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ORIGINAL ARTICLE

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Alternative therapies in cancer treatment — hope or threat? (qualitative research)

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ABSTRACT

Introduction. Oncological patients, subject to strong emotions, may find it difficult to critically evaluate the information they receive on the effectiveness of the treatment offered, and therefore are susceptible to alternative methods, often abandoning the therapy recommended by a physician. The aim of this study was to analyze the way information is communicated to cancer patients by people promoting an alternative therapy, the use of intravenous infusions of vitamin C.

Material and methods. The research technique consisted of structured individual interviews conducted with Jerzy Zięba M.Eng. — author of the books: Hidden Therapies "What a doctor won't tell you" part. 1 and 2, and with Dr Agnieszka Jagiełło-Gruszfeld — a clinician from the Warsaw Oncology Centre. The study was expanded by a review of the scientific literature on vitamin C therapy and factors influencing the behavior of patients with diagnosed cancer, including the sources of information they use.

Results. There is a significant disproportion in the assessment of the effectiveness of vitamin C treatment made by people promoting alternative medicine and clinicians. Visible differences relate to the level of objectivity, legibility, as well as the frequency of information provided about unconventional cancer treatment methods.

Conclusions. The obtained results indicate the need to increase the availability of information provided directly by physicians about the dangers of inappropriate treatments for cancer patients. In diagnostic and treatment procedures it is important to be aware of the consequences of a specific method and the quality of the conversation between the physician and the patient about alternative therapies, as it may determine the patient's decision to choose a treatment.

Key words: alternative medicine, alternative therapies, vitamin C, oncology, cancer patients, health information quality, decision making, choice of treatment

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Introduction

In recent years increased activity has been observed in the media of social movements questioning the use of established methods of treating serious diseases, including cancer. The opponents stress the adverse effects of chemotherapy, accuse pharmaceutical firms of a businesslike approach to the drugs they sell and physicians of the lack of confidence in alternative methods of treatment and lack of familiarity with the results of clinical trials of unconventional treatment methods [1].

Oncological patients, subject to strong emotions because of their serious disease, may find it difficult to critically evaluate the information they receive. They often refuse the treatment recommended by the physicians [2]. Instead, they tend to use alternative methods [3–5] which are promoted by persons without a medical education; this can lead to the deterioration of the patients' health [6].

Material and methods

Characteristics of cancer patients — psychological considerations

Patients with a diagnosis of cancer are subject to strong stress. Often the most difficult moment for the patients is not the moment of the diagnosis but a recurrence of the disease. Newly diagnosed patients hope that their treatment will be effective, but if it is not successful they are subject to a profound frustration [7]. Moreover, at that time the patients already feel the negative effects of the treatment (e.g. weight loss, weakness, hair loss). The patients must seriously face the fact that their plans for the future should be reassessed. Taking these aspects into consideration is seems understandable that cancer patients are not always capable of objectively evaluating the information that they receive about their state of health and the proposed treatment methods. Thus they can be manipulated more easily than healthy persons by presenting as true information which has limited support in the scientific literature. When people have strong emotions their rational thinking is limited, and cancer patients, as a rule, feel endangered [8].

Results

Sources of information for cancer patients about their disease

Patients with a cancer diagnosis can currently participate in the decision-making process related to their treatment; this is due to the increasing access to information about cancer and the available therapeutic options. This is particularly easy for younger and better-educated persons with higher incomes [9]. Persons giving advice related to health should be aware of the fact that the patients can check the obtained information in the available sources of knowledge and that they will obtain information from all sources available to them. Published results of the ACCESS trial [9], conducted among cancer patients, indicate that 69% reported obtaining information from other sources than the medical personnel. Additionally, 60% admitted that at least one source other than the medical personnel affected their decision concerning the mode of treatment. Such sources affecting the therapeutic decision can for example be the family (42.7%) or the internet (31.9%). Detailed data about the sources of information and their effects on the decisions concerning the treatment of cancer patients is presented in Figure 1 below [9].

It is worth pointing out the effects of the internet on therapeutic decisions. Information obtained from the internet affected the decisions of 13.3% of patients — the percentage was higher in persons under 55 years old — 21%, with better education (24.8%) and who were more affluent (31.1%). In the same groups, scientific literature affected the therapeutic decisions in 13.8%, 23.1% and 23.4% of the cases.

According to the most recent scientific reports [10] 96% of cancer patients participating in phase I clinical trials rely on their physician as the main source of information and 89% of patients use the internet to obtain information on subjects related to their disease [10].

The quality of patient-physician communication is important for the choice of therapy by the cancer patient. Research has shown that criticizing patients for using alternative therapies or poor communication and lack of empathy may be the cause of a decision to use alternative therapies or even of refusing the treatment recommended by the physicians. On the other hand, good communication may lead to undergoing alternative therapy as a complementary method but not instead of conventional treatment [2, 11].

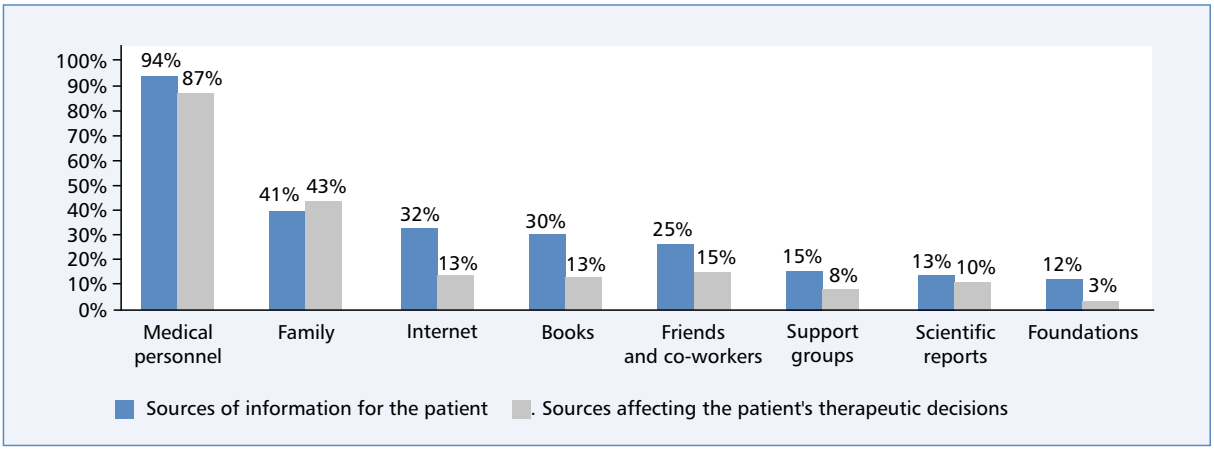

Figure 1. Sources of information for cancer patients and their effects on therapeutic decisions — ACCESS trial [9]

The information available on professional portals dedicated to cancer patients (e.g. https://www.cancer.gov/about-cancer/treatment/types http://www.nfz.gov.pl/dla-pacjenta/pakiet-onkologiczny/ http://www.sarcoma.pl/dla-chorych-i-opiekunow/abc-pacjenta-onkologicznego/ http://www.onkonet.pl/) is sufficient both with respect to quantity and quality. However, patients instead of using reliable www pages may obtain information from non-scientific portals (e.g. from youtube). Such dubious information can for example be found on the channel of Jerzy Zięba. He provides information about various types of alternative therapies od common diseases (including cancer). It should be noted that his channel has over 113 000 subscriptions whereas for comparison that of the Polish Oncological Society (PTO) does not have a single one. Moreover, Jerzy Zięba's films on anti-cancer treatment get 100,000 to 300,000 viewers while this is slightly over 500 persons for the PTO channel (by May 17, 2019).

Discussion

Alternative treatments — different viewpoints

According to the promoter of alternative therapies — Jerzy Zięba, author of the books: *Ukryte Terapie „Czego ci lekarz nie powie" cz. 1 i 2.* (*Hidden therapies — what the doctor won't tell you — part 1 and 2*) — the cause of cancer is the malfunctioning of the immune system. Therefore to cure cancer, its cause must be addressed – by increasing immunity. At the same time, Jerzy Zięba notes that chemo- and radiotherapy destroy the immune system which makes using natural therapies more difficult. According to Jerzy Zięba, anti-cancer treatment – especially in cases for which according to conventional medicine the chances of survival are small and only palliative care is used – should be based on intravenous infusions of vitamin C, which — according to him — should bring good results and allow to save the patients. In his statements, he refers to both scientific literature and reports from patients, who have described to him cases of curing a neoplasm by using vitamin C. However, he omits the fact that papers about the effectiveness of vitamin C are not unequivocal. According to the latest meta-analysis of clinical trials [12], no improvement in overall survival or in any other measurement of advanced cancer were observed in persons who received vitamin C infusions [12]. Jerzy Zięba is critical in respect to medical authorities, who doubt the treatment methods described by him: „(…) Polish physicians, including professors of medicine, who are my most frequent attackers, (…) do not understand the mechanisms of vitamin C action, and only comment on it because they are medical doctors or professors and that allows them to speak complete nonsense".

The fact that Jerzy Zięba refers to scientific research (a socio-technical method: a symbol of authority) [13], while at the same time undermining the knowledge of physicians often leads to patients abandoning conventional treatment for unconventional therapies.

Such cases have been observed by Dr Agnieszka Jagiełło-Gruszfeld M.D. Ph.D. from the Clinic of Breast Cancer and Reconstructive Surgery of the Oncology Center: "Patients often come to us at a moment when such therapy proved to be unsuccessful. The patient after his cancer diagnosis disappeared, for example for a year, and returned with much more advanced cancer. During that year he had used unconventional treatment methods. It makes the doctors angry and irritated. This should not be transferred to the patient, but one would like to say — you got what you wanted. We cannot do that, of course, but we have to deal with our feelings".

Dr Gruszfeld analyzed the literature concerning the effectiveness of alternative therapy in cancer patients. She states unequivocally: "I have become familiar with the literature concerning this form of therapy in order to be able to discuss it with patients. Of course, I am referring to typically medical literature, that is published in reliable, international journals. On the basis of this literature, I must, unfortunately, say that therapy with vitamin C is not a method whose effectiveness is in any way documented. Over a dozen trials have been performed with randomization of various groups of patients most of whom had advanced cancer. In some of these trials the patients received conventional therapy and additionally vitamin C or placebo. In some trials — even with patients with extremely advanced cancer — they received vitamin C or placebo. Practically, there were no statistically significant differences between these two groups".

The opinion of Dr Gruszfeld is confirmed by the most recent meta-analysis of clinical trials using vitamin C in cancer patients [12]. It encompassed 19 trials from the years 1974–2018. In most of them, vitamin C was not the main treatment but only an addition to other preparations. Eight trials used vitamin C intravenously. In another 8 oral supplementations was used simultaneously with intravenous administration or after it. In 3 trials only oral vitamin C was used. Publications about the trials concerned the effects of vitamin C on:

— Patient survival (10 papers);
— Response to treatment (9 papers);
— Quality of life (7 papers);
— Safety of the treatment (14 papers).

In none of the trials was the process of patient selection and randomization described in detail which negatively affects the evaluation of their quality. Of 10 trials evaluating patient survival only in one trial with randomization was a significant effect of intravenously administered vitamin C on patient survival observed. In 6 of 9 trials measuring the ef-

fects of vitamin C on the response to treatment, the observed effects were positive. However, the authors of the meta-analysis stress that the criteria of effect evaluation were highly subjective and with the exception of one trial not confirmed by pathomorphological analyses.

Conclusions

It is difficult for patients with a cancer diagnosis to objectively evaluate the soundness of the information appearing in the media on the safety and effectiveness of anti-cancer treatment. According to both Dr Agnieszka Jagiełło-Gruszfeld and Jerzy Zięba, M.Eng., cancer patients are subject to strong emotions which affect their decisions pertaining to the choice of therapy. Fundamental differences can, however, be observed in the evaluation of therapy effectiveness by the interviewed person. Dr Agnieszka Jagiełło-Gruszfeld bases her position on the results of clinical trial meta-analyses — scientific evidence of the highest level, whereas Jerzy Zięba bases his opinions on theoretical premises concerning the antioxidant activity of vitamin C described in the medical literature. He also supports his statements by citing patient testimonials. At the same time, he ignores reliable scientific evidence which does not confirm his assumptions. He draws far-reaching conclusions on the basis of dubious premises.

It is worthwhile to point out the existence of considerable asymmetry in the communication with cancer patients on the internet by medical professionals [6, 14] — in particular physicians and pharmacists — and by medical pseudoauthorities. The noted disproportions concern the level, objectivity of the information and the frequency and form of its transmission. Reliable reports from clinical trials (such as scientific papers) which could be easily understandable by people without a medical education are less accessible and less common. There is, however, easy access to information negating professional reports, and it is presented in simple, understandable words. An important step in the direction of increasing the awareness of patients about possible risks and consequences of inappropriate cancer therapies would be a more intensified transfer of information directly from the physicians. Otherwise, the number of people who decide to abandon therapy based on scientific data (EBM, evidence-based medicine) for treatment with unproven effectiveness may continue to grow.

In diagnostic and therapeutic procedures and education of physicians, attention should be paid to better awareness of the potential positive and negative effects of doctor-patient communication which in particular concerns the question of alternative therapies.

Conflict of interest

Authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

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Twist expression and content of tumour-associated macrophages in endometrial carcinoma

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ABSTRACT

Introduction. This study aimed to relations between the expression of the Twist transcription factor, the content of tumour-associated macrophages (TAMs), and clinicopathological indicators of tumour progression in patients with stages I–II and III endometrial cancer (EC).

Material and methods. Surgical specimen from 45 patients with endometrioid carcinoma of the endometrium (ECE) (average age — 60.1 ± 2.3 y.o.) were investigated using morphological, immunohistochemical, flow cytofluorometry and statistical methods.

Results. Nuclear expression of Twist was determined in 47.1% of ECE samples with individual fluctuations in the range of 6.3–43.0%, which was 16.6 ± 2.9% on average. Twist expression in G3 endometrial tumours and those with deep invasion into the myometrium tended to increase (21.4 ± 4.3 and 18.0 ± 3.5%, respectively) as compared with the expression of this marker in G2-tumors and the ones, invading < 1/2 of the myometrium (13.2 ± 3.3 and 16.7 ± 3.9%, respectively). Positive expression of Twist in ECE was associated with reduced expression of E-cadherin (44.3 ± 3.8%) and increased expression of vimentin (33.9 ± 3.4%), the content of TAMs in the stromal component of the tumour (30.2 ± 3.7 cells/f.v.), and microvessels density (MVD) (46.5 ± 5.4 vessels/mm^2) as compared with the same indices for ECE with negative expression of Twist (61.4 ± 4.7%, $p < 0.05$; 14.6 ± 3.1%, $p < 0.05$; 18.0 ± 2.4 cells/f.v., $p < 0.05$ and 34.3 ± 4.7 vessels/mm^2, respectively).

Conclusions. Higher content of stromal TAMs and higher MVD are observed in Twist-positive endometrial carcinomas as compared with the same indices in Twist-negative neoplasms which are associated with different morphological specificities of invasive processes in the endometrium.

Key words: endometrioid carcinoma of endometrium, Twist, tumour-associated macrophages (CD163), microvessels density (CD31)

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Introduction

It is known that the progression of a malignant neoplasm results from the loss of genetic control over the processes of differentiation, proliferation, and apoptosis in tumour cells and molecular changes in the tumour microenvironment, which is characterized by higher growth of the tumour, neoangiogenesis, the invasion of the tumour into adjacent tissues, and metastases [1]. It was demonstrated that one of the reasons for tumour invasion and metastases is the epithelial-mesenchymal transition (EMT) due to which epithelial cells may get transformed into the cells with mesenchymal-like phenotype [2]. During carcinogenesis, EMT may be present when several signalling pathways are activated, including such transcription factors as Twist, Snail, Slug, and Zeb1 [3, 4].

It was determined that the Twist transcription factor promotes the distribution of epithelial cells not only by binding to *CDH1* gene promoter and inhibiting the

expression of E-cadherin [5]. Twist may also trigger neoplastic progression by inhibiting p53 ("wild type"). Shown that Twist1 binds p53 C terminus through the Twist box. This interaction hinders key posttranslational modifications of p53 and facilitates its MDM2-mediated degradation [6]. It has recently been demonstrated that the Twist transcription factor interacts with oncoprotein c-Myc in a tumour, thus promoting reprogramming of the tumour microenvironment [7]. It was found that Twist and c-Myc secrete cytokines CCL2 and IL13 which conduct the polarization of type I macrophages into M2-macrophages and recruit them to the tumour. It means that Twist and c-Myc may create conditions for metastasis in the neoplasm, as, according to current data, M2-macrophages are among the leading components of the tumour microenvironment to secrete different factors, stimulating the proliferation of tumour cells, enhancing their migration ability, and activating angiogenic processes [8–12]. M2-macrophages produce chemokine CXCL12 and hepatocyte growth factor (HGF), which bind to their receptors (CXCR4 and c-MET) on tumour cells thus causing the motility of the latter [10].

It is believed that the availability of a high number of tumour-associated macrophages (TAMs) in patients with solid tumours is an unfavourable prognostic marker, associated with the aggravated clinical course [11–13]. For instance, Jackute et al. [12] demonstrated that high content of $CD163^+$-macrophages in a stromal component of the tumour was related to the decline in the survival rate of patients with non-small-cell lung cancer.

The same is true regarding endometrial cancer (EC), one of the most common gynaecological malignant neoplasms among women both in Ukraine and globally [14]. Many authors note that the clinical course of EC is associated with specific morphological and molecular traits of neoplasms and the specificities of the tumour microenvironment [3, 4, 15]. However, the issue of the integral impact of molecular changes in tumour cells and components of tumour microenvironment with immunosuppressive properties in the formation of some invasive potential of malignant endometrial tumours is studied insufficiently.

Taking the abovementioned into consideration, the work aimed to study the relations between the expression of EMT marker — Twist transcription factor, the content of TAMs, and clinicopathological indicators of tumour progression in patients with EC stages I–II and III.

Material and methods

The samples of surgical material of 45 patients with EC, stages I–III, aged 32 to 78 y.o. (average age — 60.1 ± 2.3 y.o.). All patients were treated at the Oncogynaecology department of the National Cancer Institute, Ministry of Health of Ukraine in 2014–2018 (the head of the research and experimental unit of the Oncogynaecology department — Professor V.S. Svintsitsky, Doctor of Science in Medicine). They did not have preoperative therapy and gave their informed consent to the use of their biological material for scientific studies. During the study, all the required ethical standards were complied with according to the universally accepted international requirements of the Declaration of Helsinki 2008.

The final morphological diagnosis was verified by examination of histological preparations, stained with haematoxylin and eosin (H & E).

The immunohistochemical (IHC) determination of biomolecular markers was done using the deparaffinized sections of endometrial tumours. Twist, the marker of epithelial-mesenchymal transition, was determined using the polyclonal antibody Twist1/Twist2 (Thermo Fisher Scientific, USA), catalogue No. PA5-78211. The expression of other markers was determined with monoclonal antibodies (McAbs): M2-macrophages were detected using McAb to CD163 (the one, detecting M2-macrophages [13]), the clone of Mob460-05 and *de novo* microvessels were detected by the expression of a vascular endothelium marker — antigen CD31, McAb to CD31, clone EP78 (Diagnostic BioSystems, USA).

The mentioned proteins were detected with the visualizing PolyVue HRP/DAB Detection System (Diagnostic BioSystems, USA). Cell nuclei were additionally stained with Mayer's haematoxylin.

The results of the IHC reaction were assessed by the semi-quantitative method. About 700–1,000 cells were analysed in each preparation, separately in glandular and solid structures, to determine Twist protein product. The results of IHC reaction were assessed by the semi-quantitative method, by counting the number of stained cells — the labelling index (LI, %). Usually, both cytoplasmic and nuclear localization of this protein were observed, but, since Twist is a transcription factor, only tumour cells with nuclear localization of the marker were considered.

The data obtained were compared with the results of the previous studies, in which the authors determined the expression of EMT markers in these very cases of ECE [16–18].

In addition, the authors counted the number of positively stained $CD163^+$-macrophages (TAMs) — the number of cells per one field of vision (cells/f.v.) of the microscope, analysing them in 10 fields of vision with ×400 magnification. Both the total number of TAMs and their separate amounts in intratumoural and stromal components were determined.

