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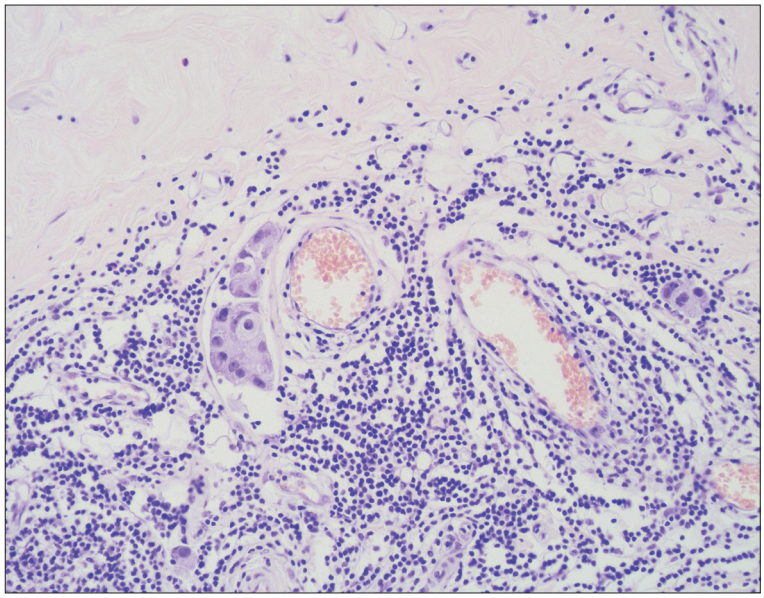

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Cover photo: Breast cancer with apocrine differentiation — tumor emboli in the lumen of vessels in breast parenchyma (LVI+); H&E stain, magnification 100x. Courtesy of Joanna Wysocka, MD

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Surgical treatment of rectal cancer in Poland — a report from a prospective, multi-centre observational study PSSO_01 conducted under the auspices of the Polish Society of Surgical Oncology

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Introduction. Since 2016, as part of the PSSO_01 multi-centre research project conducted under the auspices of the Polish Society of Surgical Oncology, clinical data on rectal cancer treatment have been collected. The objective of the study was to illustrate the state of early results of surgical treatment.

Material and methods. The research project is multi-centre in nature. Data shall be collected electronically. The study protocol does not impose or suggest any course of procedure. It only systematizes the way data are collected for scientific purposes. The analysis of early results of surgical treatment was compared with the results of population studies from other European countries (Netherlands, Belgium).

Results. By the end of June 2018, 736 patients were registered in the study. In 399 (54.2%) an anterior resection was performed. More than half of patients undergoing subsequent surgical treatment (54.2%) receive neoadjuvant treatment, with the percentage of patients undergoing radiotherapy or radiochemical treatment for lower rectal cancer being about 70%. Most patients (96%) are operated in elective procedure. The percentage of laparoscopic surgeries is

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low (8.6%). Postoperative complications are observed in 21.1% of patients. Severe complications (grades III–V according to Clavien-Dindo classification) occur in 7.6% of patients undergoing surgery. Postoperative mortality is 1.1%.
Discussion. Although the project does not have the character of a registry and does not allow for drawing wider conclusions concerning the compliance with the standards of qualification for neoadjuvant treatment, the important information is that more than half of rectal cancer patients receive preoperative treatment, and the percentage of severe postoperative complications does not exceed 10%.
Conclusions. The results of the PSSO_01 project are representative and reflect the actual situation concerning surgical treatment of rectal cancer patients in Poland.

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Key words: rectal cancer, PSSO, surgical treatment

Introduction

According to the National Cancer Registry (Krajowy Rejestr Nowotworów — KRN), 5816 cases of rectal cancer were reported in 2015 [1]. It is difficult to estimate the percentage of patients with newly diagnosed rectal cancer who underwent surgery, how many of these surgeries were of a radical nature, the percentage of combination treatment, in what percentage of operated cases sphincter-saving procedures were possible and restoration of gastrointestinal continuity, and how many patients underwent laparoscopic surgery? These are just some of the questions about the surgical treatment of rectal cancer patients that we do not have answers to. We can only rely on data from individual centers, usually specialist ones. In 2016, under the auspices of the Polish Society of Surgical Oncology (PSSO), a multi-centre observational study PSSO_01 project was launched, the main objective of which is clinical verification of the proposed risk of anastomotic leak after anterior resection. The study collects data on all rectal cancer patients operated in the participating centers. We obtain information on the pretreatment stage of cancer, type of surgery, percentage of laparoscopic surgeries, complications in the perioperative period, share of combination treatment (radiotherapy/radiochemiotherapy). In the case of anterior resection, we archive data on the occurrence of anastomotic leaks, the creation of a protective stoma and the restoration of the gastrointestinal tract continuity (closure of a protective stomata). The study is open and the size of the target group (patients undergoing anterior resection) was estimated at 846 cases. Although the study does not have the character of a register, the data collected so far make it possible to illustrate early results of surgical treatment of rectal cancer not only from the perspective of a single centre, but also on a national scale.

Methodology and material

The research project was approved by the Bioethics Commission operating at the Maria Skłodowska-Curie Institute — Oncology Center in Warsaw. The study is observational and non-interventional, which means that all patients are treated according to the applicable standards and at no stage of the study there is a need to perform any additional medical procedures other than those which, according to the doctor's knowledge and experience, constitute the optimal way of management for the patient. Research data are collected electronically using an encrypted application owned by PSSO. All data collected centrally are anonymous. Sensitive data such as PESEL number, gender, date of birth, initials of the patient's given name and surname are not collected centrally, so identification of the patient is only possible at the research centre. The study protocol does not impose or suggest any course of procedure. It only systematizes the way data are collected for scientific purposes. The PSSO_01 project is open to centers that meet the following criteria:

— the number of patients with primary rectal cancer diagnosis, surgically treated within 12 months ≥ 20
— the number of anterior resections performed within 1 year in patients with rectal cancer ≥ 10
— possibility to monitor the appearance of postoperative complications within a minimum of 30 days after surgery and distant results of surgical treatment within 12 months after surgery.

Centers in which a protective stoma is routinely (in each case) performed as an integral part of a surgery defined as "low anterior resection" cannot be included in the study, except where resections with anastomosis at a distance ≤ 3 cm from the anal verge are considered as low anterior resections. Recruitment of centers is open and including other centers is possible at any time during the project. Currently, 21 centers are registered, out of which 14 are active (Fig. 1). The target group are patients who meet the following criteria:

— primary rectal adenocarcinoma (lower limit of the tumor at a distance of up to 15 cm from the anal verge),
— anterior resection of the rectum,
— surgery according to total mesorectal excision (TME) standards or partial mesorectal excision in case of high tumor position.

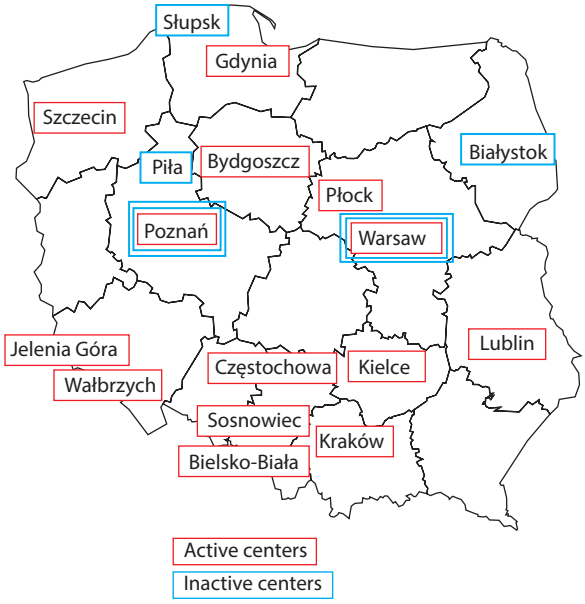


Figure 1. Centers participating in the PSSO_01 project (June 2018)

The study protocol requires that all patients with primary rectal adenocarcinoma diagnosed, who come to the centre for surgical treatment — regardless of the type of operation — must be reported. This is necessary to demonstrate that the material of patients qualified for detailed analysis of the target group was not subject to selection (the condition of publication in the indexed medical literature according to STROBE Statement criteria). Data collected in the study centre are reported electronically, after the registration of the centre and gaining access to the research application. It was assumed that the time needed to gather an appropriate group of patients to achieve the objectives of the study would be from 36 to 48 months (depending on the number of centers participating in the study). The protocol allows for the possibility of including additional centers during the implementation of the research project. The course of the study is supervised by the Coordinating Committee appointed by the Board of PSSO.

By the end of June 2018, 736 patients were registered in the study (471 men and 265 women). In 399 (54.2%) anterior resection was performed (Fig. 2). In 433 (58.8%) cases comorbidities were reported, which may increase the risk of complications in surgical treatment (diabetes, hypertension, ischemic heart disease) and/or positive history of abdominal surgery. Moreover, as early as at the time of diagnosis of cancer, distant metastases occurred in 87 (11.8%) patients qualified for surgical treatment. The current rate of recruitment allows us to assume that the size of the target group will be reached within the expected period of time.

Results of the analysis

Preoperative treatment

Neoadjuvant treatment is received by more than half of patients undergoing subsequent surgical treatment (54.2%). In the analyzed sample of 736 patients, high fractional dose radiotherapy (5 × 5 Gy) was used in 238 (32.3%) cases, while in 43 (5.8%) patients it was combined with chemotherapy. Classical "long" radiochemical treatment was received by 104 (14.1%) patients. In 13 cases the only preoperative treatment was chemotherapy, in half of them the presence of distant metastases was observed as early as at the moment of diagnosis. In 44 patients the only preoperative treatment was radiotherapy with a total dose of 50.4 Gy in the form of monotherapy (without chemotherapy). It should be noted that the study protocol allows the inclusion of patients with upper rectal cancer in whom no preoperative treatment is used. Therefore, data relating to preoperative treatment require a detailed analysis, which is done in the chapter on surgical treatment.

Surgical treatment

A vast majority of registered patients are operated in elective procedure. Collected data indicate that only 4% of patients required emergency surgery. The percentage of laparoscopic surgeries is also low: 8.6%. Radical oncological surgery (according to the surgeon) was performed in 624 (84.8%) patients. The type of conducted surgeries has been shown in Figure 3. The most common types of rectal cancer resection surgeries are analyzed below.

Anterior resection

In 198 (49.6%) patients radiotherapy or radiochemiotherapy was applied before the surgery. In the case of anterior resection with low anastomosis, the preoperative treatment was received by 72.3% of patients.

