thermoablation. This method is relatively safe, with no perioperative mortality, and a morbidity rate of 19%. Median survival in this group is 35 months [44]. Typically, patients with metastatic melanoma undergo small resections – no more than 1–2 liver segments.

The aforementioned surgical results may be subject to patient selection bias, as patients with favorable tumor biology and less advanced liver metastatic foci in number and volume are qualified for resection.

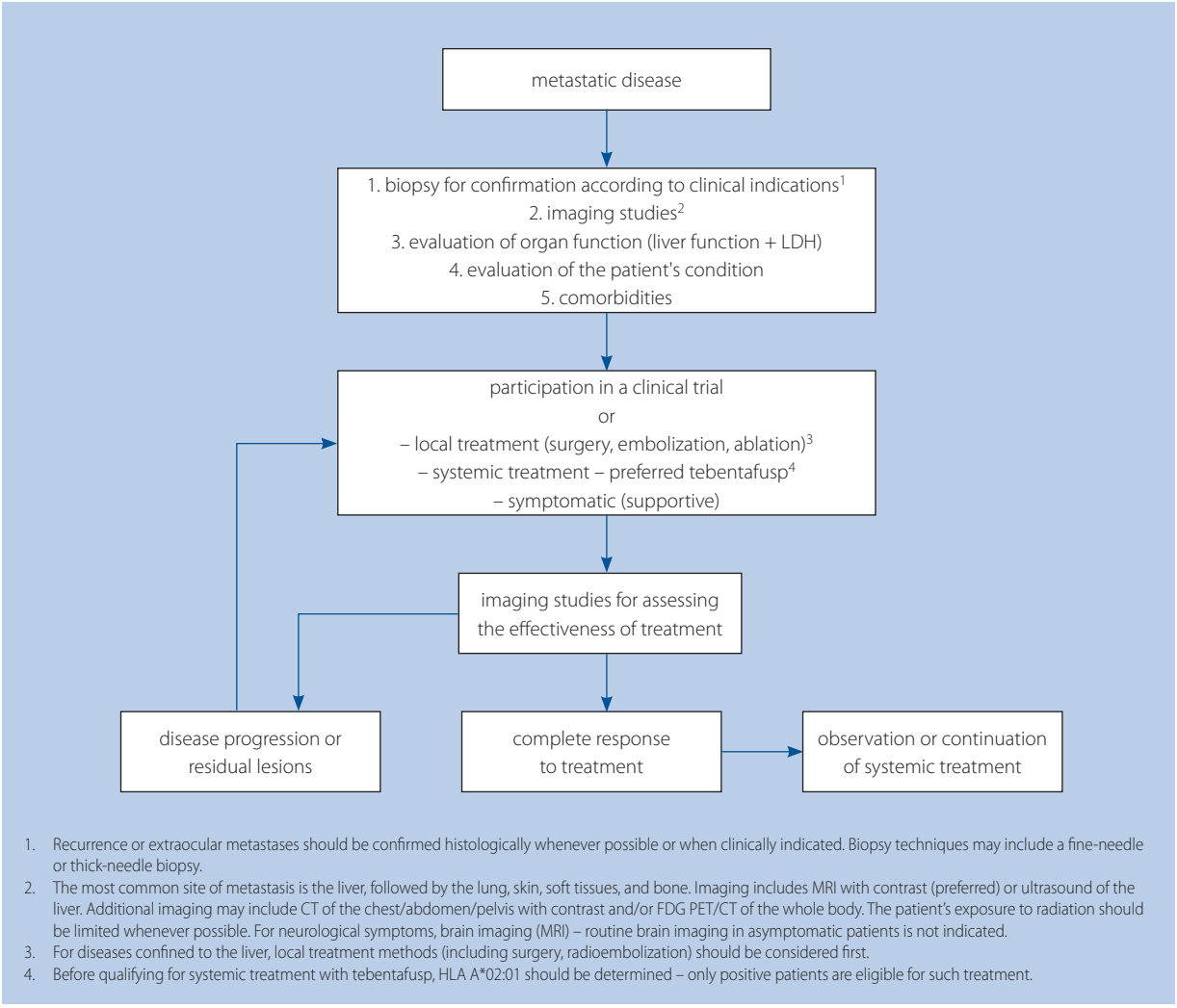
Thus, in view of the low quality of evidence, it is difficult to recommend surgical treatment in this group of patients. However, resection of liver metastases should be considered in a carefully selected group of patients in whom:

- a long survival period is anticipated,
- no extrahepatic lesions are found,
- there are technically radical resectable (R0) focal lesions.

In many studies, the median overall survival of these patients was more than 20 months after resection of metastases, and the rate of R0 resection ranged from 27% to 88%.