To determine the microvessels density (MVD) in endometrial tumours, the number of vessels in 10 fields of vision of the microscope was counted at ×100 magnification. The area of one field of vision was limited with

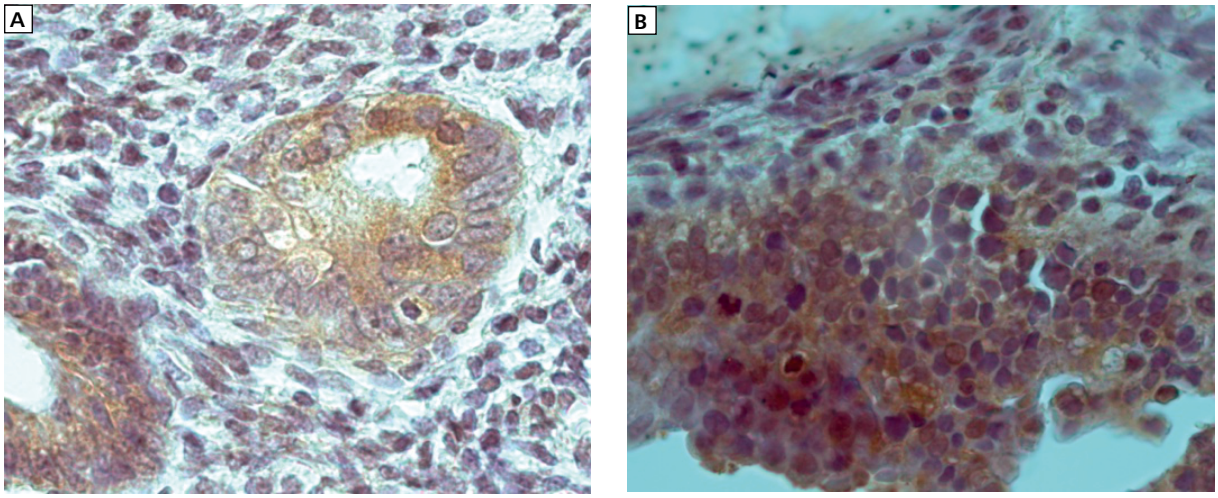

Figure 1. The expression of Twist in the glandular (**A**) and solid (**B**) areas of the moderately differentiated endometrial carcinoma (IHC method, additional staining with Mayer's haematoxylin); ×1,000 magnification, oil immersion

the measuring square grid (the side of 1.25 mm). MVD (number of vessels/mm^2) was defined by the formula: MVD = n: 1.56 vessels/mm^2, where (n) — the average number of vessels per one field of vision; 1.56.mm^2 — the area of one field of vision. The criteria for assessing the mentioned indices were as follows: the expression of Twist LI < 1.0% was considered negative; the values of M2-macrophages and MVD under the median (Me) were considered low, and the ones above or equal to Me were considered high.

The proliferative activity of the investigated endometrial carcinomas was determined by the proliferation index (PI, %) using flow cytofluorometry [19]. The studies were conducted in the flow cytofluorometer EPICS-XL (Beckman Coulter, USA).

The statistical processing of the data was conducted in Statistica 8.0 (StatSoft, Inc.) using the non-parametric Mann-Whitney test and Spearman's correlation. Here $p < 0.05$ was accepted as a reliable significance level.

Results

The morphological analysis of neoplasms demonstrated that the tumours under investigation were endometrioid carcinomas of the endometrium (ECE) of different differentiation degrees: 18 cases (40.0%) of moderate (G2) and 27 cases (60.0%) of low differentiation degree (G3). 16 (35.6%) patients had tumours, which invaded < 1/2 myometrium and 29 (64.4%) cases had tumours with deep (> 1/2) invasion of the myometrium. Most patients, 24 (53.3%), had stage I tumour progression, 13 (28.9%) — stage II, and 8 (17.8%) patients — stage III. All tumours of patients with stage III tumour progression were of low differentiation degree and invaded the myometrium deeply.

Most investigated ECE were highly proliferating tumours with the average LI value of 31.0 ± 3.1% (the range of 13.4–69.2%, Me = 29.1%).

The results of the IHC investigation demonstrated that positive expression of Twist transcription factor was mostly manifested in the cytoplasm, while in a smaller number of tumours it was found in the nucleus (Fig. 1).

The nuclear expression of this marker was determined in 47.1% of ECE samples with individual fluctuations in the range of 6.3–43.0%, which was 16.6 ± 2.9% on average. The tumours of 69.5% of patients with stage I–II EC and 50.0% tumours of patients with stage III of tumour progression were positive in terms of the expression of this protein. It was determined that positive expression of Twist was associated with the decreased expression of E-cadherin and the increased expression of vimentin as compared with these indices for ECE with negative expression of Twist [16, 18] (Tab. 1).

At the same time, neither complete absence of E-cadherin expression was found in Twist-positive endometrial carcinomas nor the complete absence of vimentin expression — in Twist-negative ECE. It allows for the assumption that most tumour cells of the endometrium are characterized by hybrid phenotype (with the expression of both epithelial and mesenchymal markers) [20]. Positive expression of vimentin in some Twist-negative ECE may probably result from the activation of other transcription factors (Snail, Slug, and Zeb) or reduced functioning of other adhesive proteins which promotes the occurrence of EMT features in tumour cells of the endometrium.

While determining the connection between Twist expression and the indices of endometrial carcinoma progression, it was found that in low differentiated endometrial carcinomas and the ones with a deep invasion of the tumour into myometrium the expression of Twist

Table 1. The comparison of the expression of epithelial-mesenchymal transition markers and Twist transcription factor in tumour cells of the endometrium

Molecular markers of EMT	Expression of EMT markers, M ± m, %	
	Twist-positive ECE	Twist-negative ECE
E-cadherin	44.3 ± 3.8	61.4 ± 4.7*
β-catenin	78.6 ± 4.2	86.3 ± 5.4
Vimentin	33.9 ± 3.4	14.6 ± 3.1*

*p < 0.05 as compared with the expression of the corresponding marker in tumours with positive expression of Twist; EMT — epithelial-mesenchymal transition; ECE — endometrioid carcinoma of the endometrium

Table 2. The expression of Twist in endometrioid carcinoma of the endometrium of different differentiation degree, depth of tumour invasion into the myometrium and the stage of tumour progression

Investigated parameters of ECE	Twist expression, LI%		
	Glands	Solid areas	Total
Degree of tumour differentiation			
G2	3.8 ± 2.2	9.4 ± 2.4	13.2 ± 3.3
G3	8.2 ± 2.9	13.2 ± 3.6	21.4 ± 4.3
Depth of tumour invasion into the myometrium			
< 1/2	8.4 ± 2.9	8.3 ± 2.9	16.7 ± 3.9
> 1/2	7.0 ± 2.3	11.0 ± 3.0	18.0 ± 3.5
Stage of tumour progression			
Ia + Ib	6.1 ± 1.9	8.7 ± 2.9	14.8 ± 3.3
Ic	2.2 ± 0.8	9.5 ± 3.0	11.7 ± 3.2
II	2.4 ± 0.9	10.0 ± 3.1	12.4 ± 3.3
III	2.6 ± 1.1	7.1 ± 2.2	9.7 ± 2.9

ECE — endometrioid carcinoma of the endometrium; LI — labelling index

tended to increase as compared with the expression of this marker in G2-tumors and the ones, invading < 1/2 of the myometrium. It was lower in the tumours of patients with stage III disease (9.7 ± 2.8%) as compared with the tumours of patients with stage I–II (13.7 ± 3.5%). It should be noted that the increase in Twist expression occurred mainly in solid areas of tumours, while in glandular structures the changes were ambiguous (Tab. 2).

Some authors believe that it may be conditioned by the fact that solid structures are located in the areas with more evident hypoxia which promotes the occurrence of EMT traits in tumour cells.

As demonstrated using breast cancer tumours, the expression of the Twist transcription factor in tubular and trabecular structures, which did not lose their contact with the surrounding stroma, was observed only in 5.0–8.0% of tumours, while in the alveolar and solid areas, characterized by the accumulation of tumour cells and limited contact with stroma, the number of tumours with Twist expression increased up to 18.0–19.0% respectively [21].

Taking into consideration the scientific data about the role of Twist in the polarization of M1-macrophages into M2-macrophages, which promotes the occurrence of immunosuppressive, proangiogenic, and invasive properties in tumours [3, 7, 9], the following stage of this study was to determine the relationship between Twist expression, the content of TAMs, MVD, and other indices of ECE progression.

The results of IHC studies demonstrated that ECE were notable for a considerable variability by the number of such components of microenvironment as the content ($CD163^+$-macrophages) of TAMs and the number of *de novo* microvessels. It was determined that individual fluctuations in TAMs content in ECE were in the range of 7.8–81.5 cells/f.v., which on average was 32.9 ± 2.9 cells/f.v. (Fig. 2).

Individual fluctuations of MVD in the ECE under investigation were in the range of 9.2–88.5 vessels/mm^2, which on average was 35.5 ± 4.3 vessels/mm^2 (Fig. 3).

It was demonstrated that the number of TAMs in the malignant endometrial tumours was related to their localization. The number of intratumoural TAMs was almost twice smaller (12.7 ± 1.4 cells/f.v.) than their number in the stromal component of neoplasms (20.3 ± 2.2 cells/f.v., p < 0.05).

We found the relationship between the content of TAMs and MVD and the expression of the Twist transcription factor in ECE. A reliable increase in TAMs content in the stromal component of endometrial carcinomas and the increase in MVD (at the tendency level)

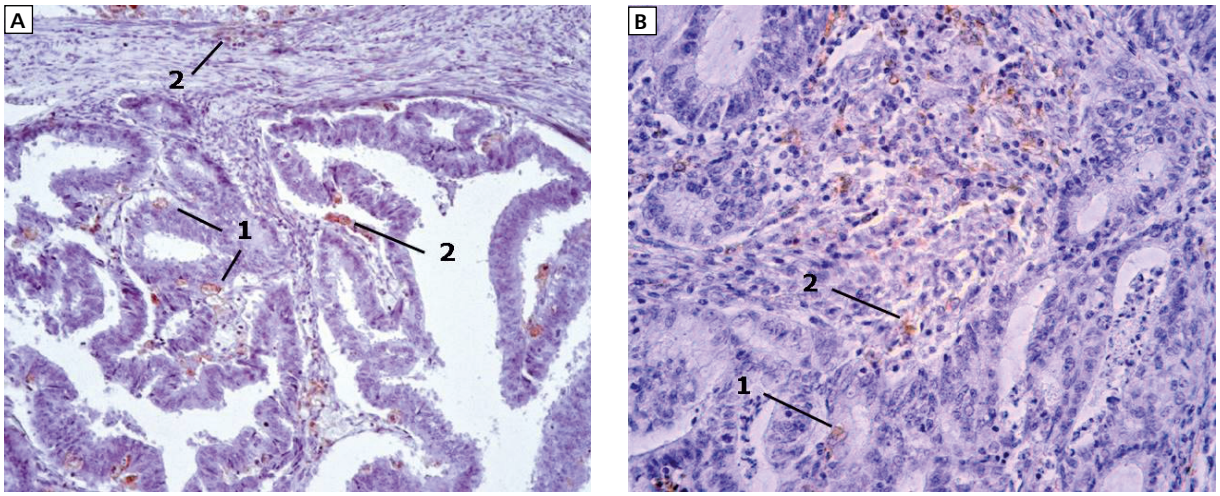

Figure 2. Tumour-associated macrophages (TAMs) in moderately differentiated endometrial carcinoma: 1 — intratumoural TAMs; 2 — stromal TAMs (IHC method, additional staining with Mayer's haematoxylin); Magnification: **A**. ×200; **B**. ×400

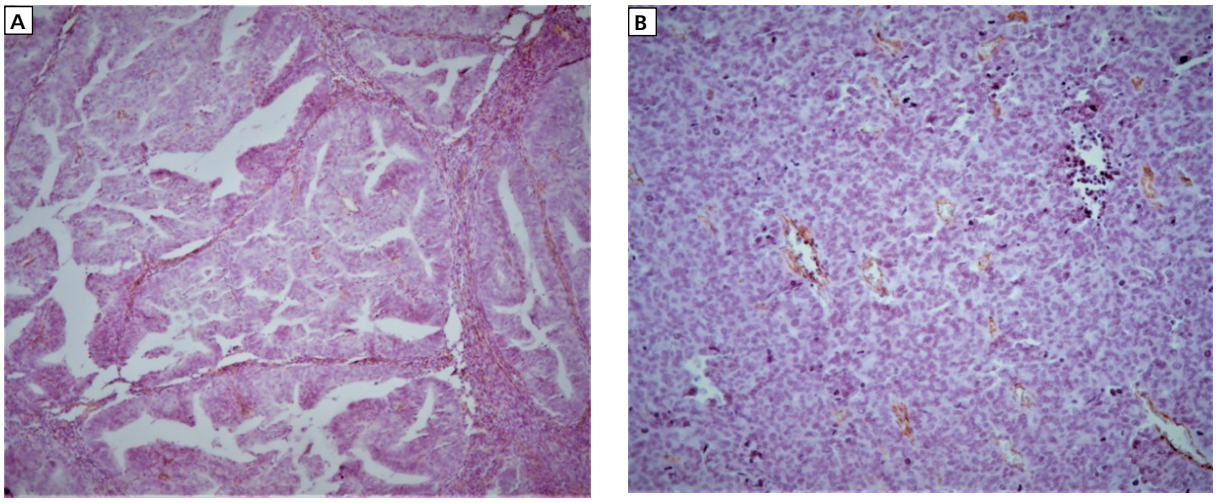

Figure 3. The microvessels (**A**) in moderately and (**B**) low differentiated endometrial carcinoma (IHC method, additional staining with Mayer's haematoxylin); Magnification: **A**. ×100; **B**. ×200

in Twist-positive ECE was demonstrated as compared with the number of these indices in Twist-negative endometrial carcinomas (Tab. 3).

At the same time, it was determined that the number of TAMs and MVD in ECE fluctuated depending on such indices of tumour progression as high proliferative potential, low degree of differentiation, deep invasion of a tumour into the myometrium, and the stage of tumour progression.

For instance, highly proliferating endometrial carcinomas were characterized by a higher content of intratumoural TAMs (15.7 ± 2.1 cells/f.v.) as compared with their number in ECE with IP < Me (10.0 ± 1.3 cells/f.v., $p < 0.05$). The number of intratumoural TAMs was also increasing in G3-tumors (14.3 ± 1.9 cells/f.v.) and in the tumours which deeply invaded the myometrium (14.3 ± 1.8 cells/f.v.) as compared with their content in G2-tumors and the tumours with the invasion of <1/2 myometrium (11.7 ± 2.1 and 9.1 ± 1.2 cells/f.v., $p < 0.05$ respectively). The content of TAMs in stroma also tended to increase in ECE with IP>Me and with a low degree of differentiation and increased reliably in the tumours which deeply invaded the myometrium as compared with ECE which had IP<Me, a moderate differentiation degree and invaded less than 1/2 of the myometrium (Tab. 4).

MVD had similar changes: it was reliably higher in highly proliferating, low differentiated, and deeply invading endometrial carcinomas as compared with the tumours of IP < Me, in G2-tumors and the ones with the invasion of < 1/2 of the myometrium. A correlative

Table 3. The content of tumour-associated macrophages and microvessels density in Twist-positive and Twist-negative endometrial carcinomas

Investigated parameters	Twist-positive ECE	Twist-negative ECE
Number of TAMs		
Intratumoural	15.3 ± 1.9 cells/f.v.	15.3 ± 2.1 cells/f.v.
In stroma	30.2 ± 3.7 cells/f.v.*	18.0 ± 2.4 cells/f.v.**
MVD	46.5 ± 5.4 vessels/mm^2	34.3 ± 4.7 vessels/mm^2

*p < 0.05 as compared with the content of intratumoural TAMs; **p < 0.05 as compared with the content of stromal TAMs in Twist-positive endometrial tumours; TAMs — tumour-associated macrophages; ECE — endometrioid carcinoma of the endometrium; MVD — microvessels density

Table 4. The content of tumour-associated macrophages and microvessels density in endometrial carcinomas with different proliferative potential, differentiation degree, depth of tumour invasion into the myometrium, and the stage of tumour progression

Investigated parameters	Number of intratumoural TAMs, cells/f.v.	Number of stromal TAMs, cells/f.v.	MVD, number of vessels/mm^2
IP < Me	10.0 ± 1.3	19.1 ± 3.7	29.5 ± 5.0
IP > Me	15.7 ± 2.1	23.1 ± 3.0	40.0 ± 6.4*
ECE differentiation degree			
G2	11.7 ± 2.1	21.7 ± 3.4	26.6 ± 4.8
G3	14.3 ± 1.9	23.9 ± 2.9	40.8 ± 5.8**
Tumour invasion into the myometrium			
< 1/2	9.1 ± 1.2	14.8 ± 2.4	24.0 ± 5.7
>1/2	14.3 ± 1.8	24.9 ± 3.0***	41.4 ± 5.3***
Stage of tumour progression			
Ia + Ib	11.4 ± 2.1	18.2 ± 2.8	27.2 ± 4.7
Ic	13.3 ± 1.8	23.9 ± 3.1	42.1 ± 5.4
II	16.0 ± 2.3	22.8 ± 2.9	50.6 ± 5.9****
III	20.7 ± 2.2****	25.8 ± 2.9	48.9 ± 5.6****

*p < 0.05 as compared with the index at LI < Me; **p < 0.05 as compared with the index in G2-tumors; ***p < 0.05 as compared with the index during the tumour invasion into the myometrium < 1/2; ****p < 0.05 as compared with the index at Ia + Ib stage of tumour progression; TAMs — tumour-associated macrophages; MVD — microvessels density; ECE — endometrioid carcinoma of the endometrium

relationship of moderate density (R = 0.4, p < 0.05) was found between MVD and IP in the investigated endometrial carcinomas.

While determining the content of TAMs and MVD in ECE depending on the stage of tumour progression, it was found that the number of both intratumuoral and stromal TAMs was gradually increasing starting with Ia+Ib towards Ic, stages II and III of the disease, and MVD was twice higher in tumours of stage II and III as compared with the tumours on Ia + Ib stages of tumour progression.

Taking into consideration the scientific data about the dependence of angiogenic processes in tumours on the content of TAMs [11, 22], MVD in ECE were determined depending on the content of TAMs. A simultaneous increase in MVD and the number of intratumoural and stromal TAMs (15.9 ± 2.3 and 22.7 ± 2.5 cells/f.v., respectively) was demonstrated as compared with their content in tumours with low MVD (MVD<Me), 10.7 ± 2.2 and 15.3 ± 2.4 cells/f.v., respectively, p < 0.05 (Fig. 4).

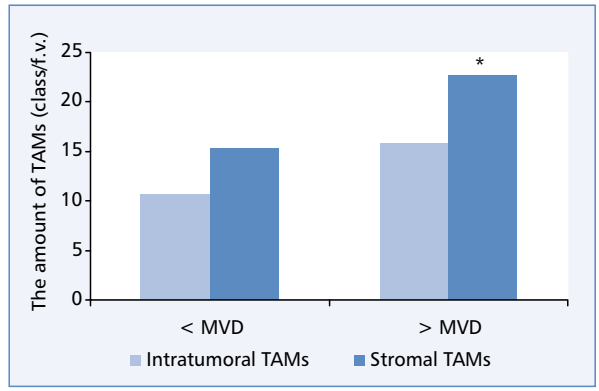

Figure 4. The determination of the relationship between the content of intratumoural and stromal tumour-associated macrophages and microvessels density in endometrial carcinomas; *p < 0.05 as compared with the index in endometrioid carcinoma of the endometrium with microvessels density < Me; TAMs — tumour-associated macrophages; MDV — microvessels density

In the group of tumours, invading less than 1/2 of the myometrium, evident correlative relationships were observed between MVD and the content of intratumoural and stromal TAMs ($R = 0.52$ and $R = 0.68$, $p < 0.05$, respectively), which confirms the dependence of angiogenic and invasive processes in endometrial carcinomas on the content of TAMs. However, the correlative relationships between MVD and the content of TAMs were absent in endometrial carcinomas, which deeply invaded the myometrium.

Discussion

The latter may be related to the fact that even in the initial stages of the invasive process, tumour cells induce the expression of the vascular endothelial growth factor (VEGF, promoting the activation of angiogenesis and remodelling of vessels) in macrophages and matrix metal proteinases (which ensure the destruction of the basal membrane). With further progression of the neoplasm, the activation of endothelial cells is most likely to result from the impact of many factors, including circulating inflammatory cytokines, such as tumour necrosis factor (TNF) and interleukins (IL), reactive oxygen intermediates (ROI), etc. [8, 9–11, 23].

Therefore, the study demonstrated the increase in Twist expression and the content of TAMs in ECE, which was associated with such tumour progression indices as low differentiation degree, deep tumour invasion into the myometrium, and the increase in MVD. At the same time, a correlative relationship was determined between such components of the tumour microenvironment as TAMs and MVD and the increase in the content of TAMs in stroma and MVD in Twist-positive ECE. The reasons for this interaction lie in the functional properties of the mentioned markers. It is well-known that Twist promotes the polarization of M1-macrophages into M2-macrophages, and the latter, in their turn, produce several cytokines, chemokines, and growth factors, including VEGF, which, in addition to activating neoangiogenesis, fulfils a function of chemoattractant, getting TAMs and tumour-associated fibroblasts (one of the main sources of VEGF) involved in hypoxic regions of the tumour, which increases MVD [10, 22–26]. It was determined that TAMs may induce EMT via the activation of EGFR which, in its turn, promotes the expression of ERK1/2, Slug, and vimentin [27].