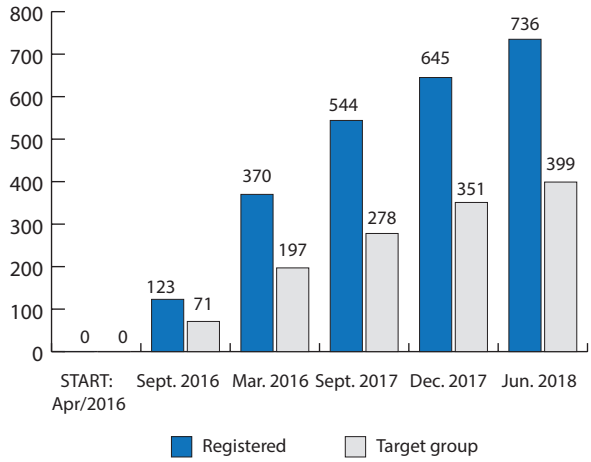


Figure 2. Recruitment in the PSSO_01 study

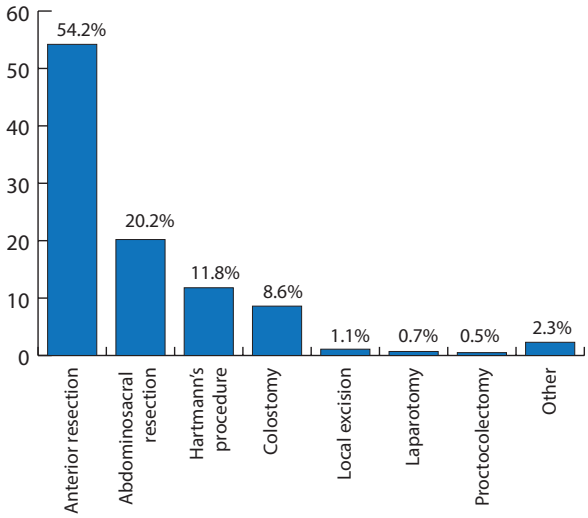


Figure 3. Type of performed surgeries

Laparoscopic surgery was performed in 36 (9.0%) patients (reports from 8 out of 14 active centers). In 95% of cases the anastomosis was performed using the stapling technique. Most of the anastomoses were performed with the end-to-end method (94.5%). End-to-side anastomosis is performed much less frequently (4.3%), while anastomosis with the J-pouch bowel reservoir is performed sporadically (only 2 such cases from one research centre have been reported). The distances between the anal verge and the anastomosis are presented in Table I. If a low anterior resection is defined as a surgery with an anastomosis up to 5 cm from the anal verge, the percentage of such procedures reaches 19.2%. In 90 (22.6%) patients, anastomosis requires initiating the left colon bend, which is a value similar to the reported percentage of resections with low anastomosis. In 91 (22.8%) cases the surgeon secured the anastomosis with a stoma. Out of 87 patients operated until the end of December 2017, in whom the surgeon secured the anastomosis with a stoma more than 6 months after surgery, 30 (34.4%) still have a stoma, including 8 (9.2%) patients with a stoma longer than 12 months after surgery and it may be assumed that the stoma is already permanent.

Abdominosacral resection

The study protocol does not distinguish between abdominosacral and abdominoperineal resections, assuming that these are cylindrical amputations with an appropriate margin within the pelvic floor and the tissues located above. All such surgeries should be classified as elective (100% of reported cases). The majority of patients undergoing abdominosacral amputation receive preoperative treatment — 77.2%. The operation is usually performed with the intention of oncological radicality — 96.6%. The percentage of laparoscopic surgeries is low — 12.8%.

Hartmann's procedure

In the majority of patients operated in this way, preoperative radiotherapy or radiochemical therapy is used (62.1%). This type of resection is more frequent in patients with a history of abdominal surgery and/or comorbidities — 66.7% and with the presence of synchronous distant metastases — 20.7% (Table II). In 16.1% of cases resection is palliative. Hartmann's laparoscopic procedure is performed rarely (2 cases reported).

Operations related to the creation of an intestinal stoma

The total percentage of patients with an intestinal stoma as a result of the surgery is 46.9%. Of these, in 12.2% of cases it is by definition a temporary stoma. However, observations made within 6 months after surgery indicate that 47.2% of patients still have an intestinal stoma and one should suspect that it may be a permanent stoma. Considering only radical surgeries, the percentage of patients with a permanent intestinal stoma is 42%.

Postoperative complications

Postoperative complications were observed in 21.1% of patients. The grade and severity of reported complications were determined according to the Clavien-Dindo classification [2] — Table III. Postoperative mortality was 1.1%. Severe complications requiring surgical treatment or ICU-management (grades III and IV) occurred in 7.6% of patients undergoing surgery. The total percentage of complications depending on the type of operation is presented in Figure 4. The highest risk of complications is associated with anterior resection with low anastomosis (up to 5 cm from the anal verge) (29.1%). The risk of anastomosis leaks is 10.6% in such case. A creation of a protective stoma reduces the risk of symptomatic leak, but it is still a high percentage of 9.9%. This is one of the reasons why a protective (tem-

Table I. Distance between the anastomosis and the anal verge

Distance range	Number of cases	%
≤ 3 cm	35	8.8
> 3–5 cm	106	26.8
> 5–10 cm	191	48.2
> 10 cm	64	16.2
No data available	3	–

Table II. Type of surgeries performed vs data from the patient history and the grade of cancer at the moment of diagnosis

	Positive medical history*	Synchronous metastases	Urgent surgery
Anterior resection	56.1%	7.5%	0.5%
Abdominosacral resection	63.1%	6.7%	0.0
Hartmann's procedure	66.7%	20.7%	8.0%
Colostomy	49.2%	41.3%	22.2%
Local excision	87.5%	12.5%	12.5%
Laparotomy	60%	20.0%	0.0
Proctocolectomy	50%	0.0	0.0

* concerns comorbidities and/or surgical treatment within the abdominal cavity

Table III. Postoperative complications according to the Clavien-Dindo classification

Grade	Definition	Number of cases n (%)
I	Any deviation from the correct *(uncomplicated)* postoperative course, without the need for pharmacological, surgical, endoscopic treatment and without interventional radiology procedures	43 (5.8)
II	Complications requiring pharmacological treatment. In addition, this group includes all cases requiring treatment: – postoperative blood transfusion, – total parenteral nutrition *(except where total parenteral nutrition is a routine procedure arising from the type of surgery performed)*	45 (6.1)
III	Complications requiring surgical or endoscopic treatment or interventional radiology procedures – without general anaesthesia (IIIA) – under general anaesthesia (IIIB)	40 (5.4)
IV	All life-threatening postoperative complications requiring treatment in ICU conditions – single organ failure (IVA) – multiple organ failure (IVB)	16 (2.2)
V	Death	8 (1.1)
No data available	–	3 (–)

porary) stoma remains open and becomes a permanent stoma. A risk of severe (grades: III–V) complications after abdominosacral amputation is 7.4% and is lower than after Hartmann's procedure: 10.3%. Overall, radical surgeries carry a higher risk of postoperative complications than palliative surgeries (22.1% vs 16.1%), but the percentage of severe complications (grades: III–V) is similar to that observed after palliative surgery: 8.7% vs 9.4% It should be noted that in the group of palliative surgeries non-resectional procedures predominate. The percentages of severe postoperative complications after certain types of rectal cancer resections are presented in Table IV.

PSSO_01 against the background of European research

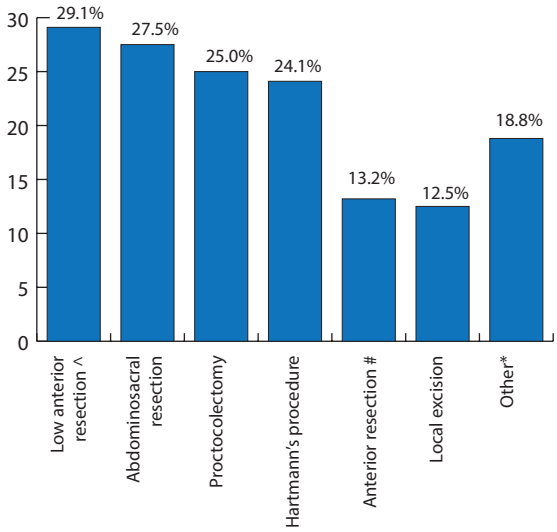
The PSSO_01 research project does not meet the requirements of the register of rectal cancer surgical treatment, however, to the best knowledge of the authors of this report it is the first study based on prospectively collected clinical material, which allows for presenting collective results of surgical treatment from both large and smaller centers in Poland. The data collected so far have been compared with the results of the Dutch Surgical Colorectal Audit [DSCA] [3] and the Belgian project PROCARE [4] — Table V. The Dutch Surgical Colorectal Audit was carried out in 2009–2011. In the following years, the audit covered 80%, 92% and 95% of patients treated surgically for colorectal cancer in the Netherlands. Rectal cancer is defined as tumors located up to 12 cm from the anal verge. The lesions located above were analyzed as colon cancer. An unquestionable success of the Dutch audit was the unification of standards of diagnostic and therapeutic management in Dutch hospitals, which resulted in the lack of differences between the results of oncological treatment of patients operated in both large and smaller centers [5]. Launched in 2006, the multi-centre PROCARE project focused on the results of treatment of patients with lower and middle rectal cancer (a cancerous tumor located 0–10 cm from the anal verge). The results obtained in PROCARE are of limited value, as only 37% of patients were included in the study.

Representativeness of the tested sample

Following the analysis made on the Dutch audit material, the PSSO_01 study identified large (over 50 rectal cancer/year operations), medium (20–50 patients/year) and small (up to 20 patients/year) centers [5]. In the analysis of the

Table IV. Type of resection surgery and risk of severe postoperative complications according to the Clavien-Dindo classification

Surgery type	Grade III	Grade IV	Grade V
Low anterior resection	8.5%	3.5%	–
Anterior resection	3.5%	1.6%	1.6%
Abdominosacral resection	5.4%	1.3%	0.7%
Hartmann's procedure	5.0%	3.4%	2.3%
Local excision	12.5%	–	–



^ anterior resection with the anastomosis ≤ 5 cm from the anal verge

anterior resection with the anastomosis > 5 cm from the anal verge

* stoma, explorative laparotomy, other

Figure 4. Postoperative complications depending on the surgery type

PROCARE study, in order to determine the "volume" of the centre, the number of surgeries performed annually was also assumed, however, four groups were identified: < 30 surgeries/year; 30–50 / year; 50–100 / year and > 100 / year [4]. In the presented study for the purpose of comparative analysis, data from the last two groups of the PROCARE study have been combined. The results of PSSO_01 study are in this respect comparable to those presented by Dutch authors. They indicate that the vast majority of the reported patients are operated in medium-volume centers performing 20–50 surgeries a year. Different numerical criteria adopted in the PROCARE study would indicate that the majority of patients are subject to surgeries in large centers (76.7%). However, if we assumed that the average Belgian centers operate between 30 and 100 patients a year, then the percentage of patients treated in this defined group would be 48%.

In the PSSO_01 study material, it is worth noting that the number of men is twice as much as women. Comparing this with epidemiological data, which indicate a sustained trend in incidence in males and a plateau in incidence in females [1], the gender differences found in the analyzed group of patients seem to be representative for the general population and comparable with the data from other reports [4, 5]. In the PSSO_01 project we are waiting for the age of registered patients analysis. Due to the fact that all sensitive data (age, PESEL) are stored in the centre, such an analysis will be possible only after the completion of the study and obtaining raw data from each centre separately.

Although the recorded percentage of patients with synchronous distant metastases is comparable to those published in Dutch and Belgian reports, it seems to be underestimated in comparison to the Polish population as far as the experience of a Polish clinician involved in rectal cancer surgery is concerned. Firstly, we do not have population data on the severity of the disease at the time of diagnosis among newly registered cases in Poland, and secondly, some of these patients are not qualified for surgical treatment at all, or are operated on a palliative basis in other centers as a matter of urgency.

Nearly 60% of participants are patients with comorbidities and/or history of abdominal surgery and this value is significantly lower than in the Dutch report (95%). However, the reason for these differences may be that the PSSO_01 test protocol requires reporting only those cases where, in the opinion of the surgeon, comorbidities or surgical history are relevant to the planned surgery.