Undoubtedly, further randomized and prospective studies that include similar patient eligibility criteria for resection, treatment protocols and endpoints are needed and necessary. Their goal should be to compare results and establish recommendations for liver resection [21]. Current treatment options for ocular melanoma patients with liver metastases are surgical resection (provided single foci are present, which is rare), chemoembolization/radioembolization or thermoablation of liver metastases, and systemic treatment [2, 45] (III, A).

Clinical trials are attempting therapies that target the PKC--MAPK pathway, modifying epigenetic mechanisms (e.g., vorinostat) or immune checkpoint inhibitors (small effects have been observed in phase II trials mainly with the combination of nivolumab and ipilimumab) [46, 47]. So far, these studies have not yielded positive results [2, 48]. One exception is the use of tebentafusp (IMCgp100), a new bispecific molecule targeting T cells in the presence of HLA-002, which allows for a benefit in overall survival (OS) time both compared to historical data (phase II study [49] – median OS 16.8 months) and the active comparator (phase III study – 1-year OS rate 73% *vs.* 58%,



1. Recurrence or extraocular metastases should be confirmed histologically whenever possible or when clinically indicated. Biopsy techniques may include a fine-needle or thick-needle biopsy.
2. The most common site of metastasis is the liver, followed by the lung, skin, soft tissues, and bone. Imaging includes MRI with contrast (preferred) or ultrasound of the liver. Additional imaging may include CT of the chest/abdomen/pelvis with contrast and/or FDG PET/CT of the whole body. The patient's exposure to radiation should be limited whenever possible. For neurological symptoms, brain imaging (MRI) – routine brain imaging in asymptomatic patients is not indicated.
3. For diseases confined to the liver, local treatment methods (including surgery, radioembolization) should be considered first.
4. Before qualifying for systemic treatment with tebentafusp, HLA A*02:01 should be determined – only positive patients are eligible for such treatment.

Figure 2. Treatment algorithm for patients with metastatic ocular melanoma

HR 0.51 [50] (I, 2A). The drug was registered in the European Union in March 2022, but is not reimbursed in Poland.

Some difficulty remains in determining the duration of treatment with tebentafusp, as improved overall survival is also observed in the treatment group after disease progression. Continuation of therapy after progression should be considered with good treatment tolerance. After the first three doses of the drug, it is necessary to observe the patient in the hospital setting with regular monitoring of vital signs for 24 hours for potential complications, including cytokine release syndrome. Treatment should be carried out in centers that have experience in the use of immunotherapy and access to an intensive care unit. Patients should be informed about the symptoms and management of cytokine release syndrome.

Data on the efficacy of chemotherapy are limited, but its use may be considered in selected situations.

Observation and treatment of local complications

After treatment of uveal melanoma, the patient should be examined ophthalmologically every 3–6 months during the first 2 years, and once every 6–12 months thereafter. The examination should be aimed at detecting potential local recurrence or complications after therapy. After conservative treatment, it should include at least:

- evaluation of visual acuity,
- measurement of intraocular pressure,
- anterior segment examination in the slit lamp and fundus examination after pupil dilation,
- ultrasound examination,
- taking photographs and OCT.

On the other hand, after the enucleation procedure, the orbit should be examined (after removal of the epiprosthesis, the orbit should be viewed and palpated) and a follow-up MR examination of the orbit should be ordered once every 6–12 months [51, 52] (III, A). In cases of suspected extraocular infiltration, palpation of regional lymph nodes is also indicated.

As a result of conservative treatment, there is a risk of complications in the form of cataracts, secondary glaucoma, iris neovascularization, retinopathy (with maculopathy) and neuropathy. All of these complications should be treated,

Table VI. Principles of follow-up after local treatment of ocular melanoma

Risk group	Features of the risk group	Recommended management
ocular melanoma patients at low risk of distant metastasis	T1 feature and in case of known molecular abnormalities (disomy of chromosome 3, multiple copies of 6p, *EIF1AX* mutation)	imaging studies if indicated
ocular melanoma patients with intermediate risk of distant metastasis	T2 or T3 or with known molecular abnormalities (*SF3B1* mutation)	imaging studies every 6–12 months and if clinically indicated
ocular melanoma patients at high risk of distant metastasis	T4 or with known molecular abnormalities (chromosome 3 monosomy, multiple copies of 8q, *BAP1* mutation, PRAME expression)	Follow-up imaging every 3–6 months for 5 years, then every 6–12 months for up to 10 years, then if clinically indicated (physical or subjective symptoms)

but above all, they should be prevented. The best treatment for retinopathy, maculopathy and radiation neuropathy, as well as iris neovascularization, are intravitreal or anterior chamber injections of anti-VEGF preparations or steroids. In the case of anti-VEGF preparations, it is recommended to initially give 3 injections at an interval of 1–2 months (depending on the type of drug), and then depending on the clinical picture [53, 54] (III, A).