It should be noted that the formation of new vessels leads to further progression of the neoplasm, as tumour angiogenesis is functionally inadequate — the endothelium of such vessels is not homogeneous in its structure — it is faulty and intermittent which promotes increased intravasation of tutor cells [28]. The uneven location of microvessels in the tumour complicates the efficient supply of oxygen, which reduces the response of the tumour to radiation therapy. In addition to the abovementioned, tumour blood vessels promote avoiding the immune response due to the absence of reaction to the activation of inflammation, thus creating an immune-tolerant tumour microenvironment [23].

The observed phenotypic characteristics of tumour cells and tumour microenvironment was associated with certain morphological specificities of endometrial carcinomas. For instance, in some tumours with positive expression of Twist, were found structures, described in scientific literature as the ones observed in ECE with EMT traits. These are areas with the accumulation of histiocyte-like cells with hyperchromatic nuclei, small groups of glands, diffusely located in the myometrium or microcystic, elongated, and fragmented glands (MELF) [29–31]. Many authors demonstrated that the mentioned morphological structures in endometrial tumours are often associated with decreased expression of E-cadherin, nuclear expression of β-catenin, and inhibited expression of ER and PR along with the deep invasion of the myometrium and unfavourable prognosis of the disease. It was shown that ECE with the MELF pattern of invasion is notable for the increase in MVD in the tumour stroma, which, in the authors' opinion, may be a predictive marker of the unfavourable clinical course [31].

On the contrary, Twist-negative endometrial tumours had a different pattern of invasive growth. Such ECEs often had large, convoluted glands, tightly surrounding the myometrium, and "invasive front areas". As it was shown in the authors' previous study while investigating the morphological traits of such neoplasms, they invaded the myometrium by large groups of tumour cells in the form of solid bands which is a morphological manifestation of collective migration [17]. These results agree with the data of other researchers who demonstrated that such morphological traits of ECE are associated with the decreased expression of EMT markers [29, 30]. As noted above, in the present study, half of the tumours of patients with metastases were Twist-negative. This is consistent with other authors providing evidence that EMT is not required for metastasis in vivo. [32]. Some authors believe that the motility of cells with preserved adhesive properties may be a more efficient way of spreading for transformed cells compared to single cells [5].

At the same time, many authors proved that tumour cells are remarkable for epithelial-mesenchymal plasticity, due to which a malignant neoplasm has cells with epithelial, mesenchymal, and even hybrid phenotype (co-expression of both epithelial and mesenchymal markers) which enhances its ability to form metastases [4, 20, 22, 33, 34].

Conclusions

Thus, the presented study demonstrated that invasion and metastasis of ECE may occur in the setting of various molecular changes in tumour cells and tumour microenvironment, particular, Twist-positive endometrial carcinomas have a higher content of stromal TAMs and MVD as compared with the same indices in Twist-negative neoplasms. The identified differences are associated with various morphological features of invasive processes in the endometrium and can be used as markers of possible ways of invasion and metastasis of endometrial cancer and the aggressiveness of the tumour process in patients.

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Conflict of interest

The authors declare to have no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Laparoscopic versus open complete mesocolic excision for right cancer colon

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ABSTRACT

Introduction. This study aims to assess and compare the pathological, oncological and perioperative surgical outcomes of CME for right colon cancer by open and laparoscopic approaches.

Material and methods. This is a prospective randomized study that included all patients that underwent radical right hemicolectomy with CME for right colon cancer at the Department of General Surgery, Assiut University between January 2017 and December 2018. Follow up of the patients continued till January 2020.

Patients were randomized into two groups: the first group for open CME and the second group for laparoscopic CME. Demographic, operative, pathologic and oncological parameters were analysed.

Results. This study enrolled 35 patients with colon cancer that were randomly sub-grouped into the open CME group (n = 18) and laparoscopic CME group (n = 17) according to the surgical approach. Both groups had insignificant differences as regard mesocolon grading, vascular tie, circumferential safety margin, total lymph nodes and positive lymph nodes. Patients who underwent open CME had significantly shorter operative time [168.83 ± 23.50 *vs*. 205.17 ± 35.70 (minutes); $p < 0.001$] and significantly higher blood loss in comparison to those underwent laparoscopic CME [353.89 ± 85.70 *vs*. 224.11 ± 96.51 (cc); $p < 0.001$].

Patients underwent laparoscopic CME had significantly shorter time of passage of flatus [1.45 ± 0.23 *vs*. 2.34 ± 0.79 (days); $p < 0.001$] and first bowel motion [1.92 ± 0.38 *vs*. 2.79 ± 0.95 (days); $p = 0.01$], and less postoperative pain score and shorter hospital stay in comparison to those underwent open CME. There was no significant difference between the open group and the laparoscopic group as regard mean overall survival duration [23.44 *vs*. 23.29 (month); $p = 0.36$]

Conclusions. Our study supports the use of laparoscopic CME for right colonic cancer if good surgical expertise is present. It is a feasible and safe procedure with better postoperative short and long-term surgical outcomes and similar pathological and oncological outcomes if compared to the open approach.

Key words: cancer colon, complete mesocolic excision, right hemicolectomy

Oncol Clin Pract 2021; 17, 4: 148–156

Introduction

Colon cancer (CC) is the third most common cancer in both men and women in the world [1]. Surgery is still the cornerstone in the therapy of non-metastatic disease. The surgical principles and techniques regarding colonic resection for cancer colon had never been changed greatly in the last century. In 2009, a new concept of colonic resection referred as complete mesocolic excision (CME) was introduced by Hohenberger [2]. The concept of CME is similar to the total mesorectal excision (TME) proposed by Heald [3]. The wide application of TME led to a major improvement in the survival and local recurrence rates of rectal cancer. The rationale of CME is to resect a sufficient length of the affected colon with its mesocolon in an intact envelope of visceral peritoneum. This aims to minimize the risk of spillage of cancer cells into the peritoneal cavity and maximize the removal of potentially involved lymph nodes in a longitudinal direction. In addition, central

vascular ligation (CVL) of the relevant blood supply is performed as an integral part of CME to improve lymph node harvesting [4, 5].

Performing CME for left-sided resections is truly not much different compared to conventional resections performed by most expert colorectal surgeons. TME/CME principles are applied due to the feasibility of central vascular ligation of the inferior mesenteric vessels [6]. However, for right-sided resections, mobilization of the mesocolon needs to be more radical than a conventional resection, fully exposing the head of the pancreas and the anterior surface of the superior mesenteric artery and vein. This allows accurate identification of the origins of the ileocolic and middle colic vessels.

The concept CME with central vascular ligation (CVL) and D3 lymphadenectomy technique — which has a concept close to CME — has been adopted by many European and Asian colorectal centres. The results reported by these centres showed that CME and D3 lymphadenectomy are associated with higher reported survival rates than conventional colon resection surgery, especially for clinical stage II and III colon cancer [4, 5, 7, 8].

Since its introduction in 1991, the use of laparoscopy for colorectal surgery has shown to be associated with faster recovery and less morbidity as compared to the standard open approach without affecting oncologic outcomes. Hence it is hypothesized that CME using the laparoscopic approach will offer the best curative surgery for colon cancer patients [9–13].

This study aimed to assess and compare the pathological, oncological and perioperative surgical outcomes of CME for right colon cancer by open and laparoscopic approaches.

Material and methods

This is a prospective study that included all patients that underwent radical right hemicolectomy with CME for right colon cancer at the Department of General Surgery, Assiut University between January 2017 and December 2018. Follow up of the patients continued till January 2020.

Exclusion criteria include stage IV disease, extracolonic infiltration (T4b), emergency conditions caused by cancer (bleeding, perforation and obstruction), recurrent cases and previous significant abdominal surgery (except appendectomy or cholecystectomy). Also, patients with deranged cardiopulmonary and hepatorenal functions not suitable for the laparoscopic surgery group are excluded from the study.

All eligible patients during the period of the study were included (total coverage) as the authors are not a specialized colorectal centre. Thirty-five patients with colon cancer were assigned to receive either open or laparoscopic complete mesocolon resection. The cases will be randomized simply into two groups: the first group for open CME and the second group for laparoscopic CME. Random assignment of intervention will be done after subjects have been assessed for eligibility and recruited. The first case will be assigned for its group by tossing a coin, the second case will be assigned for the other group and third case for the first group and so on.

History and clinical examination, basic laboratory investigations and carcinoembryonic antigen (CEA) were routinely done for all patients. All patients had computed tomography (CT) of the abdomen and pelvis, colonoscopy and punch biopsy. Routine plain chest radiograph was done as a metastatic workup and MSCT-chest was performed in some cases when indicated.

Written informed consents were taken from all patients. All patients scheduled for resection underwent bowel preparation for three days before surgery in the form of a low fibre diet, clear fluid intake and multiple enemas the day before surgery. Elastic compression stockings worn by patients and low molecular weight heparin (LMWH) given 12 hours before surgery are measures used for prophylaxis against deep venous thrombosis (DVT). The protocol of an enhanced recovery program (fast track surgery) was not followed in this study.

Surgical technique

Open approach

For open surgery, a lateral-to-medial approach is used, starting with an incision of the lateral peritoneal fold. The visceral and parietal fasciae are separated by sharp dissection to ensure an intact mesocolon. The dissection continues medially in the mesofascial interface. The mesenteric root up to the origin of the superior mesenteric pedicle is mobilized, and the dissection continues over the duodenum and pancreatic uncinate process to allow complete access to the superior mesenteric vein and artery. After the complete colonic mobilization, the supplying vessels transected close to their origin from the superior mesenteric vessels (CVL) (Fig. 1A).

For cecal and ascending colon tumours, the ileocolic, right colic (if present), and right branch of middle colic vessels are divided with a division of the mid-transverse colon. For tumours at and distal to hepatic flexure tumour, extended right hemicolectomy is performed with resection of proximal 2/3 of the transverse colon and division of middle colic vessels at their origin. In addition, a part of the greater omentum is removed en bloc with the specimen. An end-to-end or end-to-side ileocolic anastomosis is performed using a hand-sewn technique with 3–0 Vicryl suture.

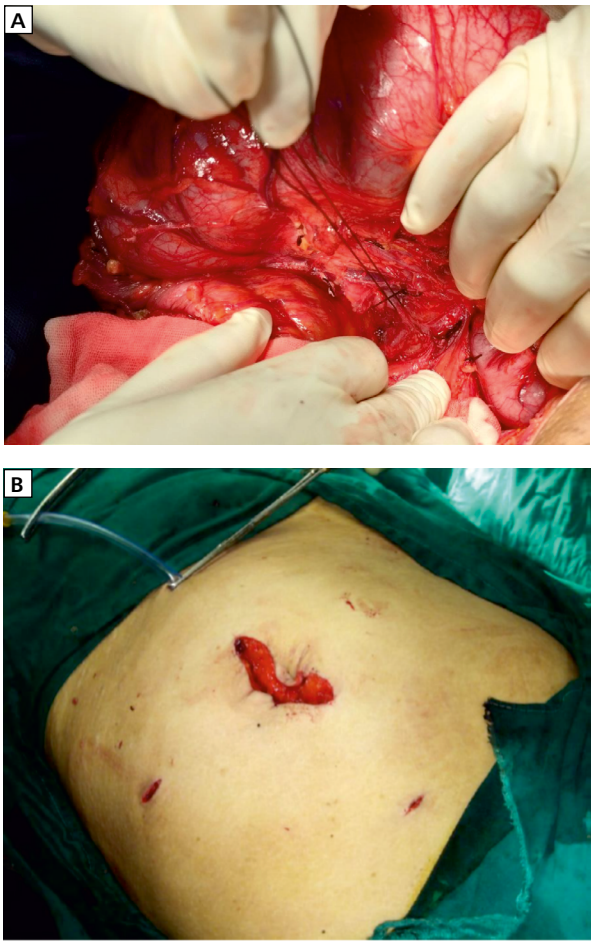

Figure 1. A. Central vascular ligation in right hemicolectomy: division of middle colic pedicle and hanging of ileocolic pedicle at their origin from superior mesenteric vessels; **B.** Periumbilical incision (5 cm) for specimen retrieval and creation of anastomosis

Laparoscopic approach

For laparoscopic cases, the medial-to-lateral approach is used. The mesentery at the junction of the terminal ileum and cecum is pulled to the right lower quadrant to identify the ileocolic pedicle. The peritoneum on the caudal aspect of the ileocolic vessels is incised to reach the retroperitoneal plane. Sharp dissection proceeds in caudal-cephalic direction and from the medial to lateral to separate the posterior layer of the mesocolon from the parietal fascia. After exposing the right gonadal vessels, ureter, duodenum, and head of the pancreas, the division of vessels proceeds in a fashion similar to that discussed in the open approach. Finally, the gastrocolic ligament and lateral peritoneum fold of the colon are divided.

The specimen was extracted from a small periumbilical midline incision (Fig. 1B). An extracorporeal end-to-end or end-to-side ileocolic anastomosis is performed using hand-sewn or stapling techniques.

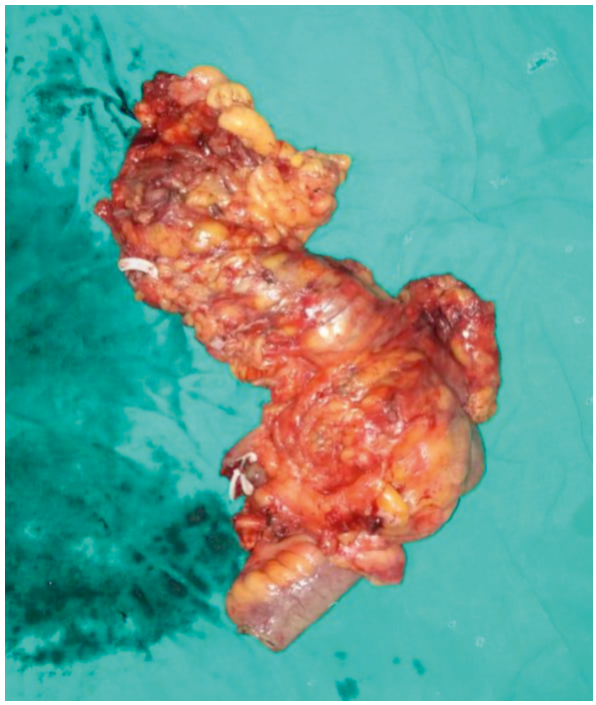

Figure 2. Resection specimen of right hemicolectomy: cancer cecum removed by laparoscopic CME show divided ileocolic and right colic pedicles marked by clips

Follow up

After completion of adjuvant therapy, all patients were subjected to follow up schedule. Patients were reviewed every 3 months in outpatient clinic visits for the 1st postoperative year, every 6 months in the 2nd year and then annually. During visits, history and clinical examination were taken and blood samples were obtained to check CEA. Computed tomography of the abdomen was done every six months and colonoscopy after one year.

Outcome measures

Surgical outcome parameters included operative time, blood loss, conversion rate, gastrointestinal recovery (time of 1st bowel motion and time of 1st passing flatus), postoperative pain score, duration of hospital stay, and postoperative morbidity and mortality within 30 days after surgery.

Pathological outcome parameters include circumferential resection safety margin (CRM), proximal and distal resection margins, number of harvested lymph nodes, number of positive lymph nodes, mesocolon grade and distance between the tumour and the central arterial high tie (Fig. 2).

Oncological outcomes include pattern and rate of recurrence and 2-years survival rate.

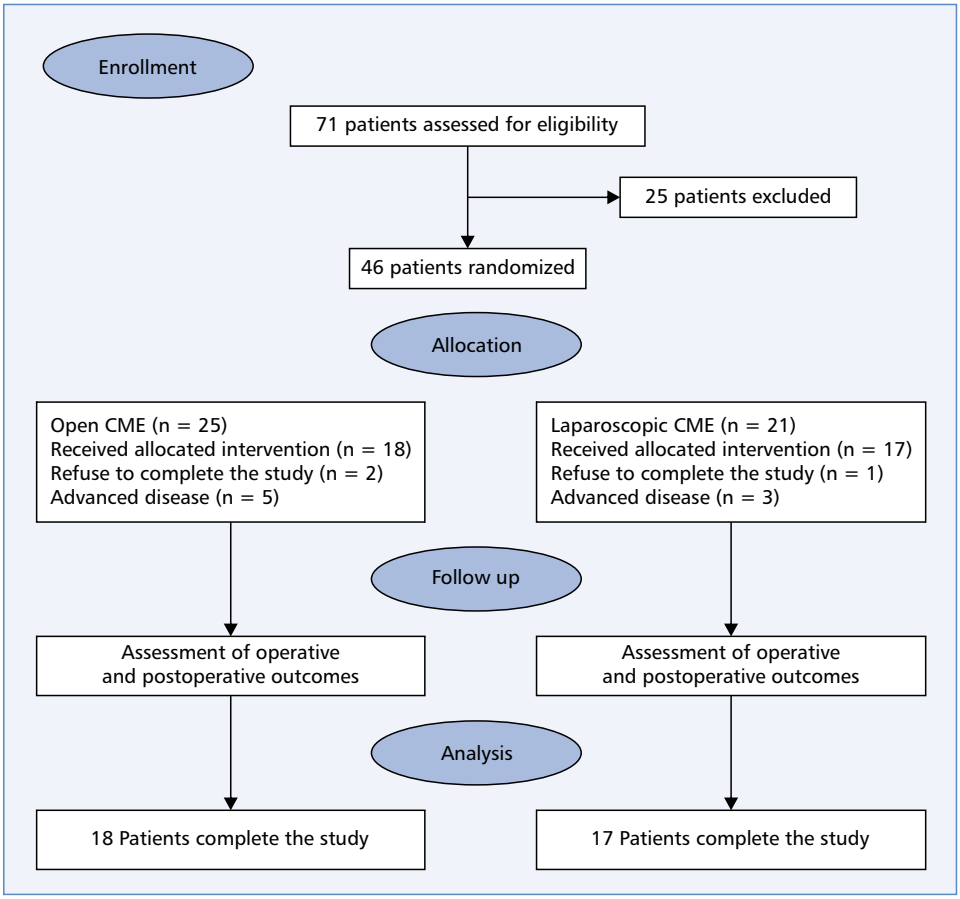

Figure 3. The enrollment process (CONSORT flow diagram); CME — complete mesocolic excision

Statistical analysis

Data analysis was performed using SPSS v20.0 (Statistical Product and Service Solutions Inc., Chicago, IL, USA). Quantitative data were expressed as medians, means, minimum and maximum and were compared by Mann-Whitney U test. Qualitative data were expressed as numbers and percentages and were compared by the Chi-square test or Fischer's exact test when appropriate. A log-rank test was used to compare the time to recurrence between the two groups. A significance level of p-value less than 0.05 was used in all statistical tests.

Results

All patients diagnosed with right colonic cancer and matching eligibility criteria were recruited to the study in the period between January 2017 and December 2018. Twenty-six patients were excluded before randomization because they are not meeting inclusion criteria. Two patients refused participation, 7 required urgent surgery, 8 were inoperable, 5 patients with T4 disease, 2 patients were had previous explorations with dense adhesions and 2 patients had cardiac problems. After allocation, 3 patients refused to complete the study while 8 patients were found to have advanced disease. This study enrolled a total number of 35 patients with colon cancer who were randomly sub-grouped into the open CME group (n = 18) and laparoscopic CME group (n = 17) according to the surgical approach. Figure 3 shows the enrollment process (CONSORT flow diagram).

Patients' demographic data

The mean age of the open group was 50.61 ± 13.69 years and the majority (61.1%) of them were males while the mean age of the laparoscopic group was 49 ± 13.55 years and, the majority (52.9%) of them were males (Tab. 1). Both groups had no significant differences as regard age (p = 0.72) and sex (p = 0.31).

Pathological outcomes

It was noticed that the common tumour location in both groups was the cecum (n = 14). The majority of

Table 1. Patients' demographic data

	Open CME (n = 18)	Laparoscopic CME (n = 17)	p-value
Age [years]	50.61 ± 13.69	49 ± 13.55	0.72
Age group			0.44
< 40 years	5 (27.8%)	4 (23.5%)	
40–60 years	7 (38.9%)	10 (58.8%)	
> 60 years	6 (33.3%)	3 (17.6%)	
Sex			0.31
Male	11 (61.1%)	9 (52.9%)	
Female	7 (38.9%)	8 (47.1%)	
Body mass index (kg/m^2)	26.53 ± 3.10	26.40 ± 3.48	0.90

CME — complete mesocolic excision

both groups had tumour stage III (n = 15). Stage T3 and stage N2 were frequently found in both groups. The majority of patients had moderately differentiated carcinoma. Regarding tumour location, TNM stage, and tumour differentiation, there are no significant differences between the studied groups (Tab. 2). Both groups had insignificant differences as regard mesocolon grading, vascular tie, circumferential safety margin, total lymph nodes and positive lymph nodes. All patients had negative proximal, distal and circumferential resection margins.

Perioperative data among the study population

Patients who underwent open CME had significantly shorter operative time [168.83 ± 23.50 *vs.* 205.17 ± 35.70 (minutes); $p < 0.001$] and significantly higher blood loss in comparison to those underwent laparoscopic CME [353.89 ± 85.70 *vs.* 224.11 ± 96.51 (cc); $p < 0.001$].

Only one patient in case of open CME had a minor injury to a superior mesenteric vein (SMV) which was easily repaired without significant morbidity.