Neoadjuvant treatment

Short-term (5-day) irradiation monotherapy up to a total dose of 25 Gy and long-term radiation therapy up to a total dose of 50.4 Gy in combination with chemotherapy are standard preoperative treatments for rectal cancer patients, depending on the cancer stage and the assessment of tumor resectivity. The results of a Polish multi-centre randomized clinical trial comparing the efficacy of classical radiochemical treatment with short term radiotherapy combined with chemotherapy in the treatment of patients with primary non-resectional rectal cancer showed that the treatment results were similar [6]. The clinical application of these results is reflected in the increasing number of subgroups of patients treated preoperatively according to the following programme: short-term radiotherapy, chemotherapy and surgery. We found that 6% of patients (n = 44) received only long-term irradiation without chemotherapy. It is an acceptable method of treatment for patients with locally advanced

Table V. PSSO_01 against the background of European studies

Feature	Poland PSSO_01	Belgium PROCARE [4, 8]	Netherland DSCA [3, 5]
Representativeness of the tested sample			
Participation of centers in recruitment:			
– small centers	7.9%	2.5% [4]	12.3% [5]
– medium-sized centers	60.7%	20.8% [4]	63.4% [5]
– large centers	31.4%	76.7% [4]	24.2% [5]
Gender:			
– male	64%	61% [4]	62% [3]
– female	36%	39% [4]	38% [3]
Synchronous distant metastases	11.8%	9.2% [4]	8.6% [5]
Neoadjuvant treatment			
Preoperative treatment, total	54.2%	59.5% [4]	83.7% [3]
– radiotherapy	32.5%	5% [4]	55% [3]
– radiochemotherapy	20%	54.5% [4]	28.6% [3]
– others	1.8%	–	–
Surgical treatment			
Surgical access:			
– laparoscopy	8.6%	–	38.1% [3]
Urgent surgeries	4%	–	2.8% [3]
Surgery type:			
– abdominosacral resection	20.2%	20.4% [4]	30.5% [3]
– Hartmann's procedure	11.8%	1.4% [4]	19.2% [5]
– anterior resection	54.2%	71.6% # [4]	45.8% *[3]
– local excision	1.1%	1.2% [4]	–
Protective stoma	22.8% ^	–	65.3% & [3]
Early results of surgical treatment			
Postoperative complications total:	21.1%	–	38.7% [3]
Anastomosis leak	6.5% ^	–	10.9% & [3]
Repeated surgery	–	–	16% [3]
Mortality (30 days after surgery)	1.1%	1.1% [8]	2.1% [3]

Percentage of surgeries defined as "sphincter-saving surgeries"
* Percentage of surgeries defined as "surgeries with primary anastomosis"
^ Percentage with reference to surgeries defined as "anterior resection"
& Percentage with reference to surgeries defined as "surgeries with primary anastomosis"

cancer and with contraindications for systemic treatment. The total percentage of patients undergoing neoadjuvant treatment is similar to that reported in the PROCARE report (54.2% vs 59.5%) and significantly lower than in the study by Dutch authors (54.2% vs 83.7%) — Table V. The Dutch audit concerned patients with the diagnosis codified as C20 according to ICD10 classification, but it should be noted that in 77.9% of registered patients cancer was located within 10 cm from the anal verge [3]. This may explain the observed difference in the percentage of patients treated with neoadjuvant treatment between the PSSO_01 study report and the results of the Dutch audit. The analysis of a subgroup of patients with anterior resection with anastomosis up to 10 cm from the anal verge or abdominosacral resection (i.e. those in whom the tumor location might indicate the need for preoperative treatment) shows that the percentage of patients receiving neoadjuvant treatment is 69.2%.

Surgical treatment

Low percentage of laparoscopic surgeries in Poland is the most significant difference observed in comparative analysis — Table V. The Dutch audit completed in 2011 indicated that the percentage of laparoscopic surgeries reached 38.1%. A study conducted in 2015 in selected centers previously participating in the DSCA showed that the percentage of laparoscopic surgeries in small centers reaches 59.8%, in medium centers — 44.8%, and in large centers — 45.7%. The difference was statistically significant, indicating that the majority of laparoscopic surgeries are performed in small centers [5]. PSSO_01 project data indicate that in Poland the total percentage of such surgeries does not exceed 10%. The reasons for these differences cannot be found in the conducted surgeries mode, as the percentage of urgent procedures reported in the PSSO_01 project and DSCA results are similar: 4% vs 2.8%

The percentage of abdominosacral resections reported in PSSO_01 is almost identical to the PROCARE project results. On a global scale, this percentage may be significantly different, as both PSSO_01 and PROCARE covered only a part of the centers.

An interesting observation is the comparison of the percentage of resections with the Hartmann's procedure,

which in the Belgian study is significantly lower than in PSSO_01 and DSCA. PROCARE shows a high percentage of sphincter-saving surgeries: 71.6%. If resections with primary anastomosis (anterior resection) are defined by this term, the corresponding data from the DSCA and PSSO_01 projects are respectively: 45.8% vs 54.2% The only explanation for these differences seems to be the selection of centers and the incompleteness of the Belgian register [4].

Also noteworthy is the high percentage of protective stomata selected in the DSCA material: 65.3%. As early as at an early stage of this audit, a clear increase in the proportion of protective stomata identified compared to previous data collected during the TME trial (1996–1999) was observed: 70% vs 57% ($p < 0.001$). However, this fact did not have an impact on the reduction of the percentage of anastomosis leaks: 11.4% vs 12.1%; $p = 0.640$ [7]. Observations made then by Dutch authors were the basis for designing and defining the main objectives of the PSSO_01 study.

Early results of surgical treatment

The total percentage of complications at the level of 21% clearly differs from that observed in the Dutch report (38.7%). However, the advantage of the PSSO_01 project is the prospective registration of the category of complications according to the Clavien-Dindo classification (Table III). Belgian authors reported the percentage of severe complications separately for sphincter-saving surgery and after abdominosacral resection: 7.8% vs 5.4% respectively. The total postoperative mortality rate was 1.1% [8]. Assuming that we consider as serious complications those that fall under category III and IV, and the death is classified as category V, the relevant percentages recorded in the PSSO_01 project are equal: anterior resection — 7.5%; abdominosacral resection — 6.7%; total postoperative mortality rate — 1.1%. As we can see, these values are almost identical to those reported in the PROCARE study. Interesting insights also apply to registered cases of anastomosis leaks. In the PSSO_01 project, the total leakage rate after anterior resection is 6.5%. The DSCA register gives a value of 11%, but it should be remembered that it concerns anastomoses after rectal cancer resection located up to 12 cm from the anal verge. Analyzing a subgroup of patients from the PSSO_01 study in which the anastomosis was performed up to 10 cm from the anal verge, i.e. comparable to DSCA material, the percentage of symptomatic leaks is 8%. The higher leakage rate recorded in the Dutch report is probably due to the fact that the audit covered almost 100% of the centers.

Final remark

The PSSO initiative through the PSSO_01 project enables the presentation of early results of surgical treatment of rectal cancer in Poland from a broader perspective than before. The results of the analysis of the collected research material within the PSSO_01 project so far seem to indicate that it is comparable to the material used to create reports presented by Dutch and Belgian researchers. This may indicate that it will be representative for the entire Polish population. Although the PSSO_01 project does not allow for drawing wider conclusions concerning the compliance with the standards of qualification for neoadjuvant treatment, the important information is that more than half of rectal cancer patients receive preoperative treatment, and the percentage of severe postoperative complications does not exceed 70%. This value is similar to that given in reports from other European countries. Observations relating to the methods of surgical treatment that emerge from comparative analysis allow us to illustrate the difference in the percentage of laparoscopic surgeries performed in Poland in comparison with other European countries. At the same time it should be noted that the percentages of particular surgery types do not differ significantly from those reported in the DSCA. Comparison with the PROCARE study reveals significant difficulties in the interpretation of results, mainly due to significant differences in the reported percentage of Hartmann's procedures. Early surgical treatment results recorded in PSSO_01 are similar to those presented in the PROCARE and DSCA studies.

The functionality of the PSSO application used to collect clinical data on surgical treatment of rectal cancer allows for its development and creation of further research projects focusing on the treatment of patients with this cancer. An example can be the PSSO_02 test module added to the application and launched in July 2018. The application can therefore be regarded as the basic platform for data collection with the possibility of attaching modules related to a specific research project (PSSO_01, PSSO_02). The PSSO_01 Research Coordination Committee and the Board of the Polish Society of Surgical Oncology invite other centers that would be interested in participating in current research projects, as well as to design new research that would be in line with the issues related to the treatment of rectal cancer.

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References

1. Didkowska J, Wojciechowska U, Olasek P. Nowotwory złośliwe w Polsce w 2015 roku. Warszawa: Centrum Onkologii — Instytut, Krajowy Rejestr Nowotworów, 2017.
2. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and result of a survey. *Ann Surg* 2004; 240: 205–213.

3. Van Leersum NJ, Snijders HS, Henneman D et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; 39: 1063–1070.
4. Jegou D, Penninckx F, Vandendael T et al.; PROCARE. Completeness and registration bias in PROCARE, a Belgian multidisciplinary project on cancer of the rectum with participation on a voluntary basis. *Eur J Cancer* 2015; 51: 1099–1108.
5. Jonker FHW, Hagemans JAW, Burger JWA et al.; Dutch Snapshot Research Group. The influence of hospital volume on long-term oncological outcome after rectal cancer surgery. *Int J Colorectal Dis* 2017; 32: 1741–1747.
6. Bujko K, Wyrwicz L, Rutkowski A et al.; Polish Colorectal Study Group. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. *Ann Oncol* 2016; 27: 834–842.
7. Snijders HS, van den Broek CB, Wouters MW et al. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? *Eur J Surg Oncol* 2013; 39: 715–720.
8. Leonard D, Penninckx F, Kartheuser A et al.; PROCARE. Effect of hospital volume on quality of care and outcome after rectal cancer surgery. *Br J Surg* 2014; 101: 1475–1482.

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Trabectedin in the treatment of patients with soft tissue sarcoma

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Soft tissue sarcomas (STS) are rare malignant tumours derived from connective tissue. They constitute about 1% of malignancies occurring in adults. We distinguish over 60 subtypes of soft tissue sarcoma, each with a unique clinical course and a diversified response to systemic treatment. The prognosis for patients with locally advanced, unresectable or metastatic disease remains poor. For years, doxorubicin — used alone or in combination with ifosfamide — has been the basis of treatment for these patients. Trabectedin is a relatively new molecule registered in the treatment of patients diagnosed with STS. The drug was originally obtained from marine tunicates (*Ecteinascidia turbinata*), currently it is obtained semi-synthetically. So far, a number of potential mechanisms of trabectedin have been described, including DNA-binding, disruption of DNA repair mechanisms and cell cycle, as well as effects on transcription factors and the tumour microenvironment. The aim of the following review is to summarize the current knowledge on the efficacy and safety of trabectedin in the treatment of patients diagnosed with STS.