The patient should remain under follow-up after ophthalmic treatment so that possible metastases can be detected and treated. Imaging studies are recommended. If liver metastatic lesions are suspected, an MRI of the liver with contrast is recommended. It should be noted that even an MRI in some cases cannot determine the actual stage of the disease [52, 55] (III, A). Post-treatment follow-up regimens should be determined by assessing the risk of metastasis, as summarized in table VI.

Conjunctival melanoma

Conjunctival melanoma accounts for 0.25% of all melanomas and 5% of melanomas located within the eye. In recent years, there has been a significant increase in the incidence of this type of malignancy [56, 57]. Molecular aspects of the development of conjunctival melanoma include mutations of the *BRAF* and *NRAS* genes, quite different from those described in uveal melanoma [1] (III, 2A).

The vast majority i.e. 74% of conjunctival melanomas develop from primary acquired melanosis (PAM) with atypia, 7% from pre-existing nevus, and 19% arise de novo [56, 58] (III, 2A).

Local relapses occurs in 30–50% of cases within 5 years [59]. Metastasis develop in about 20–30% of patients at 10-year follow-up [56]. Factors associated with a worse prognosis are:

- location of the tumor outside the ocular conjunctiva,
- multinodular type of growth,
- rapid growth of the lesion,
- tumor thickness >2 mm,
- appearance of recurrence,
- incomplete excision,
- failure to use adjuvant therapy after excision [56, 60] (III, 2A).

The mainstay of treatment remains surgical resection of the tumor after prior occlusion of the feeding vessels, with a macroscopically preserved margin of healthy tissue, the size of which remains undetermined [56, 60] (III, 2A). Some recommend the use of cryoapplication of excision sites and the application of absolute alcohol swabs [56, 61] (IIIB). In very advanced cases, enucleation and exenteration are considered [56, 62, 63] (III, 2A).

Complementary treatment

1. Local chemotherapy:
- mitomycin C, the administration of which into the conjunctival sac is started 2 weeks after surgery [56, 64–69] – an unreimbursed recommendation with very limited clinical data (IV, 2B),
- interferon alfa-2b [56, 70, 71] (IV, 2B) – also not reimbursed with limited clinical data.

2. Radiation therapy:
- radiotherapy from external fields,
- local brachytherapy.

A sentinel node biopsy should be considered. However, it is important to remember that 50% of cases have distant metastasis without the presence of tumor cells in the regional lymph nodes [56, 72, 73] (III, 2B).

In the metastatic conjunctival melanoma, the same therapies as in advanced cutaneous melanoma are used [56] (III, 2A). Molecular testing is necessary to determine the mutation status within the *BRAF* gene.

The patient should remain under constant oncologic and ophthalmologic follow-up after treatment for conjunctival melanoma (photographic documentation of the local condition each time is important; remember to check the conjunctiva after eyelid inversion).

Conflicts of interest:

P. Rutkowski received a grant from Pfizer, lecture fees from Novartis, Pierre Fabre, Eli Lilly, Merck, Sanofi, MSD, and BMS, and participation in MSD, Pierre Fabre, Sanofi, Merck, Novartis, and BMS advisory meetings. Medison Pharma. M. Dudzisz-Śledź received honoraria for lectures from Pierre Fabre, Merck KGaA, MSD, Sanofi Aventis, Novartis, Medison Pharma, and BMS – for participation in advisory meetings from Merck KGaA and Novartis, and funding for participation in conferences from Novartis. T. Świtaj received honoraria for lectures from

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Dedifferentiated liposarcoma of the retroperitoneum presenting as an ossified lesion

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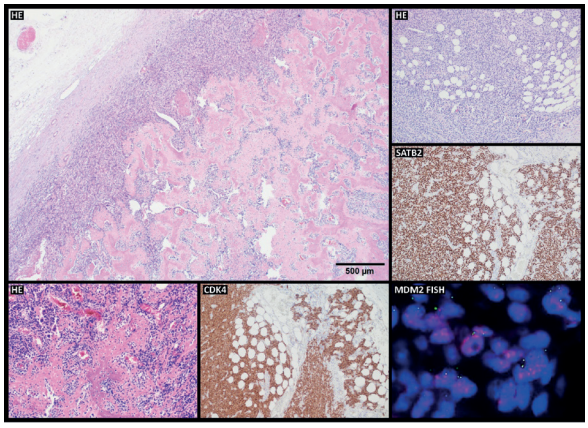

HE – hematoxylin & eosin

Figure. 1. DDLS with osteosarcomatous differentiation

Dedifferentiated liposarcoma (DDLS) develops in patients with atypical lipomatous tumors / well-differentiated liposarcomas. It may be present in the first resection but more often develops when well-differentiated liposarcoma recurs. The most frequent localization is retroperitoneum. In advanced disease, a well-differentiated component may be obscured and difficult to find. The dedifferentiated part most frequently consists of high-grade sarcoma of no special type [1]. Occasionally malignant heterogeneous elements with chondroid, osteoid, or rhabdoid differentiation may be present.