Conversion to open approach was required in 2 patients in the laparoscopic group due to extensive adhesions. Difficult adhesiolysis by laparoscopic approach with prolonged operative time lead to conversion. Yet, these patients are reported in the laparoscopic group. A smooth postoperative course ensues with no specific morbidities observed in these 2 patients.

It was noticed that patients who underwent laparoscopic CME had a significantly shorter time of passage of flatus [1.45 ± 0.23 *vs.* 2.34 ± 0.79 (days); $p < 0.001$] and first bowel motion [1.92 ± 0.38 *vs.* 2.79 ± 0.95 (days); $p = 0.01$], and less postoperative pain score and shorter hospital stay in comparison to those underwent open CME.

Ileus, leakage, pneumonia, and wound infection occurred more in patients of the open group than laparoscopic group, despite not reaching statistical significance (Tab. 3). Fourteen (77.8%) and 16 (94.1%) patients of the open and laparoscopic group respectively received postoperative chemotherapy. No reported cases of 30-day mortality.

Long-term oncological and surgical outcomes

One patient in each group developed lung metastasis during long-term follow up. Also, two patients of the open group and three patients of the laparoscopic group developed liver metastasis. Local recurrence was reported in only one case with laparoscopic CME.

Adhesive intestinal obstruction occurred in only one patient with open CME while incisional hernia occurred in three patients with open CME and one patient with laparoscopic CME (Tab. 4).

Survival analysis among the study population

Two patients (11.7%) of laparoscopic CME and two patients (11.1%) of open CME were deteriorated and died during long-term follow-up. There was no significant difference between the open group and the laparoscopic group as regards the mean overall survival duration [23.44 *vs.* 23.29 (months); $p = 0.36$] (Fig. 4, Tab. 5).

Discussion

CME is considered by colorectal surgeons as a more radical operation rather than the conventional one. There is still a significant debate regarding the safety of CME right hemicolectomy, especially if performed via a laparoscopic approach. Here, the authors report a series of 35 patients who underwent CME right hemicolectomy and were randomly assigned to receive either open or laparoscopic CME.

It is noted that most of the patients (66.7% of open group and 76.5% of laparoscopic group) had tumour stage III. This may be attributed to the patient's education in seeking medical advice late so the tumour stage was advanced.

Table 2. Pathological outcomes

	Open CME (n = 18)	Laparoscopic CME (n = 17)	p-value
Anatomical site			0.80
Cecum	7(38.9%)	7 (41.2%)	
Ascending colon	5(27.8%)	4 (23.5%)	
Hepatic flexure	2 (11.1%)	1 (5.9%)	
Proximal transverse colon	4 (22.2%)	5 (29.4%)	
Tumour stage			0.78
Stage I	2 (11.1%)	1 (5.9%)	
Stage II	4 (22.2%)	3 (17.6%)	
Stage III	12 (66.7%)	13 (76.5%)	
T stage			
T2	2 (11.1%)	2 (11.8%)	0.99
T3	14 (77.8%)	13 (76.5%)	
T4	2 (11.1%)	2 (11.8%)	
N stage			0.75
N0	6 (33.3%)	5 (29.4%)	
N1	3 (16.6%)	5 (29.4%)	
N2	9 (50%)	7 (41.2%)	
Grade of adenocarcinoma			0.03
Well-differentiated	4 (22.2%)	3 (17.6%)	
Moderately differentiated	9 (50%)	8 (47.1%)	
Poorly differentiated	3 (16.7%)	1 (5.9%)	
Mucinous	2 (11.1%)	5 (29.4%)	
Mesocolon grading			0.44
Mesocolic plane	11 (61.1%)	9 (52.9%)	
Intramesocolic plane	7 (38.9%)	8 (47.1%)	
Vascular tie [cm]	10.97 ± 0.51 (95% CI 10.3 to 11.7)	10.91 ± 0.58 (95% CI 10.6 to 11.2)	0.63
Total lymph nodes	29 ± 5.07 (95% CI 28.8 to 29.2)	27.05 ± 5.52 (95% CI 24.4 to 29.7)	0.62
Positive lymph nodes	3.67 ± 2.34 (95% CI 2.59 to 4.75)	3.29 ± 2.91 (95% CI 1.91 to 4.67)	0.29

CME — complete mesocolic excision; CI — confidence interval

Central vascular ligation (CVL) can be assessed by the distance of the tumour to the high arterial tie (vascular tie). The mean vascular tie for the open group was 10.97 ± 0.51 and for the laparoscopic group was 10.91 ± 0.58. There were no significant differences between both groups as regard to vascular tie and these results agree with a systematic review and meta-analysis reported by Negoi et al. [14]. On other hand, Munkedal et al. [15] reported significantly high vascular tie after laparoscopic CME in comparison to the open CME.

The integrity of mesocolon was commonly assessed by the method described by Hohenberger et al. and classified as a mesocolic plane, intramesocolic plane or muscularis propria plane. It was noticed that mesocolon plane and intramesocolic plane were present in 11 (61.1%), and 7 (38.9%) patients of the open group and present in 9 (52.9%), and 8 (47.1%) patients of the laparoscopic group, respectively. Both groups had no significant differences as regard mesocolon grading and these results agree with the results reported by Gouvas et al. [16] and systematic review and meta-analysis by Negoi et al. [14].

The number of lymph nodes retrieved reflects the extent of regional lymphadenectomy. It is a key indicator of the quality of CME and is associated with recurrence rate and survival rate postoperatively. The

Table 3. Operative and postoperative data

	Open CME (n = 18)	Laparoscopic CME (n = 17)	p-value
Operative time [minute]	168.83 ± 23.50 (95% CI 168 to 170)	205.17 ± 35.70 (95% CI 188 to 222)	0.01
Blood loss [cc]	353.89 ± 85.70 (95% CI 314 to 393)	224.11 ± 96.51 (95% CI 178 to 270)	< 0.001
Anastomotic technique			0.05
Hand-sewn	15 (83.3%)	14 (82.4%)	
Stapler	3 (16.7%)	3 (17.6%)	
Conversion	-	2	NA
Major vessel bleeding	1 (5.6%)	0	0.32
First passage of flatus [day]	2.34 ± 0.79 (95% CI 1.97 to 2.71)	1.45 ± 0.23 (95% CI 1.34 to 1.56)	< 0.001
First bowel motion [day]	2.79 ± 0.95 (95% CI 2.35 to 3.23)	1.92 ± 0.38 (95% CI 1.74 to 2.1)	0.01
Visual analogue scale	50.12 ± 12.43 (95% CI 44.4 to 55.9)	34.05 ± 7.67 (95% CI 30.4 to 37.7)	< 0.001
Hospital stay [day]	8.89 ± 1.49 (95% CI 8.2 to 9.58)	7 ± 0.93 (95% CI 6.56 to 7.44)	< 0.001
Overall, 30-day complications	7 (39%)	2 (11.8%)	0.07
Ileus	1 (5.6%)	0	
Anastomotic leakage	2 (11.1%)	1 (5.9%)	
Pneumonia	2 (11.1%)	1 (5.9%)	
Wound infection	2 (11.1%)	0	
Post-operative chemotherapy	14 (77.8%)	16 (94.1%)	0.18

CME — complete mesocolic excision

Table 4. Long-term oncological and surgical outcomes

	Open CME (n = 18)	Laparoscopic CME (n = 17)	p-value
Liver metastasis	2 (11.1%)	3 (17.7%)	0.58
Lung metastasis	1 (5.6%)	1 (5.9%)	0.97
Local recurrence	0	1 (5.9%)	0.30
Adhesive obstruction	1 (5.6%)	0	0.32
Incisional hernia	3 (16.7%)	1 (5.9%)	0.32

CME — complete mesocolic excision

median number of lymph node retrieval on several studies of CME and D3 lymphadenectomy range from 18–46 [5, 16–19]. In this study, the mean number of retrieved lymph nodes was 27 ± 5.52 in the laparoscopic group versus 29 ± 5.07 in the open group. The difference between the two groups is not statistically significant. In most reports comparing laparoscopic CME or D3 lymphadenectomy to open approach, there is no superiority of one approach over the other regarding the number of lymph nodes harvested [14, 18, 20]. Yet, this conclusion is not universal. Shin et al. [21], showed a statistically significant lower number of harvested LNs in laparoscopic CME compared to open CME.

The conversion rate in this study (11.8 %) is higher than that of many reports in the literature (1.9–7.6%) [18, 22, 23] as we are still in the learning curve of laparoscopic CME. However, Kim et al. reported a conversion rate of 13.8 % for T4 lesions [20].

There was one case of SMV injury in the open group. Fortunately, this was a minor injury that was repaired immediately without significant blood loss. Although it is rare (1.6%) [24], iatrogenic SMV injury is the most feared complication regarding CME. Surgeons should take great care during dissection or ligation near SMV especially at the origin of a middle colic vein and gastrocolic trunk; otherwise, a catastrophic uncontrollable bleeding or bowel ischemia will supervene.

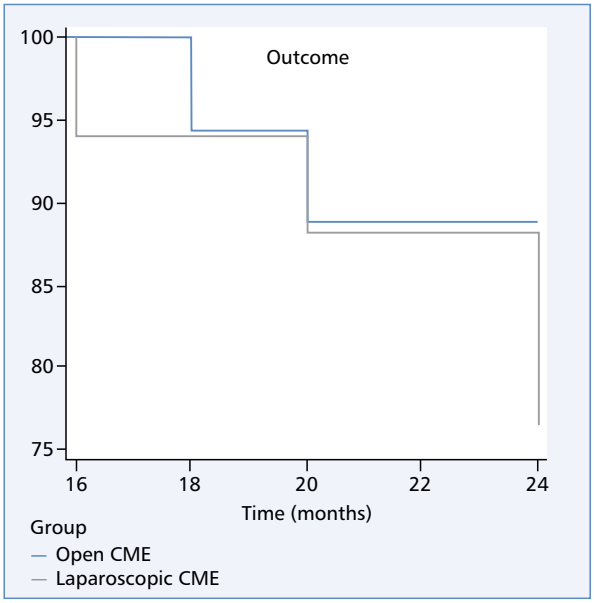

Figure 4. Kaplan Meier curve for survival analysis in the study population; CME — complete mesocolic excision

Table 5. Survival analysis among the study population

	Open CME (n = 18)	Laparoscopic CME (n = 17)	p-value
Death	2 (11.1%)	2 (11.7%)	0.95
Overall survival [months]	23.44	23.29	0.36

CME — complete mesocolic excision

Performing CME via a laparoscopic approach has major advantages regarding short- and long-term surgical outcomes. Patients in the laparoscopic group showed significantly less blood loss, less postoperative pain, enhanced gastrointestinal recovery and shorter hospital stay. These results are supported by many reports and randomized trials [12–14, 19, 25–27]. Regarding long-term surgical complications, adhesive intestinal obstruction occurred in one patient in the open group (5.6%). Three patients in the open CME (16.7%) develop incisional hernia versus one patient in the laparoscopic CME (5.9%). However, in this study, the previous two complications are statistically insignificant between the two groups. On the other hand, patients who underwent open CME had significantly shorter operative times [168.83 ± 23.50 *vs.* 205.17 ± 35.70 (minute); $p < 0.001$]. These results are consistent with the systematic reviews and meta-analyses by Negoi et al. [14] and Chaouch et al. [28]. On the other hand, the present results are inconsistent with those reported by Kim et al. [20] (175 *vs.* 175), Huang et al. [29] (177 *vs.* 194) and Bae et al. [25] (194 *vs.* 179) which show no significant difference between two groups.

The circumferential resection margin (CRM) has traditionally been an important factor for R0 resection and determining the oncologic outcomes of colon cancer surgery. One of the proposed advantages of CME is that sharp dissection in the mesofascial interface enhances the probability of attaining negative CRM which was the scenario in all cases.

In the present study, the recurrence rate was lower in the open group (11.1%) than in the laparoscopic group (17.7%) but with no significant difference. Local recurrence was detected in one case in the laparoscopic group while distant metastasis was detected in three cases of the laparoscopic group and two cases in the open group. The present results are similar to those reported by Sheng et al.[27]. Han et al. [22] and Bae et al. [25]. Also, the present results are consistent with those reported in systematic review and meta-analysis by Negoi et al. [14]. The results are inconsistent with those reported by Shin et al. [21] and systematic reviews and meta-analysis by Chaouch et al. [28] which showed statistically significant lower overall recurrence in the laparoscopic group versus open group.

This study found comparable OS among both groups. The mean OS was 23.29 in the laparoscopic group versus 23.44 in open surgery, p-value = 0.36. The cumulative overall survival probability for all stages at 24 months in the laparoscopic group was 88.2 %, as compared to 88.8% in the open group, with no significant differences being detectable between the two groups. In Negoi et al.'s meta-analysis, including more than one thousand patients, the 3-year OS was reported by four studies. The laparoscopic approach was associated with a statistically significant better 3-year OS [14]. In Sheng et al. study [27], during the follow-up period (median 20.1 ± 4.6 months), the laparoscopic and open groups were similar in terms of local recurrence rate, distant metastasis rate, and short-term survival rate (79.5% *vs.* 77.8%) which is close to these results.

Limitations of this study include recruitment of cases was slow due to low flow of colon cancer cases. This led to a low sample size which can potentially affect the accuracy of results. Moreover, a short period of follow-up in the study may jeopardize the power of this study.

Conclusions

Our study supports the use of laparoscopic CME for right colonic cancer if good surgical expertise is present. It is a feasible and safe procedure with better postoperative short and long-term surgical outcomes and similar pathological and oncological outcomes if compared to the open approach. However, a large number of cases

and a long duration of follow up are needed to better assess survival and oncological outcomes.

Conflict of interest

None.

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VIA MEDICA

REVIEW ARTICLE

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Recent progress in the systemic treatment of colorectal cancer

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ABSTRACT

Over the last decade in the treatment of colorectal cancer (CRC) patients, a significant improvement of systemic treatment approaches has been observed in terms of safety and efficacy. Regarding safety, a huge, international IDEA trial proved that for CRC patients with pT1–3 and N1 features, a short, 3-month adjuvant treatment with CAPOX does not negatively impact long-term prognosis compared to standard, 6-month, oxaliplatin-based regimens. Additionally, the shortened adjuvant treatment significantly diminishes chronic neuropathy risk, representing a detrimental symptom in CRC survivors. On the other hand, in a palliative setting, a significant improvement in mCRC patients' prognosis has been achieved with the advent of novel therapies targeting critical molecular disorders. The encorafenib and cetuximab combination in *BRAF V600E* mutated mCRC and checkpoint inhibitors in MSI-H mCRC patients are the most impressive examples of this continuous progress.

Key words: colorectal cancer, metastases, cetuximab, encorafenib, pembrolizumab, immunotherapy, microsatellite instability, *BRAF* mutation, adjuvant treatment

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Introduction

Colorectal cancer (CRC) is diagnosed in approximately 1.4 million individuals around the world every year, including over 18,000 individuals in Poland [1, 2]. Due to the unsatisfactory 5-year survival rates (< 60% in Europe, < 50% in Poland) intensive development of new, more effective diagnostic and therapeutic strategies for both, early and generalized disease stage, is necessary. Advances in improving prognosis in CRC patients has to pertain to different aspects of diagnostics, surgical and perioperative treatment at an early stage of a neoplastic process, as well as systemic and supportive therapies in patients with metastatic disease. New systemic treatment strategies based on new chemotherapeutic agents and molecularly targeted drugs have significantly improved the prognosis of patients with advanced colorectal cancer in the last 20 years. As a result, the average survival time of patients with generalized CRC increased almost four times from less than 10 months to over 30 months [3]. Despite significant progress in the diagnosis and treatment of CRC, for epidemiological reasons, the number of patients is increasing every year, both those after treatment failure, and those in whom palliative systemic treatment has exhausted its activity or was no longer active. Therefore, improving the prognosis in CRC patients must include both improvements of the effectiveness and safety of palliative and radical treatment. This review summarizes the most important recent changes in the systemic treatment of patients with colorectal cancer.

Adjuvant therapy

Adjuvant chemotherapy – based on 5-fluorouracil (5-Fu) – allowed for a significant improvement in the prognosis of patients with stage III CRC. A meta-analysis of seven clinical trials of adjuvant chemotherapy with 5-Fu showed a significant reduction in the risk of death by 13–15 percentage points [4]. The 5-year overall survival rates were 58% and 71% in patients with

1–4 lymph nodes involved, and 29% and 44% in the case of 5 or more lymph nodes involved for placebo and 5-Fu, respectively. The next step on the way to optimizing the adjuvant treatment was to identify the most safe form of 5-fluorouracil administration, which proved to be a two-day infusion. Similarly, capecitabine has been shown to be as effective as 5-Fu but less toxic compared to 5-Fu administered by injections [5]. Another progress in improving the effectiveness of adjuvant therapy was related to the introduction of two-drug regimens based on 5Fu and oxaliplatin combination [6, 7]. In the MOSAIC study, the use of the FOLFOX regimen in patients with stage III colorectal cancer significantly increased the 5-year disease-free survival rate from 59% to 66% and 6-year overall survival rate from 69% to 73% as compared to 5Fu + Lv [6]. As with 5-Fu alone, the two-drug regimen did not provide any benefit for stage II CRC. However, the improved prognosis associated with the use of oxaliplatin resulted in significant neurotoxicity, which persisted in 24% of patients beyond 18 months after the completion of adjuvant therapy and significantly influenced the quality of life. Similarly to FOLFOX, the CAPOX regimen was also more active than 5-FU monotherapy, significantly increasing the 7-year DFS rate from 56% to 63% and 7-year OS rate from 67% to 73%, with similarly increased neurological toxicity [7]. The recent progress in the adjuvant treatment of CRC is not leading to further improvement of the prognosis but is related to the increased safety of postoperative chemotherapy.

The International Duration Evaluation of Adjuvant Therapy (IDEA) study was aimed to assess the possibility of shortening the duration of adjuvant treatment by half (from 6 to 3 months). Data from six parallel, prospective clinical trials (IDEA, SCOT, CALGB/SWOG80702, ACHIEVE, TOSCA, HORG) were analysed, including a total of 13,000 patients with stage III CRC who received adjuvant chemotherapy with CAPOX or FOLFOX regimens for 3 or 6 months [8]. The study was to verify whether 3-month adjuvant therapy is comparably effective (non-inferior) as 6-month treatment; however, after a follow-up of 42 months, it was not possible to confirm the non-inferiority. The 3-year disease-free survival (DFS) rates, the primary endpoint of the study, were 74.6% in the 3-month treatment group and 75.5% in the 6-month treatment group. Patients receiving shorter adjuvant therapy had significantly fewer and less severe side effects compared to standard adjuvant chemotherapy. Grade ≥ G2 neuropathy was reported in 16.6% (FOLFOX) and 14.2% of patients (CAPOX) receiving 3-month therapy, and 47.7% and 44.9% of patients receiving 6-month therapy, respectively. Although it was not possible to prove the comparability of two adjuvant treatment approaches in the overall study population, pre-planned subgroup analyses revealed several important relationships. First, a significant advantage of 6-month FOLFOX6 regimen over 3-month treatment [hazard ratio (HR) = 1.16; 95% confidence interval (CI) 1.06–1.26; p = 0.001] was demonstrated with a difference in the 3-year DFS rates of 2.4 percentage points (73.6% versus 76%). In turn, in the case of the CAPOX chemotherapy regimen, no significant differences were found between the shorter and longer duration of therapy — HR 0.95 (95% CI: 0.85–1.06). The 3-year DFS rates for CAPOX were 75.9% (3 months of treatment) and 74.8% (6 months of treatment). In patients with disease stage not exceeding pT3 and pN1, 3-month CAPOX therapy was as effective as 6-month therapy (3-year DFS rates — 85.0% versus 83.1%, respectively; HR = 0.85; 95% CI: 0.71–1.01). On the other hand, in the group of patients with stage > pT3 or > pN1, 3-month CAPOX therapy was significantly worse than 6-month therapy [8].

The updated results of the IDEA study, after a median follow-up of 72 months, were presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting [9]. In the general patients' population, the 5-year overall survival (OS) rate was 82.8% (6-month therapy) versus 81.4% (3-month therapy), demonstrating a borderline significance in terms of non-inferiority. On the other hand, in the general patients' population, the advantage of standard chemotherapy over 3-month therapy was still maintained in relation to the 5-year DFS rates. The updated results of the IDEA study clearly confirmed the possibility of using 3-month CAPOX chemotherapy in patients with advanced disease (pT1–T3 and pN1). In this subgroup, the 5-year DFS rate was 90.4% (3 months) versus 88.1% (6 months) with a hazard ratio for DFS of 0.85 (95% CI: 0.69–1.04). The comparison of toxicity of 3- and 6-month regimens showed that shorter chemotherapy was associated with reduced incidence of various adverse events (2 to 6-fold), including a 3-fold reduction in the risk of G2 or higher neurotoxicity. Thus, based on the results of the IDEA study, the option of 3-month adjuvant chemotherapy based on the CAPOX regimen should become a routine clinical practice in patients with colorectal cancer T1–3 and N1 [9].