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Key words: trabectedin, soft tissue sarcomas, leiomyosarcoma, liposarcoma

Introduction

STS is a group of rare malignant neoplasms of mesenchymal origin. The standard treatment for locally advanced disease is radical resection of the tumour usually with pre- or post-operative radiotherapy. The place of perioperative chemotherapy is still not fully established. However, about 50% of patients diagnosed with high-grade tumours will develop metastatic disease. The prognosis remains bad, and the median overall survival (OS) is about 12 months. The basis of treatment in the case of diagnosis of metastatic disease is a systemic treatment. Unfortunately, the number of drugs with proven activity in this indication is still low. For many years, the most important drugs used in palliative treatment of STS have been doxorubicin and ifosfamide. There is also a number of new particles with proven efficacy, such as olaratumab, pazopanib, eribulin or trabecetidin, used for the longest time among this group [1].

Trabectedin is a synthetic alkylating agent, originally isolated from Caribbean tunicates *Ecteinascidia turbinata* [2]. The success of trabectedin in initial clinical trials among patients diagnosed with MTM has resulted in drug approval in many countries. Two years ago the results of a large, randomized phase III trial being the final trial approving the drug in the United States [3] were published. With limited systemic therapy options available to treat patients with STS, trabectedin is an important treatment line in this rare diagnosis.

Trabectedin — mechanism of action

A number of potential mechanisms of antitumor activity of trabectedin have been described, including cytotoxic and antiproliferative effects, inhibition of gene transcription and indirect immunological and anti-angiogenic effects. However, the effects of the drug are still not fully understood [4].

Molecular evidence suggests that the cytotoxic effect of trabectedin is due to its DNA-binding. In fact, trabectedin binds to a minor DNA groove, causing DNA double helix to be distorted with an interruption in the DNA itself. The interaction between trabectedin and the minor DNA groove determines structural changes in the molecule, resulting in

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a cascade of events that affects a number of transcription factors, DNA-binding proteins and DNA repair pathways, resulting in G2-M cell cycle arrest and eventually apoptosis [2]. It has been observed that cytotoxic mechanisms of trabectedin are affected by DNA repair mechanisms, such as nucleotide excision repair (NER) and homologous recombination repair (HRR), which recognize DNA damage and recruit various factors to repair the damaged place. Cell repair machinery, including both NER and HRR systems, is crucial for the interaction between trabectedin and DNA and appears to be the most important determinant of drug susceptibility [5]. Also the direct interaction between trabectedin and RNA polymerase II (pol II) has been described, causing the transcription process to stop, pol II degradation through the proteasome pathway and premature termination of the RNA transcript [2]. This type of antiproliferative mechanism appears to be particularly effective in MLPS (myxoid liposarcoma), which is the STS subtype most sensitive to trabectedin therapy. Furthermore, trabectedin has a stimulating effect on the differentiation of MLPS tumor cells. The tumor response to trabectedin in MLPS in vivo is characterized by tumor cell death and induction of mature adipocytes [6].

In addition to this cytotoxic activity, trabectedin modulates tumour microenvironment and it seems that this is the most important part of its therapeutic effect. The drug exerts a selected cytotoxic effect against tumour-associated monocytes and macrophages (TAM) present in tumour tissues. They are key promoters of inflammation associated with cancer. TAMs have a pro-cancer activity, including the production of growth factors that are necessary for proliferation, neoangiogenesis and the action of proteolytic enzymes. These elements degrade the extracellular matrix, determining the invasion of cancer cells and facilitating escape from the immune system [7]. It has been shown that trabectedin significantly reduces the expression of cytokines, chemokine, mediators of inflammation and angiogenesis, for example, interleukin-6, or vascular endothelial growth factor modifying the tumour microenvironment, thereby contributing to anti-angiogenic and antitumor effect of the drug [8].

The efficacy of trabectedin in clinical trials

Phase II clinical trials

The year 2004 saw the publication of the results of two phase II clinical trials that demonstrated the efficacy of trabectedin in the treatment of MTM. The first of these studies was conducted on a group of 54 previously treated patients. There was a low rate of objective response to treatment — 4%, but a high rate of disease control after six months of therapy — 24%. Trabectedin was administered at a dose of 1.5 mg/m^2, for 24 hours every three weeks [9]. The second study noted again a low response rate of 8% and one year OS amounting to 53% in 36 previously treated patients with STS. The same dosing regimen of trabectedin was also used in this study (1.5 mg/m^2, over 24 hours every three weeks) [10].

Promising results of the Phase II studies led EORTC (European Organization for the Research and Treatment of Cancer) to conduct a phase II trabectedin trial in 104 patients in the second and third line of treatment. Again, a low rate of objective responses of 8% was noted. The six-month PFS was 29% and the median overall survival was 9.2 months [11]. A further phase II trial was carried out in 36 patients to evaluate the activity of trabectedin in the first line of treatment. The treatment response rate was 17%, and the annual PFS and OS rates were 21% and 72% respectively [12].

Then a phase II randomized study was conducted, including 270 patients diagnosed with leiomyosarcomas (LMS) and liposarcoma (LPS). Patients were randomized to one of two arms — in the first the drug was given at a dose of 1.5 mg/m^2 for 24 hours every three weeks, in the other arm at a dose of 0.58 mg/m^2 for 3 hours once a week for three weeks out of four. Prior to enrolment, patients had to document the disease progression while receiving doxorubicin and ifosfamide. The 24-hour infusion regimen showed a much longer mean time to progression (TTP) (3.7 vs 2.3 months) and progression-free survival (PFS) 3.3 vs 2.3 months compared to the 3-hour infusion schedule. There was no significant difference in the overall survival between the two arms of the study, but there was a strong trend favouring the 24-hour infusion schedule (13.9 months vs 11.8 months) [13]. The results of this study led to the registration of trabectedin in the European Union in 2007.

Trabectedin is an expensive drug and has some side effects, which is why it was very important to ask whether the treatment should be continued until it is effective or it is possible to stop it after achieving control of the disease. The second phase II trial involved 53 patients with at least stabilization after 6 cycles of trabectedin. They were divided into one of the two arms of the study at random. In the first arm the treatment was continued until the disease progressed, in the second one it was discontinued. The percentage of PFS at 6 months after randomization was 51.9% in the group where trabectedin was not discontinued compared to 23.1% in the group where trabectedin was discontinued after 6 cycles. Toxicity did not increase significantly with continuation of therapy. This study confirms that treatment with trabectedin should not be discontinued after the disease has been controlled and therapy should be continued as maintenance treatment [14].

Phase III clinical trials

Trabectedin has a higher efficacy in the treatment of patients diagnosed with so-called sarcomas associated with translocation (such as, for example, MLPS or synovial sarco-

ma). Therefore, this group of patients was selected for the study in which the drug was compared with doxorubicin, which is the current standard of first-line treatment. In the phase III study, 121 patients with translocation sarcomas were randomly assigned to the arm in which they received trabectedin or doxorubicin in the first line of treatment. There was no significant difference in PFS between the two arms, which was the primary endpoint of the study. At the time of analysis, 63.9% and 58.3% of patients were still alive in the arms with trabectedin and doxorubicin (without a statistically significant difference in overall survival) respectively. The objective response rate according to RECIST criteria was significantly higher in the doxorubicin group (27%) compared to trabectedin (5.9%). However, when the response was assessed according to Choi's criteria, differences between doxorubicin (45.9%) and trabectedin (37.3%) were smaller [15]. Thus, doxorubicin (or doxorubicin based regimens) remains the standard first line treatment.

The pivotal phase III trial compared the use of trabectedin to dacarbazine in patients with locally advanced/metastatic LMS and LPS. Patients were randomized in a 2:1 ratio to the arm with trabectedin or dacarbazine. A total of 518 patients took part in the study, 345 of whom were randomly assigned to the trabectedin arm and 173 patients to the dacarbazine arm. In the final PFS analysis, the use of trabectedin was associated with a reduction in the risk of disease progression or death compared to dacarbazine by 45% (the median PFS for trabectedin was 4.2 vs 1.5 months for dacarbazine, hazard ratio 0.55; $p < 0.001$). Benefits were observed in all pre-planned subgroup analyses. An interim OS analysis (64% censored) showed a 13% reduction in the risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin was 12.4 to 12.9 months for dacarbazine, hazard ratio, 0.87; p = 0, 37). Based on a significant improvement in PFS for the arm with trabectedin, this drug was registered in the United States in October 2015 for the treatment of patients diagnosed with advanced LPS and LMS [3, 16].

At this year's ASCO 2018 meeting (American Society of Clinical Oncology) the results of the next phase III trial were presented. The study compared the efficacy and safety of trabectedin to the best supportive care (BSC) in patients diagnosed with STS after failure of at least one line of systemic treatment (no more than previous 3 lines of chemotherapy). In the case of confirmation of further disease progression, patients in the BSC arm were able to go to the arm with trabectedin (cross-over option).

The primary endpoint of the study was PFS. The study included both patients with so-called L-sarcomas (LPS and LMS) as well as other MTM subtypes. In the group receiving trabectedin, the objective response rate (ORR) was 11.8%, all responses were observed in the L-sarcoma group (ORR in this group 18.8%). 23% of patients in the trabectedin arm received more than 9 courses of treatment. The median PFS was 1.5 months in the BSC arm and 3.1 months in the trabectedin arm (HR: 0.39, $p < 0.0001$). In the L-sarcoma cohort, the median PFS was 1.4 months in the BSC arm and 5.1 months in the drug arm (HR: 0.29, $p < 0.0001$), while in the group without L-sarcomas it was 1.5 m and 1.8 m respectively ($p = 0.16$). Cross-over was performed in 92% of patients included in the BSC arm. After a median follow-up of 25.7 months, the differences between the two arms in terms of OS were not statistically significant and were 13.6 months for the drug arm vs 10.8 months for the BSC arm ($p = 0.86$) [17]. Again, these results confirm the higher efficacy of the drug in patients with the diagnosis of the so-called L-sarcomas when compared to other MTM subtypes.

Also in the published results of the extended drug access program, which included 1895 patients diagnosed with STS treated with trabectedin, the results achieved in the group of patients diagnosed with L-sarcomas are significantly better. ORR in the group of L-sarcomas was 6.9% compared to 4% in the group of other histological subtypes. OS was also significantly better in the group of L-sarcomas and amounted to 16.2 vs 8.4 months [18].

In Poland, the drug is available as part of the National Health Fund drug program only for patients diagnosed with L-sarcomas. In 2015, we published the results of trabectedin treatment of 50 patients with LPS and LMS at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. The median number of given treatment cycles was 5 (range 2–40); 18 patients (36%) received ≥ 10 cycles. Four patients (8%) had a partial response, in 23 (46%) a disease stabilization was noted (for a minimum of 3 months), and in 23 (46%) — disease progression. After six months of treatment, 47% of patients were progression-free, more in the group with LPS — 66% compared with 27% in the LMS group ($p = 0.023$). PFS was significantly longer in patients receiving trabectedin in the 2nd or 3rd line of treatment (median 7 months) than > 3rd line of treatment (median 2 months) $p = 0.038$. The median overall survival (OS) was 13 months [19]. Table I summarizes the results of clinical trials on efficacy of trabactedin in STS.

Trabectedin in the treatment of myxoid liposarcomas (MLPS)

It has been found that trabectedin is particularly effective in sarcomas associated with translocation, such as MLPS, exerting anti-tumour activity, *inter alia*, by inactivation of an oncogene FUS-CHOP, which is believed to alter expression of a protein encoding gene and induce adipocyte differentiation [6].