Here we report a rare case of a 72-year-old male patient who presented with an abdominal mass. He underwent a right hemicolectomy and right nephrectomy. On gross examination, the tumor measuring 21 x 17 x 10 cm demonstrated a lipomatous component and an abundant non-lipomatous component with extensive osseous areas, requiring decalcification. Microscopically, a well-differentiated liposarcoma with an abrupt transition to a high-grade sarcoma was present. Within the osseous component, osteosarcomatous areas with obvious osteoid and atypical lamellar bone formation were found (fig. 1). The MDM2 and CDK4 expression by immunohistochemistry and fluorescence *in situ* hybridization (FISH) are supporting tools used in pathological differential diagnosis; a positive reaction with SATB2 is characteristic of osteosarcomatous differentiation. DDLS represent an aggressive variant of liposarcomas. The sarcomatous component dictates the outcome and biological behavior. DDLS recurs locally and shows distant metastases in 40–83% and 15–30% of all cases. The findings of atypical heterogenous components is crucial as it drives the prognosis.

In conclusion, the "osteosarcoma" – resembling DDLS is a rare phenomenon [2]. The radiological image may be confusing, so we emphasize that careful sampling of the whole lesion accompanied by pathological and molecular examination is needed for correct diagnosis.

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Adrenal carcinoma in a potential organ donor: a case of "unacceptable" oncological risk for transplantation

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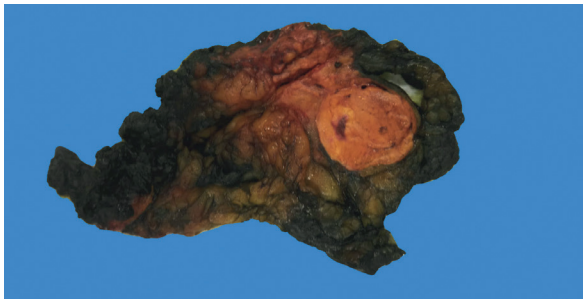

Figure 1. Macroscopic view of the adrenal lesion. A roundish, yellow-ochre mass of 38 g, 2.7 cm in maximum diameter, with haemorrhagic-necrotic micro-foci is observed

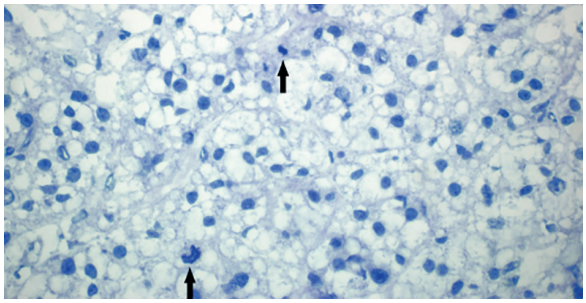

Figure 2. Microphotograph of frozen histological section (toluidine blue staining; microscopic magnification: 40x), showing the presence of scattered mitoses in the neoplastic cells (arrows)

Adrenal carcinoma is a rare aggressive neoplasm originating from the adrenal cortex, with high risk of lymph node and blood metastases [1], that exclude the transplantability of organs by leading to an "unacceptable" oncological risk for the recipient. The images refer to a right adrenal neoplasm accidentally discovered in a 77-year-old brain-dead male who was a candidate to become an organ donor. The adrenal gland was sent for fast histopathological examination (fig. 1), to quickly determine whether or not to proceed with the transplantation. An examination was performed on multiple frozen sections. Weiss histological criteria [2] were applied: diffuse architecture greater than ⅓ of the lesion: no; clear cell tumour component ≤ to 25%: no; nuclear G3/G4 (Fuhrman's grading): yes; mitotic count >5/50 high power field (HPF): yes (7 mitoses/50 HPF), (fig. 2); atypical mitotic figures: yes; necrosis: yes; venous invasion: no; sinusoidal invasion: no; capsular invasion: yes. Findings consistent with adrenal cortical neoplasia showing at least 3 positive criteria, suggesting a malignant behaviour. This histological report stopped transplantation procedures. Weiss' criteria were also applied on formalin-fixed and paraffin-embedded histological sections, confirming it to be adrenal carcinoma and demonstrating the possible applicability of these criteria even on frozen histological sections.

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