Palliative therapy

Over the last two decades, the progress in the treatment of patients with advanced CRC has been related to the introduction of new cytotoxic drugs — irinotecan, oxaliplatin, trifluridine with tipiracil and molecularly targeted drugs — anti-EGFR antibodies (cetuximab, panitumumab), VEGF scavengers (bevacizumab, aflibercept) and the VEGFR tyrosine kinase inhibitor (regorafenib). Despite a remarkable increase in life expectancy in the general population of patients with advanced CRC after introducing the new drugs and se-

quential treatment strategies, so far the smallest benefit was observed in patients with mutations of the KRAS, NRAS and BRAF kinases regulating the key intracellular MAPK (RAS/RAF/MEK/ERK) signalling pathway. It was mainly associated with the neutralization of the anti-tumour activity of anti-EGFR antibodies used both as monotherapy and in combination with chemotherapy.

The activity of the MAPK pathway induces proliferation, differentiation, migration, survival and angiogenesis processes. Abnormal activation of the MAPK pathway is a phenomenon observed in many cancers, e.g. melanoma, lung, colorectal or pancreatic cancers, and most often results from the abnormal function of RAS and BRAF signalling kinases harbouring activating mutations [10]. *RAS* mutations occur in 9–30% of all cancers, including *KRAS* (86%), *NRAS* (11%) and *HRAS* (3%) mutations [11]. The frequency of mutations in CRC depends on the location of the neoplastic process. *NRAS* mutations occur with a similar frequency throughout the intestine (about 6.5%), and *KRAS* mutations are more common in the right part of the colon (46%) than in the left part (35.8%) [12]. On the other hand, *BRAF* activating mutations occur 4 times more often in the right than the left part of the large intestine (16.3% *vs.* 4.3%, respectively) [12].

BRAF-targeted therapy

The process of neoplastic transformation of CRC with the *BRAF V600* activating mutation does not depend on the typical phenomenon commonly observed in this tumour, i.e., inactivation of the *APC* gene. *BRAF* activating mutation, occurring in about 8% of CRC patients, is a critical mutation initiating the process of neoplastic transformation in serrated polyps in which, instead of chromosomal instability, extensive DNA methylation occurs within the CpG islands (CGIs) [13]. Methylation can lead to the extinction of the promoter function of genes responsible for DNA repair, e.g., *MLH1*, which in turn causes microsatellite instability. Accordingly, microsatellite instability (MSI-H) is observed in 60% of intestinal cancers with *BRAF* gene mutation. *BRAF* activating mutations are more common in female patients and older age [14], and their presence is associated with lower differentiation, mucous histology, and greater local tumour advancement [15]. *BRAF* activating mutation is an unfavourable prognostic factor in patients with metastatic CRC. In the FOCUS study evaluating various strategies of systemic sequential CRC treatment, the risk of death was 82% higher (HR = 1.82; 95% CI: 1.36–2.43) in patients with mutated *BRAF* gene [16]. The meta-analysis of the above-mentioned study and CAIRO, CAIRO2, and COIN studies showed not only a 91% higher relative risk of death (HR = 1.91; 95% CI: 1.66–2.15), but also a significantly higher relative risk of progression or death (HR = 1.34; 95% CI: 1.17–1.54) [17].

The first attempts to block the function of mutant BRAF kinase were based on the BRAF inhibitor vemurafenib. In a study of 21 previously treated CRC patients with *BRAF V600E* mutation, clinical benefit (including one partial response) was shown in 8 patients, with median PFS and OS of 2.1 and 7.7 months, respectively [18]. In general, the obtained results were much less spectacular compared to the parallel studies in patients with advanced melanoma, but they indicated some activity of the strategy based on blocking of mutant BRAF kinase in CRC patients. Translational research identifying the mechanisms of resistance to treatment with a BRAF inhibitor in CRC patients with the *BRAF V600E* mutation showed that blocking the MAPK pathway triggers a feedback loop activating the membrane EGFR receptor and the parallel signalling pathway PI3K/AKT/mTOR cross activating the MAPK pathway downstream of BRAF kinase [19]. These findings resulted in attempts to combine vemurafenib and cetuximab. In the group of 27 CRC patients with *BRAF V600* mutation, after the failure of prior treatment (median 2 lines, range 1–6), half of the patients showed tumour shrinkage, meeting the criteria for partial response in 1 patient. Median PFS and OS were 3.7 and 7.1 months, respectively [20]. In turn, the combination of panitumumab with vemurafenib in a population of 15 CRC patients with *BRAF V600* allowed the disease control (at least stabilization) in 10 patients [21]. The combination of panitumumab with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) was evaluated in 24 patients with colorectal cancer with the *BRAF V600E* mutation, in whom this triple therapy resulted in a 21% objective response rate, with median PFS and OS of 4,1 months and 9.1 months, respectively [22]. Another BRAF inhibitor, encorafenib, in combination with cetuximab produced a 23% objective response rate and 54% disease stabilization rate, with a median PFS of 3.7 months [23]. The next step in the development of targeted therapies in the treatment of patients with a *BRAF* activating mutation were the attempts to combine targeted drugs with chemotherapy. In 2012, preclinical data appeared indicating the high effectiveness of vemurafenib, cetuximab and irinotecan combination [24]. A phase I study showed that the combination of these three drugs in CRC patients with *BRAF V600E* mutation-induced objective responses rate of 35% with a median PFS of 7.7 months. The same regimen was compared in a phase II study involving 106 patients with the combination of irinotecan and cetuximab. The addition of vemurafenib significantly reduced the relative risk of progression by more than half (HR = 0.42, $p < 0.001$) with a 4-fold increase in objective responses

(from 4% to 16%) and a 3-fold improvement in the disease control rate (from 22% to 67%) [25].

A ground-breaking phase III study (BEACON CRC) in patients with advanced CRC with *BRAF V600* mutation compared two experimental regimens: a triple [encorafenib (BRAF inhibitor), binimetinib (MEK inhibitor), cetuximab] and double therapy (encorafenib, cetuximab) with standard chemotherapy (irinotecan + cetuximab or FOLFIRI + cetuximab) [26]. In total 665 patients with metastatic CRC with *BRAF V600E* mutation were randomized in a 1:1:1 ratio to three arms receiving one of the above-mentioned systemic treatment strategies. The primary endpoints of the study were OS and objective response rate in the arm receiving triple therapy compared to standard chemotherapy. The median OS in the triple therapy arm was 9.0 months compared to 5.4 months in the control arm, which translated into a significant, almost 50% reduction in the relative risk of death (HR = 0.52; 95% CI: 0.39–0.70). Additionally, in the triple therapy arm, the objective response rate was 6 times higher than in the control arm (26% *vs.* 4%), the percentage of patients with clinical benefit was also higher (69% and 31%), and progression at first post-baseline assessment was found in 10% of patients receiving triple therapy and 34% of patients receiving chemotherapy. In the case of experimental double therapy, the median OS was 8.4 months, which translated into a significant reduction in the risk of death by 40% compared to the control arm (HR = 0.60; 95% CI: 0.45–0.79). The objective response rate in the experimental double therapy arm was 20%, clinical benefit was 74%, and progression at first post-baseline assessment was found only in 7% of patients. In the summary of adverse reactions in the BEACON CRC study, the best-tolerated regimen was the combination of encorafenib with cetuximab, for which fewer adverse events of G3 or higher severity (50% *vs.* 58% and 61%), diarrhoea (33% *vs.* 58% and 48%), including G3 severity (2% *vs.* 10% and 10%), and rash (29% *vs.* 49% and 39%) were reported compared to the triple regimen and chemotherapy. The analysis with use, among others, EORTC QLQ C30, FACT-C questionnaires, has shown a beneficial effect on the quality of life and the prolongation of time to QoL deterioration in patients receiving experimental regimens compared to chemotherapy [27]. In June this year, the European Medical Agency (EMA) has approved encorafenib in combination with cetuximab for the treatment of patients with metastatic CRC with *BRAF V600E* mutation after the failure of prior chemotherapy.

Microsatellite instability

Microsatellite instability (MSI-H) is a molecular disorder typical for Lynch syndrome that was first described in hereditary nonpolyposis colon cancer (HNPCC), accounting for 0.2–6% of this cancer. This is associated with impairment of the functions of the *MSH2*, *MLH1*, *PMS1* and *PMS2* genes belonging to the group of DNA mismatch repair (MMR) genes encoding the MMR proteins responsible for the repair of mismatched bases. The alterations in these genes lead to impaired DNA repair, resulting in microsatellite instability. Deficient MMR (dMMR) mechanisms prevent the correction of spontaneous errors that occur during DNA replication (e.g., base replacement, insertion or deletion of short fragments of DNA strands). About 15% of sporadic colorectal cancers show microsatellite instability, including 3% of cancers developing in carriers of hereditary mutations of DNA repair genes (Lynch syndrome), and the remaining 12% related to methylation of the *MLH1* gene promoter [28]. Methylation of the *MLH1* promoter region, as already mentioned, is strongly associated with *BRAF V600* mutation [29]. Colorectal cancers with MSI-H have some typical features — right-sided location, low differentiation, extracellular mucus secretion, and rich lymphocytic infiltrates [28, 30]. At the stage of metastatic disease, MSI-H colorectal cancers are characterized by a higher incidence in older patients, especially women, and synchronous metastases more often in the peritoneum or lymph nodes than in the liver [31]. Deficient MMR mechanisms lead to the accumulation of mutations in the cell and the formation of the so-called hypermutator profile. In cancer cells with dMMR, abnormal proteins formed on the matrix of damaged genes can be recognized by the immune system as foreign (antigens), which in turn leads to an increase in cell immunogenicity. As the condition for the progression of a neoplastic disease characterized by high immunogenicity is the impairment of the immune mechanisms of the specific antitumor response, tumours with microsatellite instability often express suppressor molecules such as PD-L1, PD-L2 [32]. In connection with this in the case of neoplasms with microsatellite instability, the effectiveness of immunotherapy began to be intensively assessed.

One of the first studies on checkpoint inhibitors in the treatment of patients with MSI-H CRC was the phase II MK-3475 trial with pembrolizumab. This study included 41 patients with chemoresistant solid tumours, including 32 patients with CRC (11 MSI-H and 21 without microsatellite instability - MSI-L), with > 70% patients receiving more than 3 lines of prior systemic treatment [33]. The objective response rate and disease control rate were 40% and 90%, respectively, in MSI-H CRC patients versus 0% and 11% in the MSI-L population. The use of pembrolizumab in patients with CRC MSI-H was associated with a significant reduction in the relative risk of progression and death by 90% (HR = 0.10, $p < 0.001$) and death alone by 80% (HR = 0.20, $p < 0.05$) with a median of PFS and OS in CRC MSI-L patients of

2.2 and 5.0 months, respectively. Recent publications of the MK-3475 study after 12 months of follow-up indicate that the median of PFS and OS in MSI-H patients has not yet been achieved [34].

Phase III Keynote-177 study enrolled 307 previously untreated patients with advanced MSI-H/dMMR CRC. Patients were randomized in a 1:1 ratio to either the experimental arm receiving pembrolizumab monotherapy (200 mg every 3 months for up to 35 courses) or the control arm receiving chemotherapy (mFOLFOX6 or FOLFIRI used alone or in combination with biological drug bevacizumab or cetuximab). After a median follow-up of 32.4 months, it was shown that pembrolizumab was associated with a significant reduction in the relative risk of progression by 40% (HR for PFS = 0.60; 95% CI: 0.45–0.80) with more than two-fold difference in the medians PFS (16.5 *vs.* 8.2 months) and 2-year PFS rates (48% and 19%) in the experimental and control arm, respectively [35]. In the pembrolizumab arm, there was a higher objective response rate, (43.8% *vs.* 33.1%), including a complete response rate (11.1% *vs.* 3.9%). At the same time, however, a greater percentage of patients did not respond to the treatment in the pembrolizumab arm (disease progression at the first post-baseline assessment was 29.4% for immunotherapy versus 12.3% for chemotherapy). PFS subgroup analyses showed that only patients with *KRAS* or *NRAS* genes mutations did not benefit from immunotherapy. Adverse reactions in CTC grade 3–5 were almost three times more frequent in the pembrolizumab arm (66%) than in the chemotherapy arm (22%).

Another checkpoint inhibitor evaluated in patients with MSI-H CRC was nivolumab. In the phase II CheckMate142 study, the combination of nivolumab and low-dose ipilimumab was assessed in the population of patients with metastatic MSI-H/dMMR CRC. In a group of 45 patients, nivolumab was administered every 2 weeks and ipilimumab every 6 weeks. The objective response rate was 69%, including a complete response rate of 13%, and the disease control rate of 84% [36]. The median duration of response, PFS or OS was not reached, and the 24-month PFS and OS rates were 74% and 79%, respectively. Disease progression at the first post-baseline assessment was observed in 13% of patients. Combined double immunotherapy was associated with the occurrence of CTC G3-4 side effects in 22% of patients, and discontinuation of treatment, for this reason, was necessary for 7%.

KRAS-targeted therapy

The *KRAS* gene is the most commonly mutated oncogene in human tumours. It encodes KRAS GTPase, which is an element of signal transduction within the MAPK cascade (RAS-RAF-MEK-ERK), which also has the potential to activate the PI3K-AKT-mTOR pathway. For this reason, *KRAS* mutations have a key impact on inducing an aggressive phenotype of cancer cells, inducing their proliferation, stimulating survival, production of key proteins and resistance to pro-apoptotic signals. The *KRAS* gene mutation, similarly to *NRAS* or *BRAF*, is a negative predictor of the response to anti-EGFR antibodies because it makes intracellular signalling independent of the function of the EGFR transmembrane receptor. For a very long time, it seemed that KRAS was a protein for which targeted pharmacological blockade would not be possible at all. The *KRAS* p.G12C mutation (replacement of glycine with cysteine at position 12) occurs in approximately 13% of non-small cell lung cancers and 1–3% of colon cancers and other solid tumours. In a phase I study, sotorasib — an irreversible, small molecule $KRAS^{G12C}$ inhibitor was evaluated in a population of 130 patients with advanced solid tumours with *KRAS* p.G12C mutation (including 42 CRC patients), most of whom received at least 3 lines of prior systemic treatment [37]. In CRC patients with the *KRAS* p.G12C mutation, sotorasib enabled disease control in 74% of patients (including 7% of partial responses), and disease progression was observed in 24% of patients. Serious adverse events (SAEs) of sotorasib were observed in 45% of patients in the overall population, including 7% of SAEs leading to treatment discontinuation. The most common adverse events (≥ G3) were diarrhoea, weakness, nausea and vomiting, abdominal pain, and dyspnoea and cough. Sotorasib is the first active KRAS inhibitor demonstrating the activity in patients with solid tumours with the *KRAS* p.G12C mutation; however, its activity in colorectal cancer seems to be markedly lower than in non-small cell lung cancer.

Summary

The progress that has been made in recent years in the field of treatment of patients with CRC relates not only to the improvement of effective palliative treatment but also the effective and safe pharmacological treatment with curative intent. The results of the IDEA study indicate the possibility of de-escalating adjuvant treatment and minimizing the risk of chronic side effects in a group of relatively low-stage patients who require double chemotherapy. It seems that the CAPOX regimen should be the first-line treatment in all patients with stage III CRC. In patients with T1–3 and N1 tumours, it allows to use only a 3-month adjuvant therapy, and in all patients, regardless of the initial stage, it allows to reduce the frequency of visits and prevent hospitalization, which, especially in the current epidemic situation, is of key importance for patient safety.

Regarding palliative treatment, the emergence of new targeted therapies dedicated to more and more sophisticated patient populations is observed. Contrary to the routinely available targeted therapies where anti-angiogenic treatment (bevacizumab, aflibercept, regorafenib or ramucirumab) is indicated for all patients with advanced CRC with no contraindications, and anti-EGFR antibodies are indicated in almost half of the patients, the use of new therapies will be much more limited. Immune checkpoint inhibitors are potentially intended for approximately 12% of MSI-H CRC patients, BRAF inhibitors for 8% of patients with the *BRAF V600E* mutation, and the KRAS inhibitor sotorasib for 1–3% of patients with the *KRAS* p.G12C mutation. There is no doubt, however, that better and better personalization and optimization of systemic treatment is the right direction to improve the possibilities of active and safe systemic treatment of patients with advanced colorectal cancer.

Unfortunately, in Poland, the biggest problem in improving the prognosis of patients with advanced CRC is still the reimbursement limitations in access to new, active therapies such as BRAF inhibitors or anti-PD1 antibodies. In this context, however, one should remember the possibilities offered by the procedure of individual financing of therapy as part of emergency access to drug therapies. These limitations, however, do not pose any problems in the case of adjuvant treatment, where incorporation of the IDEA study results into clinical practice is possible without delay.

Conflict of interest

Speaker, advisory honoraria from Roche, Merck, Amen, Servier. Travel grants — Merck, Roche.

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VIA MEDICA

REVIEW ARTICLE

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Systemic treatment of patients with advanced hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma is the most common histologic type among primary liver neoplasms, which are the second cause of cancer-related deaths worldwide. Resection, ablation, liver transplantation or transarterial chemoembolization can be used in some patients but majority of patients receive systemic treatment provided their performance status is good and liver function is preserved. Overall, 5-year survival remains low and in Europe is 12%. Since 2008 sorafenib was the only drug with proven survival improvement in the first-line treatment. Regorafenib and cabozantinib showed efficacy in second-line treatment. Recently published the results of IMbrave150 trial showed that combination of atezolizumab with bevacizumab is much more effective than sorafenib in the first-line treatment. These results of IMbrave150 study will most probably change a daily-practice entirely.

Key words: hepatocellular carcinoma, systemic treatment, sorafenib, atezolizumab, bevacizumab

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Primary liver cancers are the second most common cause of cancer-related deaths in the world [1]. There are app. 800,000 new cases of primary liver cancer diagnosed every year, and about 750,000 people die. HCC is almost 3-fold more prevalent among men than women, and the highest incidence occurs in the countries of Eastern and South-Eastern Asia. The incidence of liver cancer is also increasing in Western countries, e.g. according to the SEER (The Surveillance, Epidemiology, and End Results) registry data, in the United States the incidence of HCC increased from 1.51/100,000 in 1973 to 6.20/100,000 in 2011 [2].

In Poland — according to the National Cancer Registry data — in 2017 almost 1,500 new HCC cases were diagnosed, and more than 2,000 patients died of this disease [3].

The prognosis of patients with HCC is poor — the 5-year survival rate in Europe is 12% [4].

Radical treatment methods include resection of the liver parenchyma, radiofrequency ablation (RFA) and organ transplantation. A valuable method that can be used in selected patients is transarterial chemoembolization (TACE). In the case of inability to use or ineffectiveness of the above-mentioned methods a palliative systemic treatment is indicated.

The choice of treatment method depends primarily on the disease stage and liver function. Many scoring systems assessing liver function have been developed — the oldest is the Child-Pugh scale, originally intended for risk assessment in patients undergoing surgical treatment (Tab. 1). The Child-Pugh scoring system was widely used during qualification of patients for prospective clinical trials, where in majority class A was the prerequisite. A useful scale that combines the assessment of liver function, general patient's performance status and the disease stage is the so-called Barcelona scale (BCLC, Barcelona-Clinic Liver Cancer staging system). In addition to prognostic information, the BCLC scale has therapeutic implications (Tab. 2).

Table 1. The Child-Pugh scoring system [5]

Measure	Number of points		
	1	2	3
Encephalopathy (grade)	0	1–2	3–4
Ascites	None	Mild	Severe
Serum albumin [g/dL]	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3
Total bilirubin [mg/dL]	< 2	2–3	> 3
Total	5–6	7–9	10–15
Liver functional class	A	B	C
Operational risk	Low	Moderate	High

INR — international normalized ratio

Table 2. Barcelona-Clinic Liver Cancer (BCLC) staging system [6]

Stage	0	A	B	C	D
Features	Single tumor < 2 cm and Child-Pugh A and PS 0	1–3 tumors < 3 cm and Child-Pugh A and PS 0	Many unresectable tumors and Child-Pugh A and PS 0	Portal vein invasion (PVI) and extrahepatic spread (ES) and Child-Pugh A and PS 0–2	Liver transplantation not possible and Child-Pugh B-C or PS 3–4
Treatment	RFA, resection	RFA, resection, liver transplantation	TACE	Systemic treatment	Only palliative treatment

TACE — transarterial chemoembolization; RFA — radiofrequency ablation; PS — performance status

Chemotherapy

The value of classical cytotoxic drugs in patients with advanced HCC is unconfirmed. The results of a prospective, controlled study in a small group of patients were published many years ago, indicating that doxorubicin may slightly (median 10.6 *vs.* 7.5 weeks) prolong overall survival (OS) compared to symptomatic treatment; however, at the expense of significant toxicity [7]. The value of doxorubicin in systemic palliative treatment has not been confirmed in subsequent studies.