Results of two retrospective studies were published on the efficacy of trabectedin only among patients with this diagnosis. In the first one including a group of 32 patients the drug was used after failure of previous therapies. The objective response rate was 50%, 2 patients had a complete

remission (CR), 14 had partial response (PR) to treatment. The stabilization of the disease (SD) was noted in another 14 patients. 90% of patients achieved disease control (CR + PR + SD). The median PFS for the whole group was 17 months. Six months after the start of treatment, 90% of subjects were free of disease progression. Some patients after the use of this treatment were qualified for resection of residual lesions, which was not possible before starting the therapy. The median duration of treatment was 10 months and 24 subjects (75%) received more than 8 courses of treatment [20]. In another study conducted in a group of 51 patients from several centres, the results were quite similar: 2 CR, 24 PR were found, in total 51% of patients had an objective response to treatment. The median PFS was 14 months and the proportion of patients free of progression after six months after starting treatment — 88%. Interestingly, 17 of 23 responders were found to have changes in the density of neoplastic lesions assessed in the CT scan or reduced contrast uptake in the magnetic resonance imaging study, which preceded the finding of tumour size reduction [21].

Particularly good results among patients with the diagnosis of metastatic MLPS encouraged the assessment of the usefulness of the drug used as pre-operative therapy. In a study conducted by the Italian sarcoma group, 23 patients received the drug pre-operatively for 3–6 cycles of treatment. Then, the response to treatment was evaluated — in 3 patients CR was noted, confirmed in later histopathological examination, in 12 patients showed a significant response to the treatment which also manifested in the histopathological material as decreased tumour cellularity, decreased number of blood vessels, as well as greater maturity of tumour-forming lipoblasts. In 7 people, PR was diagnosed. None of the patients had progression of disease [22].

Side effects

Phase II and III trials showed that trabectedin is a fairly well-tolerated treatment, with no cumulative toxicity. The most common side effects of the drug are nausea, tiredness, vomiting, constipation and oedema. Adverse drug reactions of grade III and IV occur only in about 10% of treated cases.

Table I. The results of clinical trials on the efficacy of trabectedin in STS

Trial	Number of patients treated with trabectedin	Treatment line	Histological subtypes	Results	
Yovine et al. [9] II Phase	54	≥ 2	LMS 22 (41%) LPS 6 (11%) GIST 4 (7%) *Synovial sarcoma* 3 (6%) MFH 3 (6%) *Fibrosarcoma* 4 (7%) Other 12 (22%)	PR 2 (3.7%) SD ≥ 6 months 9 (16.7%) SD ≥ 2 ≤ 6 months 9 (16.7%) PD 28 (51.9%)	6-months PFS 24.1% Median OS 12.8 months
Le Cesne et al. [11] II Phase	99	≥ 2	LMS 43 (41%) LPS 10 (9.6%) *Sarcoma synoviale* 18 (17.3%) MFH 6 (5.7%) *Fibrosarcoma* 1 Other 26	PR 8 (8.1%) SD 45 (45.5%) PD 35 (35.4%)	6-months PFS 29% Median OS 9.2 months
Garcia-Carbonero et al. [10] II Phase	36	≥ 2	LMS 13 (36%) LPS 10 (28%) MPNST 2 (6%) *Synovial sarcoma* 6 (17%) Other 5 (13%)	CR 1 (3%) PR 2(6%)	Median OS 12.1 months OS after 1 year 53.1% Median PFS 1.7 months
Blay et al. [15] (vs Doxorubicin) III Phase	60	1	MLPS 23 (37.7%) Other translocation related subtypes 28 (45.9%) Other STS subtypes 10 (16.4%)	PR 3 (5.9%) SD 39 (76.5%) PD 6 (11.8 %)	No statistically significant difference between the study arms in PFS and OS
Demetri et al. (Dacarbazine) [3] III Phase	345	≥ 2	LMS 252 (73%) LPS 93 (27%)	ORR 34 (9.9%) SD 177 (51%)	Median PFS 4.2 months (vs 1.5 months for dacarbazine $p < 0.001$)
Le Cesne et al. [17] (vs best supportive care — BSC) III Phase	52	≥ 2	LMS 31.1% LPS 29.1% *Pleomorphic sarcoma* 10.7% *Myxofibrosarcoma* 7.8% *Synovial sarcoma* 4.9% Other 16.5%	PR 7 (13.7%) SD 34 (66.7%) PD 10 (19.6 %)	Median PFS 3.12 months (vs 1.5 months for BSC $p < 0.0001$)

The most common grade III and IV adverse reactions are: reversible elevation of aminotransferases and myelotoxicity, in particular neutropenia and anaemia [4, 23].

Transient increase of transaminases typically occurs several days after administration of trabectedin and it usually resolves spontaneously after about 15 days. If the level of transaminase does not normalize after 21 days, it is necessary to postpone treatment or reduce the dose. Intravenous premedication with corticosteroids, such as dexamethasone, is strongly recommended as an antiemetic and prophylactic for hepatic toxicity. Some clinical trials have shown that concomitant steroid treatment induces hepatic activity of the cytochrome P450 variant 3A4, reducing exposure to trabectedin in the liver and consequently correlated hepatotoxicity [24].

Rarely occurring, potentially dangerous side effects of trabectedin include neutropenic fever, rhabdomyolysis, cardiotoxicity or extravasation of the drug (the drug must be administered through a catheter inserted into the central vein due to the strong local irritant action of the drug on the vessel wall) [25].

Summary

Patients diagnosed with unresectable/metastatic soft tissue sarcoma are still a group of patients with poor prognosis. There are still not many systemic treatment options available. Research in recent years has, however, resulted in a number of new drug registrations in this indication. One of them is trabectedin — a drug with proven efficacy, especially in patients diagnosed with so-called L-sarcomas. The unique anti-tumour activity of trabectedin is not only its cytotoxic activity, but also its ability to modulate the tumour microenvironment. Trabectedin in subsequent studies shows a constant activity in patients after failure of treatment with doxorubicin, allowing to obtain long-term control of the disease.

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References

1. Casali PG, Abecassis N, Bauer S et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018 [Epub ahead of print].
2. D'Incalci M, Galmarini CM. A review of trabectedin (ET-743): a unique mechanism of action. *Moll Cancer Ther* 2010; 9: 2157–2163.
3. Demetri GD, von Mehren M, Jones RL et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol* 2016; 34: 786–793.
4. Recine F, Bongiovanni A, Riva N et al. Update on the role of trabectedin in the treatment of intractable soft tissue sarcomas. *Onco Targets Ther* 2017; 10: 1155–1164.
5. Friedman D, Hu Z, Kolb EA, Gorfajn B et al. Ecteinascidin-743 inhibits activated but not constitutive transcription. *Cancer Res* 2002; 62: 3377–3381.
6. Forni C, Minuzzo M, Virdis E et al. Trabectedin (ET-743) promotes differentiation in myxoid liposarcoma tumors. *Mol Cancer Ther* 2009; 8: 449–457.
7. D'Incalci M, Badri N, Galmarini CM et al. Trabectedin, a drug acting on both cancer cells and the tumour microenvironment. *Br J Cancer* 2014; 111: 646–650.
8. Germano G, Frapolli R, Belgiovine C et al. Role of macrophage targeting in the antitumor activity of trabectedin. *Cancer Cell* 2013; 23: 249–262.
9. Yovine A, Riofrio M, Blay JY et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol* 2004; 22: 890–899.
10. Garcia-Carbonero R, Supko JG, Manola J et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. *J Clin Oncol* 2004; 22: 1480–1490.
11. Le Cesne A, Blay JY, Judson I et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. *J Clin Oncol* 2005; 23: 576–584.
12. Garcia-Carbonero R, Supko JG, Maki RG et al. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. *J Clin Oncol* 2005; 23: 5484–5492.
13. Demetri GD, Chawla SP, von Mehren M et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol* 2009; 27: 4188–4196.
14. Le Cesne A, Blay JY, Domont J et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. *Lancet Oncol* 2015; 16: 312–319.
15. Blay JY, Leahy MG, Nguyen BB et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. *Eur J Cancer* 2014; 50: 1137–1147.
16. Barone A, Chi DC, Theoret MR et al. FDA approval summary: Trabectedin for unresectable or metastatic liposarcoma or leiomyosarcoma following an anthracycline-containing regimen. *Clin Cancer Res* 2017; 23: 7448–7453.
17. Le Cesne A, Blay J-Y, Cupissol A et al. Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS). *Ann Oncol* 2016; 27 (Suppl 6): 13960.
18. Samuels BL, Chawla S, Patel S et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. *Ann Oncol* 2013; 24: 1703–1709.
19. Koseła-Paterczyk H Kozak K, Klimczak A et al. Skuteczność i bezpieczeństwo stosowania trabektedyny w leczeniu pacjentów, u których rozpoznano zaawansowane tłuszczakomięsaki i mięśniakomięsaki gładkokomórkowe (L-mięsaki). *Nowotwory J Oncol* 2015; 65: 451–457.
20. Grosso F, Sanfilippo R, Virdis E et al. Trabectedin in myxoid liposarcomas (MLS): a long-term analysis of a single-institution series. *Ann Oncol* 2009; 20: 1439–1444.
21. Grosso F, Jones RL, Demetri GD et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. *Lancet Oncol* 2007; 8: 595–602.
22. Gronchi A, Bui BN, Bonvalot S et al. Phase II clinical trial of neoadjuvant trabectedin in patients with advanced localized myxoid liposarcoma. *Ann Oncol* 2012; 23: 771–776.
23. Petek BJ, Loggers ET, Pollack SM et al. Trabectedin in soft tissue sarcomas. *Mar Drugs* 2015; 13: 974–983.
24. Grosso F, Dileo P, Sanfilippo R et al. Steroid premedication markedly reduces liver and bone marrow toxicity of trabectedin in advanced sarcoma. *Eur J Cancer* 2006; 42: 1484–1490.
25. 25. http: //www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000773/WC500045832.pdf.

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Paragangliomas of the head and neck region

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Paragangliomas of the head and neck are a group of neoplasms which occur very rarely. Most of them are benign tumours. Tinnitus, headaches and dysfunction of the cranial nerves are typical symptoms. Some paragangliomas have metastatic abilities and they can produce catecholamines. There are some typical imaging features in CT and MRI scans which help to determine the correct diagnosis without the necessity of performing a biopsy which can be associated with a haemorrhage risk. Therapeutic management consists of the choice between an active observation, surgical procedure, as well as radiotherapy and systemic therapy in the case of malignant paragangliomas.

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Introduction

Paragangliomas comprise a group of rarely occurring, richly vascularised, slowly growing, encapsulated neuroendocrine tumours, which develop in various locations of the body, most frequently between the third and sixth decade of life. Taking into consideration the usual benign pathology of paragangliomas, it might seem that they do not pose a serious problem for oncologists specialising in the treatment of malignant tumours of the head and neck region. Such an opinion may also result from the published epidemiological data which specify the incidence of paragangliomas below 0.5% of all tumours of the head and neck region, which makes up about 0.03% of all cancers [1, 2] as well as from the data from the National Cancer Register: in 2000–2015 only 397 cases of tumours developing from the paraganglial tissue in adrenal and extra-adrenal locations were reported [3]. On the other hand, however, it must be remembered that within the course of the disease, distant metastases might occur; the multifocal character of these tumours paired with their ability to produce catecholamines can lead to a direct threat to patients' lives.

Etiopathogenesis

These rare tumours develop from paraganglia, which are the accumulations of endocrine cells originating in the neural crest [4]. Paraganglia are dispersed along the autonomic nervous system in the vicinity of sympathetic and parasympathetic neural ganglia or along cranial nerves

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and large blood vessels. Sympathetic paraganglia have a secretory character and thus secrete catecholamines, whilst parasympathetic paraganglia belong to chemoreceptors and have a receptive character [5]. The division of paragangliomas is presented in Table I. The largest accumulation of paraganglial tissue is located in the adrenal cortex. Tumours originating in this location are defined as pheochromocytomas, and, according to published data, they are the most frequently occurring tumours of the paraganglial system. In the WHO classification, neoplasms developing from extra-adrenal paraganglia are defined as paragangliomas [5, 6]. Paragangliomas of the head and neck region are very rare, making up less than 1% of all paragangliomas. Their most frequent location in the head and neck region are the following areas: carotid bodies (60% cases), the jugulotympanic area and vagal nerve area (most frequently within a distance of 2 cm from the skull base) [7].

Nomenclature

The nomenclature of paragangliomas requires systematisation. The generally operating term, *chemodectoma*, should in fact refer solely to the tumours of the area of the carotid and aortic bodies, as paraganglia which originate from them, also play the role of *chemoreceptors*. The most misleading term for paraganglioma, which is frequently used, is glomus tumour. In histology this term refers to the classification of tumours originating from the dermis and subdermal tissue, precisely from the blood vessels, most frequently with a subungual location. Therefore, the use of the term glomus tumour in reference to paraganglioma is an essential error. Recommended terminology, according to the WHO, is meant to refer to paragangliomas with reference to their location, e.g. vagal paraganglioma [7].

In accordance with the classification of head and neck tumours presented by the World Health Organisation (WHO) in 2017, head and neck paragangliomas can be divided into the following:

— carotid body paraganglioma
— laryngeal paraganglioma
— middle ear paraganglioma
— vagal paraganglioma

In comparison with the previous edition of the classification of these tumours, the term *jugulo-tympanic paraganglioma* was changed into *middle ear paraganglioma* [8].

The characteristics of paragangliomas

In the past, paragangliomas were most frequently treated as sporadic, which involved about 90% of cases [9]. The remaining 10% were regarded as familial cases. Current studies show that up to 40% of cases of tumours originating from paraganglial tissues may have a hereditary character [10].

There are 14 various genes which have been identified where germinal mutations can predispose one to the development of pheochromocytomas and paragangliomas. The most frequently identified mutations concern the SDH gene (succinate dehydrogenase complex) and are connected with the familial complex of pheochromocytomas and paragangliomas (PCC/PGL). In the head and neck area this concerns, in particular the D and C subunits (SDHD, SDHC). Gene VHL mutations are also frequent in von Hippel-Lindau syndrome, and also in the RET protooncogene (rearranged during transfection protooncogene) leading to the development of the MEN2 multiple endocrine neoplasia as well as in the NF1 (neurofibromin 1) in the neurofibromatosis type 1 [6, 11].

Paragangliomas usually form isolated lesions, whilst multifocal paragangliomas occur less frequently [12]. Multifocal paragangliomas more often occur among familial ones than in sporadic paragangliomas, which has its justification in the Knudson hypothesis (in sporadic cases, there must be 2 independent mutations in suppressor genes, whilst in hereditary cases, one mutation is congenital and the other — acquired).

Paragangliomas may also be classified with regards to their secretory abilities, into secretory (> 90%) and non-secretory (< 5%). The process of secretion is possible due to the presence of main cells, which are the building component of paraganglia. The main cells are the ones which are able to produce catecholamines. Not all secretory paragangliomas produce sufficient amounts of the substance to induce clinical symptoms, that is why some authors define secretory paragangliomas as only those which cause clinical symptoms [13].

Table I. The division of paragangliomas

	Paragangliomas of sympathetic system	Paragangliomas of parasympathetic system
Chromium salts staining	Pheochromocytomas	Non-pheochromocytomas
Location	Located along sympathetic trunk	Located in the vicinity of the large vessels of head and neck
Secretory abilities	Secretory (noradrenaline, adrenaline)	Non-secretory
Examples	Para-aortic body paragangliomas (ogan of Zukerkandl)	Carotid body paraganglioma, jugulo-tympanic paraganglioma, vagal nerve paraganglioma Rare locations: paraganglioma of the orbit, oral cavity, larynx, naso-pharynx, parathyroids

From a clinical point of view, paragangliomas may be either benign or malignant tumours. Malignant paragangliomas are regarded as only those which are diagnosed after distant metastases have been found in the places where chromogenic tissue does not exist physiologically e.g. to the lymph nodes, bones, lungs or liver [1]. In the current WHO classification, it is assumed that all paragangliomas have metastatic potential. The term_malignant paraganglioma was thus replaced with metastasising paraganglioma or paraganglioma with metastases [8]. Thus the current nomenclature refers to the term "metastasising paraganglioma" instead of "malignant paraganglioma". The prevalence of metastatic paragangliomas is described as ranging between 10–17%. However, this risk strictly depends on the type of germinal mutation underlying the hereditary forms. A mutation in subunit B of succinate dehydrogenase (SDHB) in a hereditary syndrome of pheochromocytomas and paragangliomas may lead to the development of metastases even in 40% of cases [6].

It must be stressed that 25% of paragangliomas located in the orbit and larynx are malignant. Also, about 15% of vagal paragangliomas and 5% of carotid and jugulotympanic have malignant potential.

Histopathologically, paragangliomas are built out of 2 cell types:

— main cells with excessive eosinophilic cytoplasm and atypical cellular nuclei;
— sustentacular cells of a spindle shape, located on the circumference of the main cell nests.

Tumour cell nests are surrounded with a rich vasculature. The lack of polarisation of the cells on the nest circumferences is a morphological property which allows for the differentiation between paragangliomas and neuroendocrine tumours as this polarisation occurs in the latter The main cells are characterised with the expression of synaptophysin, chromogranin A, CD56 and somatostatin receptors 2A, whilst they do not reveal the expression of cytokeratins, carcino-embryonic antigen (CEA) and calcitonin. Sustentacular cells may be visualised after the application of S-100 or GFAP. No expression is found in these cells, neither there are epithelial or neuroendocrine markers present in them [8]. There are no well-defined and recognised histopathological criteria on the basis of which a metastatic (formerly — malignant) type of paraganglioma can be diagnosed. In some isolated reports, in which in the postoperative histopathological assessment of the necrosis, peri-neural infiltrations, capsular infiltration, increased mitotic activity and atypical mitotic figures, the patients were qualified for postoperative RTH, as the above properties have been regarded as the malignancy criteria [9].

In 2005 Kimura et al., published the scale of the evaluation of pheochromocytomas and extra-adrenal parasympathetic paragangliomas on the basis of the criteria of histological texture, cellularity, coagulative necrosis, vascular invasion and tumour capsule, proliferative index Ki-67 and the types of catecholamines secretion [14]. The application of the above scale allows to classify paragangliomas to one of the three groups: well, moderately or poorly differentiated tumours. The differences between the groups correlate with the metastatic potential and survival rates. Yet, there is a group of well differentiated tumours which still produce metastases, which is indicative of the limitations of the practical application of the Kimura scale [15]. The histopathology of paragangliomas and metastatic tumours is usually the same. Only some metastatic tumours are characterised with a higher proliferative index or lower number of sustentacular cells [15]. The collective analysis of the patients with the diagnosis of paraganglioma or pheochromocytoma, 10-year probability or malignancy is estimated to be about 20% [16].

Symptoms

Clinical symptoms presented in the patients with diagnosed paraganglioma are closely connected with the tumour location. The most frequent symptoms are comprised of pulsation in the ears or tinnitus, hearing defects or loss, ear exudate, headaches or cranial nerve dysfunction, comprising: glossopharyngeal *nerve* (IX), vagal (X), auxiliary (XI), sublingual (XII), in particular in patients with a large tumour mass. Larger tumours in the area of the carotid body are visible in a laryngological assessment in the mid-pharynx or are palpable in the neck, which is the first symptom of paraganglioma, leading to the referral to a specialist and the commencement of a diagnostic proves. Sometimes hoarseness (resulting from the palsy of recurrent laryngeal nerve — branch X) and dysphagia are present.

The main symptom of the jugulotympanic paraganglioma is pulsating tinnitus and conductive hearing defects. In the otoscopic assessment, it is often possible to find a blueish tumour mass shining through the tympanic membrane. Once positive pressure is applied to the tympanic membrane, during the examination with a pneumatic speculum, this mass may go pale. This phenomenon is named Brown's symptom and is indicative of the vascular character of the tumour. Sometimes, paragangliomas are accompanied with atypical clinical symptoms such as excessive sweating (diaphoresis), facial redness, anxiety, vertigo, irregular heart beat and arterial hypertension. These symptoms are the effect of catecholamines secretion, and, in extreme cases may be life threatening. In some isolated cases, the loss of body weight and bone pain may suggest the malignant character of paraganglioma [17].

Imaging diagnostics

On account of its accessibility, the classical and Doppler ultrasound examinations are used mainly for the lesions

located in the area of the carotid body — non-homogenous, solid tumours with rich vasculature require extensive diagnostics. The examination which usually suggests a diagnosis of paraganglioma as the first one is the contrast CT.

On account of the rich vascularisation of paragangliomas, the typical CT image is a well delineated hyperdense tumour. CT also allows the visualisation of bone destruction, whose confirmation or exclusion allows to determine the advancement stage of paraganglioma (see Appendix). In the case of a suspected paraganglioma on contrast enhanced CT, MRI must be performed in order to verify it. Upon the administration of a gadolinium contrast agent, paragangliomas reveal strong enhancement. Moreover, the characteristic image of "salt and pepper" in T2-weigthed images allows confirmation of the character of a tumour, which in CT raised a suspicion of paraganglioma [18, 19]. That is why, first of all because of the large risk of a tumour haemorrhage, biopsy is not required in order to confirm diagnosis. The examination necessary for the qualification of patients for paraganglioma resection is angiography which allows visualisation of the network of vessels supplying blood and efferent vessels. The term, "the lyra symptom" encountered in publications, refers to the characteristic image of paraganglioma in angiography, when internal and external carotid arteries are pushed away from each other by the tumour mass developing between them. In the diagnostics of paragangliomas, some other imaging methods, belonging to the domain of nuclear medicine are used as well, comprising: positron emission tomography (^{68}Ga-DOTATATE, ^{18}F-FDG, ^{18}F-DOPA tracers) and MIBG 131-I scintigraphy (iodine-labelled metaiodobenzylguanidine), also with the use of the labelled somatostatin analogues. An indication to perform such examinations is the diagnosis of multi-focal paragangliomas and familial paragangliomas (in particular with the presence of the SDH mutation) in order to exclude distant metastases [16].

Laboratory diagnostics with the suspicion of secretory paragangliomas

In all patients in whose cases paragangliomas were diagnosed on the basis of imaging diagnostics, it is necessary to perform biochemical diagnostic work comprising the determination of the excretion of fractionated methoxy-catecholamines (metanephrine, normetanephrine, methoxytyramine) in 24-hour urine sampling or free methoxy-catecholamines in serum, depending on the possibilities of the centre in charge; chromogranin A level should be assessed as well [6]. The catecholamines metabolism and metabolites are presented in Figure 1.