Antiangiogenic drugs

The era of therapeutic nihilism in patients with advanced HCC ended in 2008, when the results of the Phase III SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) were published [8]. The study included 602 previously systemically untreated patients with overall performance status according to ECOG from 0 to 2 and liver efficiency class A according to the Child-Pugh classification. Patients were randomly assigned to experimental arm receiving sorafenib or control arm with placebo. Sorafenib is an inhibitor of RAF-1 and BRAF serine/threonine kinases, as well as VEGFR1-3 and PDGFR-β tyrosine kinases. The primary endpoint of the SHARP study was OS and time to symptomatic progression defined as a deterioration in quality of life of at least 4 points on the FHSI-8 (FACT Hepatobiliary Symptom Index) questionnaire for at least 3 weeks or worsening of performance status to 4 or death. The study turned out to be positive only for the first endpoint — sorafenib increased the median OS by 2.8 months (10.7 *vs.* 7.9 months), with the hazard ratio (HR) of 0.69 (95% CI: 0.55–0.87; $p < 0.001$). The median symptomatic progression-free survival (sPFS) was 4.1 *vs.* 4.9 months ($p = 0.77$).

The value of sorafenib was also confirmed in a study with no formal endpoints conducted among China, South Korea and Taiwan residents [9].

Sunitinib is multitargeted inhibitor of receptor tyrosine kinases, including VEGFR1-3, PDGFRα, PDGFRβ, KIT, FLT3, CSF-1R and RET. Therefore, a phase III study SUN1170 HCC was conducted comparing sunitinib to sorafenib in the first-line palliative treatment of HCC patients [10]. The study enrolled over 1,000 patients, the primary endpoint was OS, and it was assumed that sunitinib would be more effective, or at least not inferior as compared to sorafenib. The study was terminated prematurely due to the futility analysis results and for safety reasons — the OS of patients receiving sunitinib was shorter and the toxicity of the drug was higher.

The phase III CALGB 80802 study showed no improvement of prognosis after addition of doxorubicin in patients treated with sorafenib [11].

Lenvatinib is a multi-kinase inhibitor that inhibits VEGFR1-3, FGFR1-4, PDGFRα, RET and KIT. A non-inferiority study comparing lenvatinib to sorafenib was planned and performed [12]. The primary endpoint was OS, non-inferiority hypothesis was scheduled first, and if proven, testing the superiority hypothesis was assumed. It was also assumed that lenvatinib would retain at least 60% of the effect of sorafenib in prolonging OS compared to placebo. The delta value was thus defined as the upper limit of the 95% CI for a HR OS less than 1.08. In total 954 patients were enrolled to the study, and the HR OS in the intent-to-treat population was 0.92 (95% CI: 0.79–1.06), which allowed to reject the null hypothesis. It was also confirmed in per-protocol population, involving 929 patients. However, lenvatinib did not improve the quality of life and reduce the toxicity of the treatment. Obviously, lenvatinib was not more effective than sorafenib.

Regorafenib is a multi-kinase inhibitor of VEGFR1-3, TIE2, KIT, RET, RAF-1, BRAF, PDGFR, FGFR and CSF1R. The phase III RESORCE study involved 843 patients with progression during sorafenib therapy, provided that the drug is well tolerated (daily dose of at least 400 mg for at least 20 days during the last 4 weeks of sorafenib use) [13]. Patients were randomized in a 2:1 ratio to regorafenib or placebo. The primary endpoint of the RESORCE study was OS. The study was positive, median OS was 10.6 months *vs.* 7.8 months, HR OS 0.63 (95% CI: 0.50–0.79). Grade 3 or 4 treatment-related adverse events occurred in 67% of patients receiving regorafenib recipients compared to 39% in the placebo group.

Another drug that has shown an improvement in prognosis in the next line of systemic treatment in patients previously receiving sorafenib was cabozantinib, which is an inhibitor of VEGFR1-3, MET and AXL tyrosine kinases. The CELESTIAL study included 707 patients after no more than 2 lines of previous systemic treatment including sorafenib (approximately 30% of patients) [14]. Patients were randomized in 2:1 ratio to cabozantinib or placebo. The primary endpoint was OS. During the second of three pre-planned interim analyzes the observed difference met the assumptions of statistical significance. The median OS in the experimental arm was 10.2 months compared to 8.0 months in patients receiving placebo (HR 0.76; 95% CI: 0.63–0.92; $p = 0.005$). Grade 3 or 4 side effects occurred in 68% of patients in the experimental arm and in 36% of patients in the control group.

Immunotherapy

Patients with advanced HCC previously treated with sorafenib were enrolled to various cohorts of the CheckMate 040 uncontrolled study with objective response rate as the primary endpoint. Monotherapy with nivolumab (anti-PD-1 antibody) resulted in 20% of objective responses, and in the case of combined use of nivolumab and ipilimumab (anti-CTLA-4 antibody), the objective response rates ranged between 27% and 32%, depending on the doses and administration schedule [15, 16].

A phase III CheckMate 459 study was also conducted, comparing nivolumab with sorafenib in a group of 743 previously systemically untreated patients with advanced HCC. The primary endpoint of the study was OS. The outcome was negative – it was not possible to demonstrate a statistically significant difference in favor of nivolumab [17].

Pembrolizumab (anti-PD-1 antibody) was used in patients previously treated with sorafenib in a phase II uncontrolled KEYNOTE-224 study [18]. In the group of 104 patients, 17% of objective responses were achieved. However, the results of the phase III KEYNOTE-240 study, including 413 patients previously treated with sorafenib, were very disappointing [19]. Patients were randomized to pembrolizumab or placebo, and the co-primary endpoints were OS and PFS. There were no differences meeting the specified criteria of statistical significance for OS and PFS. Adopting a more conventional study design with a single endpoint of OS would likely be considered formally positive as the median OS of patients receiving pembrolizumab was 13.9 months compared to 10.6 months in the placebo group (HR 0.78; 95% CI: 0.61–1.00; nominal $p = 0.02$).

When it seemed that sorafenib would remain the standard of first-line palliative treatment, and immunotherapy would only be used in selected patients in subsequent treatment lines, the results of the IMbrave150 study were presented for the first time at the 2019 ESMO-Asia congress [20]. The study enrolled 501 previously untreated patients with advanced HCC who were randomized in 2:1 ratio to atezolizumab (anti-PD-L1 antibody) with bevacizumab (anti-VEGF antibody) or sorafenib arm. One of the exclusion criteria was the presence of an active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Randomization was stratified by geographic region (Asia without Japan *vs.* other countries), presence of large vessel infiltration or extrahepatic dissemination (yes *vs.* no), baseline AFP level (400 *vs.* ≥ 400 ng/mL), and ECOG performance status (0 *vs.* 1). The primary endpoints of the study were OS and PFS. After a median follow-up of almost 9 months, a significant increase in OS was achieved (HR 0.58; 95% CI: 0.42–0.79; $p < 0.001$; median not reached *vs.* 13.2 months; estimated 1-year survival rate was 67% *vs.* 55%). Median PFS was 6.8 months *vs.* 4.3 months (HR 0.59; 95% CI: 0.47–0.76; $p < 0.001$). Grade 3 or 4 adverse events occurred in 57% of patients in the experimental group and 55% of patients in the control group. The incidence of serious adverse events was 38% *vs.* 31%. Importantly, the quality of life of patients in the experimental group was maintained longer. The median

Table 3. The most important phase III studies, the results of which shaped the strategy of systemic treatment in patients with advanced hepatocellular carcinoma

Author, year and reference	Sample size, N	Treatment line	Experimental arm	Control arm	Primary endpoint	Outcomes
Llovet 2008 [8]	602	1.	Sorafenib	Placebo	OS Time to symptomatic progression	Median OS 10.7 *vs.* 7.9 months (SS) Time to symptomatic progression (NS)
Kudo 2018 [12]	954	1.	Lenvatinib	Sorafenib	OS	The hypothesis that lenvatinib is inferior to sorafenib has been rejected
Bruix 2017 [13]	846	2.	Regorafenib	Placebo	OS	Median OS 10.6 *vs.* 7.8 months (SS)
Abou-Alfa 2018 [14]	707	2. or 3.	Cabozantinib	Placebo	OS	Median OS 10.2 *vs.* 8.0 months (SS)
Finn 2020 [20]	501	1.	Atezolizumab with bevacizumab	Sorafenib	OS and PFS	HR OS 0.58; 95% CI: 0.42–0.79 (SS). Median PFS 6.8 *vs.* 4.3 months (SS)

CI — confidence interval; HR — hazard risk; NS — statistically non-significant; OS — overall survival; PFS — progression-free survival; SS — statistically significant

time to a significant deterioration in the quality of life was 11.2 months *vs.* 3.6 month, respectively [21].

At the end of May 2020, the US Food and Drug Administration (FDA) approved atezolizumab with bevacizumab in the first-line treatment of patients with advanced HCC.

Table 3 summarizes the results of the most important phase III studies.

Summary

Since the publication of the SHARP study results, several clinical trials have been conducted to improve the effectiveness of systemic treatment in patients with advanced HCC. Most of them failed. It has been shown that regorafenib and cabozantinib improve prognosis in patients previously treated with sorafenib, and modern immunotherapy in some patients allows obtaining an objective response with moderate toxicity, but without a proven effect on the improvement of OS. In this context, the results of the IMbrave150 study should be considered a very significant advance defining a new first-line treatment strategy.

Conflict of interest

Advisory and lecture fees from Roche and Ipsen; travel grants from Roche.

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REVIEW ARTICLE

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Primary breast lymphoma (PBL) in men — a systematic review

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ABSTRACT

Primary breast lymphoma (PBL) is a rare type of lymphoma, especially in men. Details of the clinical course are not well recognized, and a consensus on the treatment of PBL in male is not available. The objective of presenting this study was to find the most common presentation and the best treatment options for male PBL by collecting and analysing data of all reported cases published between 1985 and 2019.

A comprehensive search in Google Scholar, Ovid Medline, PubMed, and Scopus databases for any case of PBL presenting in men between 1985 and 2019 was performed. Patient information such as age, diagnosis, type of treatment(s), time to follow-up and patient status were recorded.

A total of 28 studies containing data of 34 male patients with PBL were included in this review. The mean age of patients was about 61 (range: 26–85) years. The mean tumour size was 46.05 ± 20.37 mm. The majority of cases were presented with a palpable breast mass (unilateral or bilateral). Nine patients (26.5%) had previous comorbidities. Diffuse large B cell lymphoma was the most common histologic diagnosis (85.3%). Treatment consisting of systematic therapy combined with radiotherapy showed benefit outcome.

The results of the analysis showed that the response to different therapies was better in younger patients with PBL. It seems that systemic therapy combined with at least a 30 Gy dose of radiation has the best outcome in male patients with PBL. Considering limited data in each group of treatment modality, further follow-up studies in these patients are necessary.

Key words: breast, lymphoma, male, systematic review

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Introduction

Primary breast lymphoma (PBL) is a rare type of lymphoma involving only the breast, with or without axillary lymph nodes; and no extra-mammary disease [1, 2]. Overall, PBL accounts for approximately 1% of non-Hodgkin lymphomas (NHL) [3], less than 3% of extranodal lymphomas, and 0.5 % of breast malignancies [4]. More than 95% of PBL cases are female and the most frequent histological subtype is diffuse large B-cell lymphoma (DLBCL) [5, 6].

Owing to the limited number of male patients, details of treatment or clinical course are not sufficiently reliable, and no standard therapy has been established. Local control seems poor with surgical resection alone, so the combination of chemotherapy and radiation has been recommended [6, 7].

This review aimed to find all published cases of male PBL to understand the course of disease more precisely and also to reach a consensus about the optimal therapy.

Methods

Search strategy

A comprehensive search was performed in Google Scholar, Ovid Medline, PubMed, and Scopus databases for any case or detail of PBL presenting in men between

1985 and 2019. This date range was chosen because the earliest study was found in 1985. The keywords "breast" OR "mammary" AND "lymphoma" combined with "male" OR "man" OR "men" were used for the search. The initial screening was based on titles and abstracts of the returned results. Studies were included if they contained information about male patients with PBL and excluded if they reported secondary involvement of the breast in lymphoma, or did not report the male patient data in detail. To avoid bias with linguistic restriction, at first, the studies were selected regardless of the language of publication. Papers with available English abstracts were included in the first screening. In the next stage, full texts of all selected abstracts were studied. As in the first screening, articles that contained PBL as defined previously were included. Non-English papers were included if the abstract gave all the necessary information. References and tables of the included articles were also checked out for any omitted study, and detected papers were screened and included with the same criteria thereafter.

Types of studies selected

All observational studies (case report, case series) that reported PBL presenting in men were selected. Because of the scarcity of PBL in male, all studies were included even by incomplete data.

Data extraction

A data extraction form was designed a priori and three academic experts (two breast surgeon and one investigator) confirmed its face validation and ease of use for data extraction. Data items consisted of the name of the first author, publication year, patient's age, laterality of breast mass, tumour size, first presentation, diagnosis, stage of the disease, treatment, drug and comorbidity history, follow-up time and status. Patients' outcomes were categorized as no evidence of disease (NED); alive with the disease (AWD); dead of disease (DOD). Two reviewers extracted the data out of the included studies independently, and all data was checked by a third party. Continuous and proper monitoring of newly published papers went on until final data extraction.

Statistics

The statistical analyses were performed using IBM SPSS 26 (IBM Corp. Released in 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

Results

Totally 28 studies containing data of 34 male patients with PBL were included in this review (Tab. 1). Two studies had no English full text, so data was limited to the abstracts [8, 9]. The data of 5 cases were extracted from one study which was a case report and review article [10] and the review part of this study included data of 4 cases whose original articles (case reports) were not found.

Data of the 34 PBL male cases are summarized in Table 2. The mean age of patients was about 61 (range: 26–85) years. The majority of cases presented with a palpable breast mass (unilateral or bilateral). Nine patients (26.5%) had previous comorbidities including other cancers, HIV, hepatitis, cirrhosis, and previous history of a kidney transplant. Ten cases in this review had gynecomastia (4 bilateral & 6 unilateral) and one of the patients was transgender. Three patients had a previous history of hormone therapy with oestrogen (3 m, 5 y, and 9 y), two patients received hormone therapy (hormone pills and sex hormone), one patient had received 10 years of immunosuppressive therapy, and the other had undergone antiviral treatment for 4 years. Two patients had a brain and adrenal metastasis.

The most frequent histopathology was DLBCL, reported in 29 (85.3%). As far as information was available, the majority of patients in stage I (14 patients) reported no evidence of disease at the time of follow-up. Chemotherapy was the most frequently administered therapy and 27 patients had received chemotherapy, alone (8 patients) or in combination with surgery or radiotherapy (15 patients). Multi-agent chemotherapy consisted of CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) or CHOP-like regimen in 15 patients. Four out of five patients (80%) with available status received immunochemotherapy (R-CHOP: rituximab + CHOP) showed complete remission and one patient was alive with disease. However, in 9 patients who treated with CHOP without rituximab, two deaths occurred and one patient was alive with disease. Five patients were treated only by surgery. Treatment data of three patients were not available.

The treatment and outcome were not available in seven patients and one patient died due to other condition (cerebrovascular accident) while the final information about the outcome of their lymphoma was not reported. Therefore, after the mean follow up time of 19 months (range: 0–123) in 27 patients, the number of patients with NED, AWD, and DOD outcomes were 19, 3, and 5, respectively. In Table 3 are demonstrated the effects of some variables on disease outcomes (Alive or Dead) in 27 patients. Eight patients who received radiotherapy combined with other modality were alive.

Discussion

The breast is a rare extranodal site of involvement by lymphoma, especially in men. However, breast lymphoma should be included in the differential diagnosis of breast masses in male patients, particularly in immunocompromised ones [11].

Table 1. Characteristics of 34 male pr imary breast lymphoma patients

No	Ref	Author, Year	Age	Laterality	Diagnosis	Stage	Chemotherapy	RT, Gy	Surgery	Follow-up (month)	Status
1	24	López-Rodríguez, 2019	81	Lt	DLBCL	IE	4 × CP	Y, NA	No	0	NED
2	29	Bozkaya, 2019	82	Bilateral	DLBCL	IIIA	2 × R-CHOP	No	No	0	NED
3	30	Jonckheere, 2019	80	Lt	DLBCL	NA	NA	NA	NA	NA	NA
4	8	Tokuyama, 2017	74	Rt	DLBCL	IIA	6 × R-CHOP + 4 × intrathecal	No	No	0	NED
5	9	Goto, 2017	85	Rt	DLBCL	NA	NA	NA	NA	NA	NA
6	25	Corobea, 2017	56	Rt	DLBCL	IE	3 × R-CHOP	Y, 50Gy	MRM	17	NED
7	10	Ishibashi, 2016	75	Bilateral	DLBCL	IE	8 × rituximab monotherapy	Y, 40Gy, 50Gy	No	8	NED
8	10	Ishibashi, 2016	69	Unknown	DLBCL	IIE	Poly	No	MRM	18	DOD
9	10	Ishibashi, 2016	45	Unknown	DLBCL	IIE	No	No	Tumour excision	5	NED
10	10	Ishibashi, 2016	65	Unknown	DLBCL	IE	Poly	No	MRM	20	NED
11	10	Ishibashi, 2016	81	Unknown	LL	NA	No	No	MRM	4	AWD
12	11	Yim, 2015	63	Lt	DLBCL	IE	R-CHOP	No	No	11	AWD
13	31	Jung, 2014	46	Rt	FL	IEA	No	No	Surgery	40	NED
14	32	Lokesh, 2013	60	Lt	SLL	IIEA	9 × (COP)	No	No	Lost to follow-up	NA
15	32	Lokesh, 2013	46	Rt	DLBCL	IIEA	3 × CHOP	No	No	0	Dead
16	33	Mukhtar, 2013	50	Lt	DLBCL	IIB	CHOP	Y, 50Gy	No	0	NED
17	34	Mouna, 2012	76	Lt	DLBCL	IBE	No	No	Tumour Excision	3	DOD
18	35	Ko, 2012	51	Lt	DLBCL	IA	5 × CHOP	No	No	12	NED
19	36	Rastogi, 2012	48	Rt	DLBCL	IE	CHOP	No	No	0.63	DOD
20	37	Li, 2012	33	Rt	DLBCL	IA	CHOP	No	MRM	29	NED
21	37	Li, 2012	63	Rt	DLBCL	IA	No	No	Tumour Excision	NA	NA
22	26	Alhabashi, 2011	26	Rt	DLBCL	II	6 × CHOP	Y, 40±50Gy	No	24	NED
23	38	Rathod, 2011	48	Lt	DLBCL	II	14 × CHOP	No	No	7	AWD
24	39	Duman, 2011	62	Lt	MZBL	IIE	R-CHOP	Y, NA	Tumour Excision	NA	NA
25	40	Mahmood, 2011	50	Lt	DLBCL	IIE	NA	NA	NA	NA	NA
26	27	Miura, 2009	64	Lt	DLBCL	IEA	6 × R-CHOP	Y, 50Gy	No	12	NED
27	41	Gualco, 2009	65	Rt	ALCL	IE	Yes	Y, NA	No	18	Alive
28	42	Mpallas, 2004	67	Rt	DLBCL	II	Yes	No	MRM	12	DOD
29	28	Cabras, 2004	44	Lt	DLBCL	IIAE	ACOP-B	Y, 36Gy	Tumour Excision	123	NED
30	43	Evans, 2002	27	Lt	DLBCL	IA	Poly	No	No	NA	NED
31	20	Sashiyama, 1999	69	Lt	DLBCL	IE	3 × CHOP	No	MRM	12	NED
32	44	Hinoshita, 1998	65	Lt	DLBCL	IIAE	CPA, VDS, 6-mercaptopurine, Daunorubicin, PSL	No	LMRM	24	NED
33	45	Murata,1996	76	Rt	DLBCL	IE	5 × post-op CHOP	No	RMRM	39	NED
34	1	Hugh, 1990	81	Bilateral	DLBCL	IE	Yes	No	No	5	DOD

Rt — right; Lt — left; ALN — axillary lymph node; DLBCL — diffuse large B cell lymphoma; LL — Lymphoblastic lymphosarcoma; FL — follicular lymphoma; SLL — small lymphocytic lymphoma; MZBL — marginal zone breast lymphoma; Poly — multiagent chemotherapy; RT — radiotherapy; MRM — modified radical mastectomy; LMRM — left MRM; RMRM — right MRM; CP — cyclophosphamide and prednizone; CHOP — cyclophosphamide; adriamycin; vincristine; prednisolone; R-CHOP — rituximab + CHOP; ACOP-B — doxorubicin; cyclophosphamide; vincristine; prednisone; bleomycin; NA — not available; NED — no evidence of disease; AWD — alive with the disease; DOD — dead of disease

Table 2. Patient and disease characteristics of all patients

Variables		
Continuous variables	**Min–Max**	**Mean ± SD**
Age [years]	26–85	60.97 ± 16.04
Tumour clinical size [mm]	20–85	46.05 ± 20.37
Follow-up [months]	0–123	16.43 ± 24.16
Categorical variables	**Frequency**	**Percentage**
Breast side		
Right	12	35.3
Left	15	44.1
Bilateral	3	8.8
Unknown	4	11.8
Symptoms		
Palpable	16	47.1
Pain	9	26.5
Unknown	9	26.5
Diagnosis		
Diffuse large B-cell lymphoma	29	85.3
Anaplastic large cell lymphoma	1	2.9
Follicular lymphoma	1	2.9
Lymphoblastic lymphosarcoma	1	2.9
Marginal zone breast lymphoma	1	2.9
Small Lymphocyte lymphoma	1	2.9
Stage		
I	17	50
II	13	38.2
III	1	2.9
Unknown	3	8.8
Treatment		
Surgery	15	44.1
Chemotherapy	26	76.5
Radiotherapy	8	23.5
Unknown	3	8.8
Comorbidity	9	26.5
Cancer (colon and prostate)	2	5.9
HIV positive	2	5.9
Cirrhosis (alcoholic, non-alcoholic)	2	5.9
Hepatitis (B and C)	2	5.9
Kidney Transplant	1	2.9
Drug history		
Oestrogen	5	14.7
Antiviral	1	2.9
Immunosuppressive	1	2.9

PBL includes a lesion in the breast with or without the involvement of axillary lymph nodes, without any other extra-mammary lesion and a technically adequate pathologic exam confirms the presence of breast tissue near lymphoma [12, 13]. Diagnosis of primary breast non-Hodgkin lymphoma needs adequate histologic evaluation, presence of breast tissue close to the lymphoma in the specimen, no previous diagnosis of lymphoma, and no extramammary disease except ipsilateral axillary lymph nodes [1, 4]. The most common subtype is diffuse large B-cell lymphoma (DLBCL), but other subtypes including follicular lymphomas (FL), mucosa-associated lymphoid tissue (MALT) lymphomas and Burkitt's lymphomas (BL) are also seen [6, 14].