Treatment

The treatment of paragangliomas is a multidisciplinary task. The choice of therapeutic procedures depends on the tumour location and measurements, the patient age, comorbidities, secretory function and the patient's decision. The most appropriate final criterion, used for the analyses comparing the effectiveness of specific methods is local control (LC) and preservation of the nerve function. The overall survival (OS) is here of minor importance with respect to the benign character of the majority of lesions [1].

The following methods of treatment are used:

— active observation;
— surgical resection;
— embolization;
— radiotherapy;
— systemic treatment;
— pharmacotherapy.

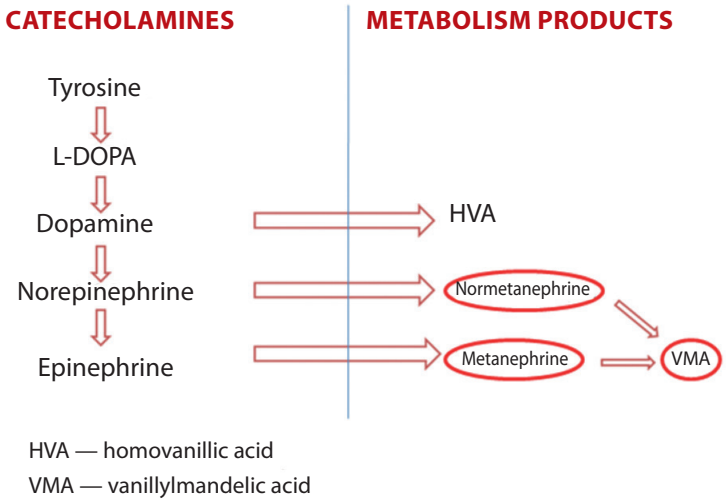

Figure 1. Catecholamines metabolism (on the basis of [13])

Active observation

This method of treatment is recommended especially in elderly patients with an asymptomatic disease, with significant comorbidities. The justification for an active observation is the slow tumour growth (0.5–5 mm annually) and the time of tumour doubling time of between 6 months to 21 years [20, 21].

Surgical resection

Surgery is possible in the majority of paraganglioma locations (especially in the case of cervical paragangliomas with a size below 5 cm). Tumour resection is the treatment of choice in patients with metastatic paragangliomas (tumorectomy with cervical lymphadenectomy) or with secretory paragangliomas (in the comparison of the tumour resection with RTH alone, tumour stabilisation was achieved after irradiation with some minor effect regarding the inhibition of secretion). Rich vascularisation and head and neck location areas burden such surgery with a risk of neural and vascular damage as well as with the loss of baroreceptors reflex; this is especially true with bilateral resection of cervical paragangliomas, which is connected with the deregulation of arterial blood pressure. In the case of vagal paragangliomas, the reported rate of nerve X damage is almost 100% [7]. The risk of death in patients with cervical and vagal paragangliomas undergoing surgery is 1.6% [22].

The contraindications for surgical resection comprise:

— skull base tumours (difficulties in obtaining complete tumour resection)
— bilateral head and neck paragangliomas
— multifocal paragangliomas
— tumours > 5 cm (require the reconstruction of cervical vasculature)

Embolisation

The administration of a vasoconstrictor is rarely used as an independent treatment method. The most frequently used embolization is done in combination with tumour resection which should be at best performed within 48 hours of the application of the embolising agent (polyvinyl alcohol, tris-acryl gelatine microspheres, ethanol, platinum spirals) in order to avoid inducing collateral circulation [23]. Embolisation was for the first time described and recommended by Robertson in 1972. The time span between embolisation and the decision concerning consecutive treatment, including surgical intervention, depends on the resolution or decrease of the symptoms existing before embolisation; it is also necessary to perform follow-up examinations, including an angio-CT [24]. The advantages of this course of treatment comprise the decrease of the tumour mass, which improves resectability conditions and also the decrease of the vascular flow or even a complete occlusion of the vessels, leading to the reduction of the risk of bleeding during the procedure. It must be remembered, however, that in the case of the displacement of the occlusion material, the risk of ischaemic brain stroke increases.

Radiotherapy

Irradiation is a generally recognised method of treating paragangliomas, the result of which is the loss of their cell division capability, the creation of vascular emboli and a consecutive vascular fibrosis. Currently, radiotherapy is regarded as the best method of paraganglioma treatment, irrespective of the evaluation of the tumour resectability. The objective of this type of treatment is not complete tumour regression, but the inhibition of its growth. The efficiency of RTH evaluated in follow-up imaging examinations is defined as the lack of tumour progression or its partial regression (partial regression in 61% patients — a reduction of the baseline tumour dimension by 23% on average). In comparison with surgery, radiotherapy allows the preservation of the neural function and is connected with a significantly lower risk of vascular complications. It is the method of choice in patients with a diagnosed skull base paraganglioma and vagal nerve paraganglioma. The applied radiotherapy methods are comprised of the standard 3D external beam radiotherapy (EBRT), stereotactic radiotherapy (SBRT) and radiosurgery (SRS). The conventionally fractionated EBRT is usually applied irrespective of the tumour size, up to a total dose of 45 Gy for 5 weeks [25]. There are reports suggesting that the recurrence rate increases above 1% when the total irradiation dose is below 40 Gy [26]. The techniques of stereotactic radiotherapy administered in a few fractions (usually 3–5) up to a total dose of 21–25 Gy or radiosurgery (12–32 Gy administered in a single dose) are applied in particular in the case of tumours which are not larger than 3 cm. Fractionating depends also on the tumour volume. There is also evidence of a higher risk of neuropathy after stereotactic treatment in comparison with EBRT. Better results were observed after a single dose of 15 Gy in comparison with a single dose of 13 Gy. It was proven that the radiotherapy results are independent of the radiotherapy technique which has been applied (EBRT vs SBRT vs SRS). However, an important aspect is the qualification criterion for each of these methods, which is the tumour size [1]. It was also proven that surgery performed after RTH does not improve the treatment results [27]. In secretory paragangliomas, in spite of increasing EBRT doses to 64–70 Gy, no satisfactory effect inhibiting secretion is achieved; as a result, in such cases the method of choice is tumour resection with a potential postoperative RTH after the consideration of the histopathology results. American researchers performed a metanalysis of paraganglioma treatment methods, comprising: complete resection, partial resection, radiosurgery and partial resection in combination with radiosurgery. The best results with respect to disease recurrence were

obtained with the application of radiosurgery as an independent method [28]. The generally accessible data from many publications point to a 5-year and 10-year local disease control after the application of radiotherapy in 99% and 96% of patients respectively which shows that irradiation results are at least comparable or better than surgery [29]. On the basis of the American register, National Cancer Data, 5-year survival totals 60% in the cases of paragangliomas metastasising to regional lymph nodes [7]. Radiotherapy is also connected with some adverse effects such as mucositis, xerostomia, nausea, progressive hearing loss leading to deafness, osteonecrosis, soft tissues fibrosis, brain necrosis, chronic otitis, otorrhea, nerve VI, VII, VIII palsy — after the administration of doses > 64 Gy, trismus (lockjaw), and also secondary cancers (sarcomas) [21, 30–32]. Mortality connected with conventional radiotherapy is estimated to be about 2%. No deaths related with radiosurgery have been reported [22]. According to Cummings, the treatment results after radiotherapy, depending on the symptoms, were as follows: in 79% patients tinnitus was reduced, 30% of patients reported hearing improvement and 5% complete hearing recovery. 62% of patients do not experience neither improvement nor deterioration in hearing [33]. The improvement of the function of remaining cranial nerves concerns about 30% patients [1].

Systemic treatment

In the cases of diagnosing malignant paragangliomas, which, as was mentioned here, concern patients with metastases, systemic treatment is the basic therapeutic option. The treatment should be conducted by experienced teams consisting of specialists in endocrinology, nuclear medicine and clinical oncology. For the treatment, radionuclides are applied, such as ^{131}I-MIBG (in the case of adequate uptake confirmed in scintigraphy: ^{123}I- or ^{131}I-MIBG), and also isotope-labelled somatostatin analogues (in the cases of confirming the presence of somatostatin receptors: 99mTc Tectrotid or PET^{68}Ga-Dotatate). Fast progression of the lesion may be an indication for the use of chemotherapy based on the CVD regimen (cyclophosphamide, vincristine, dacarbazine). Also etoposide, cisplatin and cytosine arabinoses are applied. There are also isolated reports about the efficiency of temozolomide. There are clinical trials in which the targeted treatment with the use of axitinib, pazopanib or sunitinib is studied [16].

Pharmacotherapy

Pharmacological therapy has not used in a causative treatment although it is frequently applied in the cases of secretory paragangliomas especially before a planned surgery. The medication of first choice comprises selective alpha-1-blockers as these drugs control arterial pressure and prevent *catecholaminergic crisis* and tachycardia during surgery. In the case of a lack of satisfactory haemodynamic control, it is also possible to include calcium channel blockers into the therapy. Beta-blockers may be used in order to control tachycardia as late as 2–3 days after the use of an alpha-1-blocker. If the drugs inhibiting the beta receptors are introduced sooner there is a risk of developing hypertensive shock [6, 34].

Conclusions

Paragangliomas, in spite of their very rare incidence, with respect to their biological properties, present themselves as a heterogenous group of cancers. The symptoms of disease are strictly connected with the location of the tumour and the characteristic image observed in CT and MRI is sufficient to make a diagnosis without the necessity of a cytological or histopathological assessment. The therapeutic pattern provides some options for choice between observation and on-going check-ups, surgery and conservative treatment. The most significant criteria determining the treatment method are tumour location, size and hormonal activity. Comparable results after tumour resection and radiotherapy conclude that the choice of treatment is determined by the number of possible complications after the application of each of the methods. Subsequently, radiotherapy may be regarded as the treatment of choice in the treatment of head and neck paragangliomas.

Conflict of interest: none declared

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References

1. Hu K, Persky MS. Treatment of head and neck paragangliomas. *Cancer Control* 2016; 23: 228–241.
2. Śniatowska M, Waliszewska-Prosół M, Koszewicz M et al. Przyzwojak przebiegający z objawami niedystonicznego kręczu karku. *Pol Przegl Neurol* 2015; 11: 178–182.
3. Baza Krajowego Rejestru Nowotworów.
4. Sawicki W. *Histologia*. Warszawa: Wydawnictwo Lekarskie PZWL, 2003: 377–379.
5. *Endokrynologia kliniczna: praca zbiorowa*. Milewicz A (ed.). Wrocław: Polskie Wydawnictwo Endokrynologiczne, 2012: 424–445.
6. Lenders J, Duh QY, Eisenhofer G et al. Pheochromocytoma and paraganglioma: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2014; 99: 1915–1942.
7. Bernier J. *Head and neck cancer: multimodality management*. New York; Springer, 2011: 569–579.
8. El-Naggar AK, Chan JKC, Grandis JR et al. (eds.). *WHO classifications head and neck tumors*. Lyon: IARC, 2017: 276–284.
9. Kiziltan HS, Ozucer B, Eris AH et al. Bilateral carotid paraganglioma: surgery and radiotherapy. *Clin Med Insights Case Rep* 2014; 7: 53–57. doi: 10.4137/CCRep.S14223. eCollection 2014.
10. Pillai S, Gopalan V, Smith RA et al. Updates on the genetics and the clinical impacts on phaeochromocytoma and paraganglioma in the new era. *Crit Rev Oncol Hematol* 2016; 100: 190–208.