Because of the rarity, only a few scattered reports of these cases are published and many published series of breast lymphoma are a mixture of patients with PBL, extra-mammary lymphoma, secondary breast lymphoma, and recurrence of lymphoma in the breast. Additionally, many of the articles reported both male and female cases, so accurate and detailed data on the clinical course of the disease in men; its treatment and follow up is limited. The increasing number of reports in the recent past few years may represent increasing awareness toward the disease and the need for a comprehensive agreement about the management.

Age and laterality

The mean age of patients in this study (60.97 ± 16.04) was compatible with other studies [1, 4, 15]. In contrast to the Hugh et al. [1] study in women diagnosed with PBL (2 out of 20 cases were male) and Uesato study in Japanese cases (9 out of 380 cases were male) [16], that showed younger cases had poorer prognosis and lower survival, the result of the current study in males showed that younger male cases had a better response to different therapies. Furthermore, left breast involvement in the authors' review of male patients was more common, however, the involvement of the right breast was more frequently observed in women [1, 4, 6, 15]. Bilateral involvement was seen in 3 patients (8.8%), nearly similar to female studies which reported bilaterality in 4–13% at the time of diagnosis [1, 4, 6, 15]. Based on previous studies, bilateral breast disease was thought to be associated with aggressive disease [17]. In the presented study, 1 out of 3 (33.3%) patients with bilateral PBL died of the disease, whereas the frequency of death due to PBL was 11.1% in unilateral cases (2 out of 18). These numbers are too small for any deduction; it can only be said that bilateral male patients with PBL had poorer outcome regarding disease-related death.

Comorbidity and drug consumption

In this review, nine cases had a previous history of comorbidities. Three common comorbidities were cancer, HIV positivity, and Cirrhosis. Overall, it is known that non-Hodgkin lymphoma is the second most common AIDS-associated malignancy [18]. In this review two patients were HIV-positive and one of them died after 19 days of treatment, which consisted of a CHOP regimen only. Ten reviewed cases had gynecomastia, and five patients had a history of hormone therapy.

Table 3. Disease outcome based on tumour features, patient comorbidity and type of treatment.

	NED and AWD (n = 22)	DOD (n = 5)	Total
Age [years]	58.45 ± 17.13	68.20 ± 12.60	60.97 ± 16.04
Laterality			
Unilateral	17 (85)	3 (15)	20
Bilateral	2 (66.7)	1 (33.3)	3
Stage			
I	13 (81.3)	3 (18.8)	16
II	7 (77.8)	2 (22.2)	9
III	1 (100)	0 (0)	1
Unknown	3 (100)	0 (0)	3
Comorbidity			
No	16 (80)	4 (20)	20
Yes	6 (85.7)	1 (14.3)	7
Diagnosis			
DLBCL	19 (79.2)	5 (20.8)	24
ALCL	1 (100)	0 (0)	1
FL	1 (100)	0 (0)	1
LL	1 (100)	0 (0)	1
Treatment			
Only Surgery	3 (75)	1 (25)	4
Only Chemotherapy	6 (75)	2 (25)	8
Surgery + Chemotherapy	5 (71.4)	2 (28.6)	7
Chemotherapy + RT	6 (100)	0 (0)	6
Surgery + Chemotherapy + RT	2 (100)	0 (0)	2

Data are presented as mean ± standard deviation and number with percentages in parenthesis; DLBCL — diffuse large B-cell lymphoma; ALCL — anaplastic large cell lymphoma; FL — follicular lymphoma; LL — lymphoblastic lymphosarcoma; RT — radiotherapy; NED — no evidence of disease; AWD — alive with the disease; DOD — dead of disease

Sex hormone dependency was reported in two female cases of a study with 20 PBL cases (all but two cases were female patients) and their tumour cells were positive for estrogen and progesterone receptors [1]. Also, a large cohort study in women has shown that the risk of non- Hodgkin lymphoma in females who received oestrogen therapy was 29% higher than those who never used hormone therapy, for follicular lymphoma and DLBCL [19]. This evidence suggests that non-Hodgkin lymphoma in the male breast may involve patients with elevated oestrogen levels [20]. Although the role of oestrogen in the aetiology of this disease is not clear, several biologic mechanisms like immunomodulatory effects have been proposed [19]. Meanwhile, the rare occurrence of PBL in males may suggest a role for oestrogen in its pathogenesis.

Treatment

Due to the heterogeneity of the information, comparison of cases and conclusion on the best treatment method in PBL male patients is not possible but it seems that in recent studies with a majority of women cases, a non-surgical approach is preferred and chemotherapy has become the first choice of therapy either in combination with other treatment strategies (radiation and surgery) or alone.

The result of a large retrospective study in 204 cases (including five male patients) of DLBCL of the breast with various types of treatment regimen reported that anthracycline-containing chemotherapy and radiation therapy was associated with longer survival, and mastectomy had no benefit as opposed to biopsy or lumpectomy alone; the authors proposed that extensive surgeries may have detrimental effects by delaying the commencement of systemic therapy [6]. This study reported the outcome for males did not differ from female cohort cases, with 5-year overall survival of 60% and a wide confidence interval due to the small sample size of male patients [6]. In a Japanese article of 380 cases (including 9 men) of PBL [16], they concluded that five-year survival for stage I and II was lower by surgical treatment alone compared with surgery and systemic therapy (40.5% and 25% *vs.* 57.2% and 47%). They also showed that minimal surgery for confirming diagnosis and planning treatment was necessary, but mastectomy, wide local excision, and axillary dissection seemed unnecessary. They did not report the results of treatment in females and males separately.

ESMO Guideline in 2016 confirmed surgical resection is inadequate in local control and mastectomy is associated with poor outcomes and they suggested that initial surgery should be offered only if chemotherapy delays can be avoided [21].

In the present review of PBL presenting in men, 1 out of 4 patients who were treated by surgery alone died due to lymphoma. One patient was alive with the disease after 4 months and two patients were alive with no evidence of disease after 5 and 40 months of follow-up. Although the majority of the previously reported studies were conducted in female patients, the presented study can confirm that surgery is not an appropriate treatment for male PBL patients.

The role of radiotherapy in local control of PBL was shown in many studies [1]. Radiotherapy is considered for the prevention of subclinical disease in the breast, however, the optimal dose and radiation fields are various among different reports. A randomized prospective study by Avilés on 96 patients with PBL in the early stage is consistent with the presented study finding and showed a better survival for patients who received combined chemotherapy and radiation therapy compared to either therapy alone [22]. The median dose in most studies was 40 Gy (range 30.6 to 60 Gy) [1, 15] and involved site radiotherapy include ipsilateral breast plus any additional site of pre-chemotherapy disease in the regional node or contralateral breast has replaced involved-field radiotherapy [12]. Radiotherapy to the whole breast with a dose of 30 Gy after receiving R-CHOP for complete response is recommended [23].

Interestingly in the present review, all eight male patients who received radiotherapy combined with other treatment modality were alive without evidence of disease after a median of 17 months [10, 24–28]. Four patients received higher than 30 Gy (they mostly received 50 Gy), and information about radiation dosage was not available in one patient [24].

The presented data may confirm that chemotherapy (with or without rituximab) is the optimal choice in combination with other modalities, especially with radiotherapy (Tab. 3) in male patients. However, chemotherapy alone didn't provide a good prognosis, as 2 out of 9 (22.2%) deaths occurred in those who received chemotherapy alone and 2 cases were alive with disease. In patients who received immunochemotherapy (R-CHOP), 80% had complete remission, and only one patient who didn't receive another modality is alive with disease.

ESMO clinical guideline in 2016, confirmed rituximab improves the progression-free survival and overall survival in PBL patients [21]. Although ESMO recommended six cycles of R-CHOP plus RT in patients who tolerate therapy well [21], the review of male cases shows five patients who received R-CHOP less than 6 cycles (2–5 cycles) were alive without evidence of disease during follow-up time (Tab. 1). It may be related to a hormone dependency of this disease and the difference in hormonal profiles of males and females. Further studies in male patients are recommended to find less aggressive treatment.

Study limitation

Considering limited data and a scant number of patients in each group of treatment modality, any conclusions about the best treatment strategy in male PBL seems impossible.

Conclusions

For the time being, with rely on female's studies, which have shown that surgery has no therapeutic role beyond obtaining a histologic diagnosis to guide definitive treatment of PBL, the presented results in males also show surgery is not a good choice for treatment of PBL.

The presented study concludes some differences between previous female studies and males in the presentation of PBL disease, prognosis, and treatment. In contrast with females, left breast involvement in male patients was more common and younger age is associated with better outcomes and prognosis. In similar to females patients' treatment, immunotherapy accompanied with radiotherapy with a dose of at least 30 Gy, is the optimal treatment in male patients too, however, it seems fewer immunotherapy cycles may be enough to complete recovery. Further reports and series of the long-term follow-up of male patients with PBL after treatment are necessary to compare outcomes and achieve a consensus about a standard treatment strategy.

Conflict of interest

The authors have no conflict of interest to declare.

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REVIEW ARTICLE

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Pregnancy and malignant diseases — principles of management

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ABSTRACT

Pregnancy-associated malignant diseases introduce multiple dilemmas to the multidisciplinary boards, related to both the oncological treatment as well as to obstetrical management. The most frequent oncological diseases diagnosed during pregnancy are breast cancer, oncohematological conditions, uterine cervix cancer and skin cancers. There are different clinical scenarios: interruption of the pregnancy and further use of the most appropriate oncological strategy; it is also possible to postpone the oncological treatment for the postpartum period with a watch-and-wait strategy until the foetus is mature and the delivery is planned. The third scenario includes concurrent treatment of both conditions: use of chemotherapy, radiotherapy and surgery during an ongoing pregnancy. Choosing among these scenarios is considering many factors, including type and stage of the malignant tumour, pregnancy term, desire and informed decision of the pregnant woman to keep or interrupt the pregnancy. The current review is focused on the basic principles of the oncological modalities (surgery, chemotherapy and radiotherapy) during pregnancy as well as their influence over the pregnant woman and the foetus, over the obstetrical management and the timing and mode of delivery, delivery anaesthesia, lactation and breastfeeding from the point of view of the evidence-based medicine.

Key words: pregnancy, malignant diseases, radiotherapy, chemotherapy, surgery

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Introduction

Pregnancy and neoplasia are a rare combination and thus evidence-based data and recommendations are limited [1]. In such a situation, the care for the mother and the foetus, the obstetrical and the oncological management should run in parallel, which may be rather challenging. The diagnosis of "cancer during pregnancy" introduces not only medical but many other problems, including ethical, personal, religious or even legal issues. Every cancer, diagnosed during pregnancy, qualifies the pregnancy as high-risk and thus the woman should be taken care of in specialized centres with experience both in oncology and obstetrics [2, 3]. It is known that the pregnancy itself does not worsen the oncological prognosis, but both the mother and the foetus may be susceptible to potential side effects of the different oncological treatments. Potential obstetrical complications include but are not only limited to intrauterine retardation of the foetus, preterm delivery with the delivery of an immature or small for the gestational age foetus. [1–4]

Epidemiology

— The rate of cancer during pregnancy is reported between 17–25/100,000 pregnancies [1].
— The most frequent neoplasia are:

1. breast cancer,
2. oncohematological diseases (lymphomas, leukaemia),
3. uterine cervix cancer,
4. skin cancers (basocellular, melanoma) [1].

Obstetrical therapeutic options

Obstetrical management depends on many patient-, foetus- and cancer-related factors, but treatment decisions most frequently take into consideration:

— cancer type,
— cancer disease stage,
— gestational age of the foetus (correctly determined) with screening for malformations)
— (lack of) Desire to keep the pregnancy [1–4]

The obstetrical management may be divided into:

1. Interruption of the pregnancy before the time when the foetus would capable of life [< 24th gestational week (g.w.)]. This is a relevant strategy in aggressive rapidly progressive cancers with poor prognosis, especially if diagnosed in the early weeks or months of the pregnancy.
2. Delay of the oncological treatment until the second trimester of the pregnancy in case of diagnosis in the first trimester (except for some haematological malignancies).
3. Oncological treatment during pregnancy. The oncological treatment is multimodal and consists of different therapeutic strategies, including surgery, chemotherapy and/or radiotherapy. They may be delivered in a different sequence given both the term of the pregnancy and the type and stage of the oncological disease.
4. Delay of the oncological treatment until after delivery. All modalities of the complex anticancer treatment or only some of them could be postponed, depending on the stage of the oncological disease, the possibility to deliver the treatment during pregnancy and the age of the pregnancy. This is another potential clinical scenario, considered in cases of a diagnosis of cancer close to the expected date of delivery [1].

Factors, influencing the treatment decisions in cancer during pregnancy

The general pregnancy and cancer management principles are related to the following aspects:

1. **Cancer-related factors** — oncological characteristics as a stage of the disease, histological type and potential treatment options. These determine the indications for anticancer management as well as the use of one or more treatment modalities (surgery, chemo- or targeted therapy, radiotherapy, etc.). The most appropriate treatment sequence is also crucial and may be modified by other non-cancer related factors.
2. **Foetus-related factors —** the age of the foetus and the stage of development and the degree of maturation are crucial. It strongly influences anticancer treatment choices as potential neonatal issues may develop as a consequence of the anticancer treatment.
3. **Mother-related factors** — treatment decisions are the priority of the pregnant woman and her family. Besides the decision to keep or not the pregnancy or the possibility for further pregnancies, the health status of the mother is essential when planning the anticancer treatment. Potential obstetrical issues and mode of delivery (Caesarean section versus vaginal delivery) are also considered, aiming at the most precise as a possible prediction of the time of delivery. Obstetrical factors are roughly summarized as:
   - time of delivery and choice of mode of delivery (vaginal versus Caesarean section),
   - anaesthesia during delivery (general versus local),
   - histological examination of the placenta,
   - breastfeeding and lactation [1].

Anticancer treatment during pregnancy — general principles

The oncological treatment is complex and consists most frequently of a multimodal approach. Systemic chemotherapy, radiotherapy or surgery may be used in sequence or different combinations and sequences.

Principles of surgery during pregnancy

General statements

Surgery is safe for the foetus after the first trimester. If the condition of the pregnant woman and the stage of the oncological disease permit, it is recommended to delay surgery until after delivery; it could also be done during delivery with an elective Caesarean section. Regional anaesthesia techniques are given preference over general anaesthesia [5].

Physiological changes, related to pregnancy and modifying the surgical process

Some physiological changes in the body of the mother are typical for the pregnancy period and may be relevant in the case of cancer during pregnancy. Between

the 6th and 34th g.w. the extracellular liquid increases with 3–4 litres due to the antidiuretic hormone (ADH) and the renin-angiotensin-aldosterone system (RAAS). This leads to haemodilution, a drop in the haemoglobin, haematocrit and albumin levels and the pharmacokinetics is therefore changed [6]. Additionally, the enlargement of the uterus and the increase of the pressure over the abdominal organs may lead to the development of gastroesophageal reflux with subsequent risk of aspiration syndrome, most frequently during the third trimester. Moreover, the pregnancy increases the thrombogenic risk as the coagulation factors VII, VIII, IX, X, XII and the plasminogen are in increased levels. The thromboembolic risk may be additionally increased due to venous stasis in the lower extremities or the neoplastic process itself. The postoperative immobilization with the damage of the vascular endothelium leads to the liberation of inflammatory mediators and may also increase the thrombogenic risk [1, 5].

Recommendations for surgery during pregnancy

— Recommendations for preoperative care
Conditions as diabetes, hypertension and medication intake should also be considered, compensated, controlled and if needed — corrected. The ultrasound examination with a record of the foetal heart sounds under obstetrical monitoring are safe, providing information for the foetal development and the actual status of the foetus. Corticosteroids (CS) may be prescribed in cases of risk for preterm delivery [5].

— Recommendations for intraoperative care
Interventions between 3rd and 5th g.w. should be avoided if possible due to a risk of defects in the neural tube. In case of surgery, the pregnant woman should be positioned in the left lying position after the 20th gestational week (not to compress the v. cava and to overload the heart). The risk of aspiration increases in the position of Trendelenburg (especially during laparoscopic procedures). Hemodynamic stability should be observed — hypotonia should be avoided, which could lead to a drop in the uteroplacental blood transfer, especially in foetal distress. The abdominal surgery could be planned for the second trimester when the risk of abortion is low, and the size of the uterus permits an adequate approach to the abdomen. A laparoscopic approach is not routinely recommended later than 26–28 g.w. The risks in laparoscopy are the development of hypercapnia, decreased blood flow due to the pneumoperitoneum and aspiration syndrome. The recommendations for the laparoscopic procedure, in case it should be done, include its performance by an experienced surgeon with a duration of the procedure less than 90 minutes, intraabdominal pressure 10–13 mm Hg; open approach for the first trocar, monitoring of the foetal heart sounds via cardiotocography and avoidance of intraprocedural hypotension [5, 7, 8].

— Recommendations for postoperative care
In postoperative care, an assessment of the foetal condition via ultrasound and obstetrical monitoring should be carefully performed. The pain control should be done via paracetamol, tramadol or NSAIDs. The use of these drugs during the 3rd trimester should be avoided as in 50–80% they may induce a preterm closure of the arteriosus duct with subsequent pulmonary hypertension. Prophylactic use of low-molecular heparin is mandatory in the postoperative period [9–11].
The risks in surgery during pregnancy are in general related to potential postoperative infections, that may induce preterm rupture of the foetal sac, which may subsequently induce foetal death, respiratory distress syndrome, need of mechanical ventilation, intraventricular haemorrhages or necrotic enterocolitis. In risk of preterm delivery, tocolytics are recommended to delay the delivery for 48 hours with the use of corticosteroids for stimulation of the foetal lungs' maturation [1, 3].

Principles of chemotherapy during pregnancy

Table 1 summarizes the main effects of chemotherapy on embryo and foetus development [12].

A. It cannot be done during the first trimester [1].
B. Chemotherapy, if used during the implantation period leads to the "all or nothing" phenomenon. It may cause malformations if used during days 10 to 56 of the pregnancy which the organogenesis period. This is the reason why chemotherapy treatment should not be used before 14th g.w. It should not be used after the 35th g.w. because chemotherapy can lead to neutropenia which increases the risk for infection of the mother and the baby [13, 14].
C. The risks for the foetus are intrauterine foetal retardation, preterm delivery, immaturity, neonatal toxicity — suppression of the bone marrow. This is the reason to recommend a minimum 3-weeks interval between chemotherapy and the expected time of delivery [15–18]. It is thus not routinely recommended to give chemotherapy after the 35th g.w.
D. The risk for the pregnant woman is of potential haematopoiesis suppression with further infections, bleeding or anaemia risks [19, 20].
E. Long-term (delayed) consequences over the foetus due to exposure to chemotherapy during their intrauterine foetal life. This is the reason to forbid the use of some target or cytotoxic agents (e.g., trastuzumab, bevacizumab, platinum salts, methotrexate, etc.).

Table 1. The main effects of chemotherapy during pregnancy on embryo and foetus development [12]

Period of pregnancy	Impact on embryo or fetus	Impact on the perinatal period	Long-term impact
First 4 weeks	Either pregnancy loss or no adverse effect	Not known	Not known
From 4 weeks to the end of 1st trimester	Malformations in 7–17% of children born to mothers receiving a single drug or 25% in case of combination therapy	Not known	Not known
Second or 3rd trimester	Case reports of reversible fetal heart toxicity for treatment with anthracyclines, particulary when trastuzumab is associated in the regiment	Preterm delivery and low birth weight (11%)	In general neuropsychological development is not affected. When retard is demonstarated, it is ascribed to prematurity
	Malformations are as frequent as in children barn to healty mothers	Myelosuppression (1–43% according to time of therapy suspension)	Older children frequently have internalzing behavioral problems Progressive left ventricular dysfunction several years afteranthracycline exposure

Endocrine therapy is contraindicated during pregnancy especially in breast cancer because is teratogenic and has been associated with birth defects in children of women who inadvertently have utilized the treatment during pregnancy [21, 22].

The incorporation of immunotherapy into clinical practice during pregnancy is recent and there is no sufficient data to speculate about their security in humans. For the time being, the utilization of these drugs during pregnancy is not recommended [23]. In animal models, anti-PD-1/PD-L1 and anti-CTLA-4 inhibitors during pregnancy are associated with an increase in abortion rates, stillbirths, premature delivery and higher incidence of infant mortality, especially when utilized during the third trimester [24–27].

Molecularly targeted agents are increasingly being used in modern oncology practice.[23] Most of these drugs are considered new in the practice and have no collected data of their effects while using during pregnancy. Imatinib increases the risk of spontaneous abortion and major malformations — exencephaly, encephalopathies and abnormalities in the skull bones. [23]. Trastuzumab is associated with oligohydramnios. Bevacizumab causes hypertension and proteinuria and it is assumed hypothesized that it might induce pre-eclampsia. Rituximab can cause immunosuppression by B-cell depletion in neonates [28].

— Neurocognitive development and results at school. There are several trials on this topic. A trial of Hahn (2006) on 40 children of age 2 months to 13 years reports one case of Dawn syndrome and 1 case of syndrome of deficit of attention [29]. In 70 children of age 1,5 to 17,6 years, Amant (2012) reports 2 cases with development of mental retardation but they are considered to be due to foetal immaturity [30]. The same author in 2015 reports poor cognitive results in 96 children of age 1.5–3 years that is also related to their prematurity in comparison non-exposed to the chemotherapy control group [31]. A study by Cardonick (2012) does not find a significant difference in cognitive development in 35 children of age 1,5 to 10,4 years in comparison with healthy controls [32].
— Behavioural changes (depression, anxiety, aggression or issues with the discipline). There are 2 studies with data on this topic: Amant (2012) reports 29% of such behavioural changes in 6 of 21 children of age 5–16 years. [29] Cardonick (2015) reports 23% cognitive issues (8 out of 35 children) in the exposed to chemotherapy group of children in comparison with 18 % (4 out of 22) in the control group [33].

Future trials are needed to study the long-term effects of chemotherapy on foetal fertility or the rates of secondary cancers.

Some non-antineoplastic medications which are widely used in oncology practice as supportive care also can be a cause of concern during pregnancy.

Bisphosphonates are generally contraindicated in pregnancy because they may reduce the calcium delivered to the foetus and induce skeletal malformations (reduced bone growth), low birth weight [34–36]. The granulocyte colony stimulation factors (GCS-F) can be used only in cases of severe neutropenia. In animal studies is observed that the use of GCS-F during the pregnancy can increase the spontaneous abortion rate and low birth weight with no increase in malformations. There is no such observation in human [37].

Table 2. Risks to the foetus of radiotherapy during pregnancy [39]

Gestational age (weeks)	Risks
Preimplantation (1)	Lethality
Organogenesis (2–7)	Lethality, gross malformations, growth retardation, sterility, cataracts, other neuropathology, malignant disease
Early foetal (8–15)	Lethality, gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Mid foetal (16–25)	Gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Late foetal (> 25)	Growth retardation, sterility, cataracts, malignant disease

Principles of radiotherapy during pregnancy — general recommendations

A. Malignant diseases, treated with radiotherapy (RT) — treatment recommendations for use during pregnancy. In cases of breast cancer, RT could be delivered until 18–19 g.w. as there is enough distance of the irradiated area to the pregnant uterus. In cases of supradiaphragmatic lymphadenopathy, RT could also be delivered in e.g., lymphomas. In brain tumours or head and neck cancers RT could be delivered at any time during pregnancy whereas in the uterine cervix RT cannot be delivered as it induces foetal death [38].

B. The risks for the foetus during RT (foetal dose < 0.1 Gy) are: intrauterine retardation of the foetus (small for their gestational age, risk of cardiovascular or metabolic complications, malformities (3–8 g.w.), mental retardation (8–25 g.w) and secondary neoplasia — 0–38 g.w. (e.g., leukaemia or solid paediatric tumours) (Tab. 2) [1, 38].

The combination of pregnancy and oncologic diseases leads to some specific neonatal and obstetrical problems.

The neonatal problems are due to the immaturity and/or the preterm delivery, both iatrogenic or as a result of intrauterine chemotherapy exposure. These are respiratory distress syndrome, temperature instability, excessive body weight loss, sepsis, hypoglycaemia, jaundice, risk of neuro-behavioural problems (poor results at school, need of special additional education) [1, 2].

The obstetrical problems are related to time and mode of delivery, anaesthesia of delivery, histological assessment of the placenta, breastfeeding and lactation.

1. Time of delivery
   Efforts should be made not to permit delivery before 37th g.w. to avoid iatrogenic immaturity. If chemotherapy is delivered during pregnancy, its last cycle should be no later than 3 weeks of the expected date of delivery [4, 40–42] to allow foetal bone marrow recovery [6].
2. Delivery mode
   It is determined by obstetrical indications. Vaginal delivery is the first method of choice and should be given priority due to the decreased blood loss, the shorter hospital stay and the lower risk of infections. The rates of elective Caesarean section in pregnant women with cancer is reported to be about 35% in the literature. There are some contraindications for vaginal delivery that should be considered: metastatic bone disease, brain metastases, uterine cervix cancer (the Caesarean sections aims at avoiding the trauma of the lower uterine segment) and vulvar cancer [1, 3].
3. Anaesthesia during delivery
   The gold standard for anaesthesia during and after delivery are the regional techniques: spinal or spinal-epidural anaesthesia. Contraindications to the regional anaesthesia may be brain tumours or metastases, metastatic bone disease, haematological neoplasia (e.g., acute leukaemia) due to the risk of hematoma and infection, leucopoenia and/or thrombocytopenia (risk of hematoma and infections) [1, 7].
4. Histological assessment of the placenta
   The histological assessment of the placenta is indicated in the search of metastases and most frequently these are registered in melanoma, lymphoma as well as in leukaemia [43].
5. Breastfeeding and lactation
   Chemotherapy during pregnancy leads to a decrease or interruption of lactogenesis. On the other hand, lactation during breastfeeding is not recommended as the cytostatics may be eliminated with the milk [13, 14, 41, 42]. Breastfeeding is possible after breast surgery or RT to the breast [44].

Conclusion

The management in case of pregnancy-associated cancer has different treatment strategies: interruption of the pregnancy and starting the treatment, a delay of the treatment after delivery or starting the treatment during the pregnancy. The most frequent complications of the chemotherapy during pregnancy are related to preterm

delivery risk as well as the risks, arising from the metabolism of the cytostatics, which mandates if possible, prediction of the last chemotherapy cycle no later than 3 weeks before the expected date of delivery. Surgical treatment and chemotherapy should be avoided before the 14th g.w. RT could be delivered as long as there is sufficient distance of the irradiated field from the pregnant uterus. Laparoscopy could be considered before the 26th g.w., taking into consideration the increased risk of aspiration and hypercapnia. The hemodynamic should be closely monitored during surgery and hypotonia should be rigorously avoided. Low molecular heparins are recommended in the postoperative setting and the foetus should be monitored via ultrasound and recording of the foetal heart sounds. During delivery, for the anaesthesia, local techniques should be given preference, whereas in the postoperative period, anaesthesia is given with analgesics. The mode of delivery is preferably vaginal.

Conflict of interest

The authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Genetically burdened transgender man during gender reassignment process with two primary neoplasms: a case report

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ABSTRACT

Transgender is defined as an incongruence between the assigned at birth sex and an experienced gender identity. The biological sex is neither familiar nor acceptable to transgender people. Gender-affirming hormone treatment (GHT) is a multidisciplinary approach aiming to develop and maintain physical characteristics of the desirable sex. The influence of exogenous hormones on the cancer pathogenesis and development is a subject of ceaseless studies and observations. However incomplete statistical and epidemiological data hamper deducing about the risk of cancer among these people. The article describes a case of a transgender female-to-male (FtM) patient during gender transition with two primary neoplasms (endometrial cancer and colon cancer) as well as Lynch syndrome and von Recklinghausen's disease confirmed by next-generation sequencing (NGS).

Key words: transgender, transgender man, cross-sex hormone therapy, Lynch syndrome, von Recklinghausen disease, colon cancer, endometrial cancer

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Introduction

The number of transgender people is increasing. As neoplastic diseases could be also diagnosed in this population, it is necessary to approach the problem of cancers in transgender people properly. We present a case of a transgender male undergoing sex transition with two concomitant primary neoplasms (endometrial cancer and colon cancer), in which DNA (deoxyribonucleic acid) testing using next-generation sequencing (NGS) revealed Lynch's syndrome and von Recklinghausen's disease (VRD).

Case report

A 31-year-old female-to-male transgender patient during the first stage of sex transition (hormone therapy) came to the Oncology Clinic of the University Clinical Center in Katowice in October 2018 after radical surgical treatment for endometrial cancer to have adjuvant treatment introduced. In accordance with the applicable gender criteria and the patient's gender identification, despite the lack of a judicial determination of gender and a non-binary phenotype, the patient was addressed in a male form.

In childhood, the patient was diagnosed with neurofibromatosis type 1 on the basis of clinical symptoms (von Recklinghausen's disease, NF1). The genetically determined disease is caused by *NF*-1 suppressor gene mutation and is inherited as autosomal dominant. The physical examination revealed disturbances in the eyes (Lisch nodules of the iris, disorders of the optic nerves), the skeletal (curvature of the spine, short stature) and the nervous system (numerous neurofibromas), as well as the skin (café-au-lait spots, freckles of the inguinal and axillary areas) and additionally characteristic image of brain in magnetic resonance imaging (MRI) with the presence of focal areas of signal intensity (FASI). The patient was under constant ophthalmological and neurological care. He is a technician masseur by profession. A burdened family history suggested NF-1 disease in the father and synchronous breast and ovarian cancer in the maternal grandmother, who died at the age of 50.

At the age of 20, the patient started administrative and medical procedures related to qualification for the FtM gender correction. Having positive opinions from a psychologist, psychiatrist and sexuologist, as well as after endocrinological and ophthalmological consultations and the karyotype examination, the patient began the first stage of gender transition in 2010, i.e., testosterone hormone therapy. Until 2015, he had been taking testosterone preparations orally and then in the form of intramuscular injections. In May 2017, the attending physician diagnosed grade 1 microcytic anemia [hemoglobin concentration — 10.7 g/dL, mean erythrocyte volume (MCV) — 65 fL]. For financial reasons, the patient took testosterone preparations irregularly, which resulted in irregular menstruation. The attending physician recognized it as the cause of the anemia and continued the process of gender transition.

In October 2017, he was admitted to the plastic surgery ward to perform the second stage of sex reassignment [gender reassignment surgery (GRS), i.e. mastectomy]. Ultimately, the surgery was not performed due to upper respiratory tract infections, anemia, and coagulation disorders. The patient did not set another date for the procedure.

Subsequently, when the hormone therapy regimen was maintained, menstrual bleeding ceased, but the microcytic anemia gradually worsened and the patient was referred for diagnostics. In March 2018, a colonoscopy was performed in the internal medicine ward, which revealed the presence of multiple large intestine polyps. Numerous samples from the entire colon were taken and based on pathomorphological examination some benign changes were identified. Endoscopic examination of the upper gastrointestinal tract showed no abnormalities. With the diagnosis of adenomatous polyposis of the colon, the patient was referred for a surgical consultation at a reference center. In August 2018, due to a genital hemorrhage, he was hospitalized in the gynecology department, where diagnostic abrasion of the uterine cavity and cervical canal was performed. While waiting for the results of the pathomorphological examination, the patient was scheduled to be admitted to the surgical ward in September 2018 in order to perform additional tests and qualify for restorative proctocolectomy. In an abdominal computed tomography (CT) examination, in addition to the previously identified multiple large intestine polyps, uneven contours of the uterus were described with a thickened endometrium pathologically enhancing after contrast medium administration up to 23 mm. Due to the results of the examination of uterine cavity and cervical scrapings, which revealed endometrial adenocarcinoma, the surgical procedures were stopped and the patient was referred for oncological treatment. Testosterone hormone therapy applied since 2010 in the process of gender reassignment has been suspended.

The patient was qualified for radical treatment due to endometrial cancer. In September 2018 laparoscopic hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy was performed. Pathomorphological examination of the postoperative material revealed the presence of endometrial adenocarcinoma with focal necrosis (*adenocarcinoma endometriales G2 cum necrosi focali*), neoplastic infiltration of the muscular layer 5 × 3 cm and metastasis 2.5 cm in diameter in the right ovary and lymph nodes 21/0+ (stage — pT3aN0M0 = CS IIIA).

Taking the cancer stage into account, the patient was qualified for adjuvant treatment with sequential chemoradiotherapy. From October 2018 to April 2019, systemic treatment was administered at standard doses without complications (6 cycles — carboplatin 400 mg/m^2 + paclitaxel 175 mg/m^2 every 21 days), followed by 3D-IMRT teleradiotherapy up to a total dose of 50.4 Gy in 28 fractions. Due to the unfavorable anatomical conditions, it was not possible to carry out brachytherapy after the hormonal therapy. During the treatment, spectral mammography was additionally performed, which showed no pathological lesions in the mammary glands.

Before resuming the interrupted hormone therapy with testosterone in the process of gender reassignment, it was decided to extend the diagnostics to include molecular tests. The patient performed a DNA test using the next-generation sequencing (NGS) method in the commercial program *badamygeny.pl*. The examination detected the Leu1511Pro mutation (c.4532T>C) in one allele of the *NF1* gene, the Ile157Thr mutation (c.470T>C) in one allele of the *CHEK2* gene, and the Arg211Ter mutation (c.631C>T) in one allele of the *PMS2* gene. The disclosed *PMS2* gene mutation — in the context of the previously diagnosed endometrial cancer

— confirmed the diagnosis of Lynch's syndrome (hereditary nonpolyposis colorectal cancer, HNPCC). The consulting clinical geneticist pointed to the extremely rare situation in which one person has two pathogenic, clinically relevant lesions.

Genetic counseling was also provided to the patient's immediate family. The father had a confirmed *NF1* gene mutation, and the mother and younger brother had *PMS2* gene mutation. They are both waiting for diagnostic tests of the digestive tract, and until the publication of the article, neither of them had been diagnosed with cancer.

In September 2019, an endoscopic attempt to remove colon polyps was carried out. Multiple and non-pedunculated laterally spreading type granular (LST-G) and laterally spreading type non-granular (LST-NG) polyps were found in the cecum, ascending colon, hepatic flexure and proximal transverse part. Additionally, in the descending colon and sigmoid colon, single sessile polyps up to 2 mm were visible, and in the sigmorectal flexure, a single 20 mm polyp was revealed and removed. The remaining lesions, due to their extensive scope, did not qualify for endoscopic removal. The histopathological examination of the samples taken from the cecum revealed G2 adenocarcinoma.

After diagnostics to assess the disease stage, in November 2019, an extended right hemicolectomy with omentectomy was performed. Despite providing comprehensive information regarding the high risk of multifocal neoplastic lesions in the large intestine, the patient did not consent to the proposed pancolectomy.

The postoperative histopathological report revealed moderately differentiated, partially ulcerated, partially mucinous G2 adenocarcinoma (*adenocarcinoma mediocre differentiatum G2 exulceratum partim mucinosum*), bifocal tumor located in the cecum and ascending colon, and lymph nodes 17/0+. Two omental and metastatic and one mesenteric metastases were found (disease stage — pT3mN0M1c).

The tumor markers CEA and Ca19-9 remained within the normal range. The patient was qualified for systemic treatment. Chemotherapy was used from January to July 2020. Due to prolonged grade 3 neutropenia after the first cycle of the XELOX regimen (oxaliplatin 130 mg/m^2, day 1st + capecitabine 1000 mg/m^2 twice daily — day 1st–14th), the chemotherapy regimen was changed from the second cycle to FOLFOX (oxaliplatin 85 mg/^{2} day 1st + fluorouracil 400 mg/m^2 bolus day 1st and 2nd + fluorouracil 600 mg/m^2 22-hour infusion on days 1st and 2nd — every 14 days) with prophylactic administration of a short-acting granulocyte colony-stimulating factor (G-CSF). The treatment was complicated twice. First by short-term grade 3 neutropenia and then by grade 1 neuropathy and asthenia. In the third and sixth month of chemotherapy, follow-up CT were performed, which did not reveal local recurrence and dissemination of the neoplastic disease, and the markers CEA and Ca19-9 remained normal.

Currently, the patient is awaiting a surgical consultation in order to qualify for subcutaneous mastectomy and possible removal of the remaining part of the large intestine. Until now, the previously interrupted testosterone hormone therapy has not been resumed.

Discussion

In everyday life, transsexual people face a lack of social understanding, discrimination, stigma and numerous prejudices (also in the area of health care). For this reason, these people, more often than heteronormative people, avoid contact with a doctor. This translates — among other things — into neglecting periodic tests and screening programs [1, 2]. They are invisible in cancer registries (both in Poland and in the world) [1–3] because the data do not include information about the patient's gender identification and possible gender transition. There is no data on the types and duration of hormone therapies and often information on disease stage and the state of hormone receptors in the case of hormone-sensitive neoplasms. For these reasons, it is impossible to estimate realistically the incidence of neoplasms in the discussed group and the risk of neoplastic diseases related to the conducted hormone therapy [1, 2].

The patient, whose medical history is analyzed in cancer registers and statistics still appears as a woman and is an example of the limitations of the system in this respect. The growing number of transsexual people seeking oncological care prompts a revision of the current, rather indifferent, approach of doctors to the problems of transsexual patients [1–4].

Transgenderism is the lack of compatibility between the biological sex assigned at birth and an experienced gender identity. Biological sex for a transgender person is perceived as alien and unacceptable [5]. Transgender people receive hormone treatment to achieve external sexual characteristics of the desired sex. The influence of exogenous hormones on pathogenesis and development of neoplasms in the discussed population is the subject of research and observation [3].

Moreover, hormone therapy in the process of sex transition is not the only cancer risk factor in this group of patients. Lifestyle (obesity, nicotinism, alcohol abuse), carrying specific gene mutations, sexually transmitted viral diseases (e.g. human papillomavirus or immune deficiency) are other potential risk factors for cancer, and surgically reconstructed neo-organs can also be a starting point of a neoplastic process [2].

Undoubtedly, the occurrence of two primary neoplasms in the patient presented above was primarily as-

sociated with the cumulative genetic burden and was not dependent on the hormone therapy used. The risk of developing colorectal cancer associated with *PMS2* gene mutation in Lynch syndrome is up to 21% in women, and the risk of endometrial cancer is 24% compared to 2–3% in the general population [6–8]. A *NF1* gene mutation increases the risk of hematopoietic and lymphatic neoplasms as well as solid cancers, and it is estimated that the lifetime risk may be up to 60% [9, 10]. There has been no evidence to date that exogenous testosterone administration during FtM sex transition increases the risk of endometrial cancer. In studies of postoperative material after removal of the sexual organ, involutional changes of the uterine body are reported, which are analogous to the changes observed in postmenopausal women [11–13]. Hormone therapy stops menstrual bleeding after a few months, and incidental chronic spotting from the genital tract requires increasing the dose of testosterone [14]. Androgens are physiological precursors of estrogens in the process of peripheral aromatization of testosterone; hence, an increase in serum estrogen levels and the secondary induction of estrogen-dependent tumors in transgender men would be a concern. However, hormone therapy aimed at maintaining testosterone levels within the physiological limits of cisgender men (men with the same gender assigned at birth and gender identity) does not increase serum estrogen levels [15].

Oncologists should consider the possibility of breast cancer in transgender people. The risk of cancer in FtM patients after mastectomy is lower, and in the absence of mastectomy is similar compared to the population of cisgender women [16]. Before an elective mastectomy, it is suggested to perform a mammography, especially in people with a family history, and the postoperative material should undergo pathomorphological examination in order to exclude cancer [17]. Transgender women and transgender men who have not undergone mastectomy should have a mammogram every 2 years from the age of 50, if the duration of hormone therapy is longer than 5 years [16]. On the other hand, in transgender men after mastectomy, the decision to screen for breast cancer should be made individually. In this group, breast cancer may develop in the glandular tissue, which is usually preserved to achieve a good esthetic result. In individuals with a burdened family history, ultrasound examinations or magnetic resonance imaging of the remaining breast gland should be considered [16–18].

Summary

The occurrence of two primary neoplasms in the presented transgender FtM patient was mainly related to the cumulative genetic burden, and not to administered hormone therapy. Incomplete data on the occurrence, treatment and recurrence of neoplastic diseases in the population of transgender people do not allow for an unequivocal assessment of hormone therapy safety. A transsexual patient with cancer requires the participation of a sexuologist, endocrinologist and psychologist as part of multidisciplinary cancer care.

Conflict of interest

The authors declare no conflict of interest.

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