11. Baysal BE, Willett-Brozick JE, Lawrence EC et al. Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas. *J Med Genet* 2002; 39: 178–183.
12. Myssiorek D. Head and neck paragangliomas: an overview. *Otolaryngol Clin North Am* 2001; 34: 829–836.
13. Castrucci WA, Chiang VL, Hulinsky I et al. Biochemical and clinical responses after treatment of a catecholamine-secreting glomus jugulare tumor with gamma knife radiosurgery. *Head Neck* 2010; 32: 1720–1727.
14. Kimura N, Watanabe T, Noshiro T et al. Histological grading of adrenal and extra-adrenal pheochromocytomas and relationship to prognosis: a clinicopathological analysis of 116 adrenal pheochromocytomas and 30 extra-adrenal sympathetic paragangliomas including 38 malignant tumors. *Endocr Pathol* 2005; 16: 23–32.
15. Mete O, Asa SL (eds.). *Endocrine pathology*. Cambridge: Cambridge University Press, 2016.
16. Angelousi A, Kassi E, Zografos G et al. Metastatic pheochromocytoma and paraganglioma. *Eur J Clin Invest* 2015; 45: 986–997.
17. Parenti G, Zampetti B, Rapizzi E et al. Updated and new perspectives on diagnosis, prognosis, and therapy of malignant pheochromocytoma/paraganglioma. *J Clin Oncol* 2012; 2012: 872713. doi: 10.1155/2012/872713.
18. Hu K, Persky MS. Multidisciplinary management of paragangliomas of the head and neck, Part 1.*Oncology (Williston Park)* 2003; 17: 983–993.
19. Brink I, Hoegerle S, Klisch J et al. Imaging of pheochromocytoma and paraganglioma. *Fam Cancer* 2005; 4: 61–68.
20. Kataria T, Bisht SS, Mitra S et al. Synchronous malignant vagal paraganglioma with contralateral carotid body paraganglioma treated by radiation therapy. *Rare Tumors* 2010; 2: e21.
21. Farr HW. Carrotid body tumors. A thirty year experience at Memorial Hospital. *Am J Surg* 1967; 114: 614–619.
22. Suárez C, Rodrigo JP, Bödeker CC et al. Jugular and vagal paragangliomas: Systematic study of management with surgery and radiotherapy. *Head Neck* 2013; 35: 1195–1204.
23. Andrews JC, Valavanis A, Fisch U. Management of the internal carotid artery in surgery of the skull base. *Laryngoscope* 1989; 99: 1224–1229.
24. Lund VJ, Howard DJ, Wei WI et al. *Tumors of the nose, sinuses and nasopharynx*.Stuttgart; New York: Thieme, 2014.
25. Evenson LJ, Mendenhall WM, Parsons JT et al. Radiotherapy in the management of chemodectomas of the carotid body and glomus vagale. *Head Neck* 1998; 20: 609–613.
26. Mendenhall WM, Parsons JT, Stringer SP et al. Radiotherapy in the management of temporal bone chemodectoma. *Skull Base Surg* 1995; 5: 83–91.
27. Kim JA, Elkon D, Lim ML et al. Optimum dose of radiotherapy for chemodectomas of the middle ear. *Int J Radiat Oncol Biol Phys* 1980; 6: 815–819.
28. Gottfried ON, Liu JK, Couldwell WT. Comparison of radiosurgery and conventional surgery for the treatment of glomus jugulare tumors. *Neurosurg Focus* 2004; 7: E4.
29. Gilbo P, Tariq A, Morris CG et al. External-beam radiation therapy for malignant paraganglioma of the head and neck. *Am J Otolaryngol* 2015; 36: 692–696.
30. Powell S, Peters N, Harmer C. Chemodectoma of the head and neck: results of treatment in 84 patients. *Int J Radiat Oncol Biol Phys* 1992; 22: 919–924.
31. Dawes PJ, Filippou M, Welch AR et al. The management of glomus jugulare tumours. *Clin Otolaryngol Allied Sci* 1987; 12: 15–24.
32. Lybeert ML, van Andel JG, Eijkenboom WM et al. Radiotherapy of paragangliomas. *Clin Otolaryngol Allied Sci* 1984; 9: 105–109.
33. Cummings BJ, Beale FA, Garrett PG et al. The treatment of glomus tumors in the temporal bone by megavoltage radiation. *Cancer* 1984; 53: 2635–2640.
34. *Interna Szczeklika 2015*. Gajewski P (ed.). Kraków: Wydawca Medycyna Praktyczna, 2015: 1352–1357.
35. Trombetta M, Silverman J, Colonias A et al. Paraganglioma: a potentially challenging tumor. *Oncology (Willston Park)* 2008; 22: 341–343.
36. Jackson CG, Harris PF, Glasscock ME 3rd et al. Diagnosis and management of paragangliomas of the skull base. *Am J Surg*1990; 159: 389–393.
37. Fisch U. Mattox DE. *Microsurgery of the skull base*. Stuttgart; New York: Thieme-Verlag, 1988: 149–152.
38. Capatina C, Ntali G, Karavitaki N et al. The management of head-and-neck paragangliomas. *Endocr Relat Cancer* 2013; 20: R291–R305.
39. Shamblin WR, ReMine WH, Sheps SG et al. Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. *Am J Surg* 1971; 22: 732–739.
40. Luna-Ortiz K, Rascon-Ortiz M, Villavicencio-Valencia V et al. Does Shamblin's classification predict postoperative morbidity in carotid body tumors? A proposal to modify Shamblin's classification. *Eur Arch Otorhinolaryngol* 2006; 263: 171–175. [Errata in: *Eur Arch Otorhinolaryngol* 2006; 263: 1161].
41. Ng E, Duncan G, Choong AM et al. Sclerosing paragangliomas of the carotid body: A series of a rare variant and review of the literature. *Ann Vasc Surg* 2015; 29: 1454.e5–1454.e12.

Appendix

Glasscock-Jackson Classification

Cervical body paragangliomas [35]

- I — small tumour covering the area of the jugular vein bulb, middle ear and mastoid process
- II — tumour growing below internal acoustic meatus – intracranial expansion possible
- III — tumour expanding to the top of the petrous pyramid of the temporal bone — intracranial expansion is possible
- IV — the tumour expanding beyond the top of the petrous pyramid of the temporal bone to the clivus or subtemporal fossa — intracranial expansion is possible

Tympanic paragangliomas [36]

- Period I — small tumour in the area of promontorium
- Period II — the tumour fills the tympanic cavity
- Period III — the tumour fills the tympanic cavity, penetrating into the mastoid process
- Period IV — the tumour fills the tympanic cavity, mastoid process, external acoustic meatus and may infiltrate towards internal carotid artery

Fisch and Mattox classification [37, 38]

The classification of jugulo-tympanic paragangliomas (former nomenclature)

- stage A — tumour develops from tympanic plexus
- stage B — tumour develops is hypotympanum, infiltrates middle ear and mastoid process
- stage C1 — tumour destroys the foramen of the carotid artery without infiltrating carotid artery
- stage C2 — tumour destroys the vertical part of the carotid artery canal
- stage C3 — tumour destroys the horizontal part of the carotid artery canal, without infiltrating foramen lacerum
- stage C4 — tumour infiltrates foramen lacerum and cavernous sinus
- stage De1/2 — tumour proliferates intracranially, but epidurally: De1 not more than 2 cm, De2 — more than 2 cm;
- stage Di1/2/3 — tumour proliferates intracranially and in intradural manner: Di1 do 2 cm; Di2 — between 2 and 4 cm; Di3 — more than 4 cm.

Table II. Shamblin's classification of paragangliomas [39]

Stage	Tumour	Difficulty degree of tumour resectability	Surgery
I	The tumour separates ICA and ECA, attaches to the bifurcation	Low	Routine dissection
II	Partly covers the vessels	Medium	Subintimal dissection
III	Closely covers the vessels	High	Partial or complete vascular resection

Table III. Shamblin's modified classification of paragangliomas [40, 41]

Stage	Tumour size	Cervical vessel involvement or infiltration in the tumour area	Difficulty degree of tumour resectability
I	< 4 cm	The tumour does not involve or infiltrate cervical vessels	No difficulties
II	> 4 cm	Partially involves cervical vessels	Difficult
IIIA	> 4 cm	Closely involves cervical vessels	Difficult, requires vessel correction, removal, or replacement
IIIB	Each	Stage I, II or III in Shamblin's original classification with the infiltration of cervical vessels	The clinical and/or histopathological confirmation of the vascular wall invasion is necessary

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Review article

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Progress in adjuvant treatment of melanoma patients

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Surgery is therapy of choice in melanoma patients. However, prognosis of patients at stage IIC–IV even after radical resection is very heterogenous and related to high risk of disease relapse. Positive results of clinical trials indicate that in the nearest future systemic adjuvant therapy in high risk melanomas will become the standard of care. New treatment modalities, both molecular targeted therapy with BRAF+MEK inhibitors dabrafenib with trametinib and immunotherapy anti-PD-1 with nivolumab or pembrolizumab have been approved in US and EU.

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Key words: melanoma, adjuvant therapy, BRAF, MEK inhibitors, immunotherapy, anti-PD-1

Surgery is therapy of choice in melanoma patients, however, prognosis in patients at stage IIC–IV melanomas even after radical resection is very heterogenous and to a large extent related to high risk of disease relapse [1–5].

Adjuvant therapy after surgical treatment is currently used in specific cases, although studies indicate that systemic adjuvant therapy in the discussed group of melanoma patients will become the standard of care. New systemic therapies have already been registered in the United States and the European Union. In view of the combination of surgery and conservative treatment, the basic and binding principle should be the management by multi-specialist teams, whose members have experience in the diagnosis and treatment of patients with melanoma at locoregional and generalised settings.

Adjuvant radiotherapy

In individual cases, after surgery in patients with high risk melanoma, adjuvant radiotherapy (RTH) is possible — the dosing regiment includes hypofractionation using 3–8 Gy/fraction or conventional fractionation depending on the location. The indications for adjuvant RTH after primary tumour excision may include:

— diagnosis of desmoplastic melanoma excised with narrow margins,
— the presence of 'positive' surgical margins (especially after the local recurrence resection) while no surgical radicalisation is possible,
— the presence of satellite lesions,
— enhanced neurotropism,
— location in the head and neck region (caution: RTH as an exclusive treatment method can be used with extensive LMM lesions).

In case of local resection and lymphadenectomy due to metastases at regional lymph nodes, the indications for complementary RTH may be:

— the presence of extracapsular node invasion,
— spread to ≥ 4 lymph nodes (stage IIIC)
— metastasis diameter > 3 cm,
— metastases in the neck lymph nodes (from 2 metastatic lymph nodes or at a minimum metastasis size of 2 cm),
— relapse after prior resection [1, 2, 4, 6].

The results of the only completed randomized clinical trial , which evaluated the value of adjuvant radiotherapy (48 Gy in 20 fractions) after lymphadenectomy in case of high risk of relapse, confirmed the improvement of local

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control after irradiation, but at the same time no effect on overall survival was observed, with an increase in frequency of late locoregional complications and deterioration of patients' quality of life. Therefore, the conclusions from this study indicate that the use of adjuvant radiotherapy should be limited [7, 8]. It should also be emphasized that there are no indications of an adjuvant RHT after the completion lymphadenectomy following a positive sentinel lymph node biopsy (CLND).

Systemic adjuvant therapy

At present, there are no Polish and European recommendations for routine systemic adjuvant therapy in clinical practice at patients after the radical resection of primary lesions and lymphadenectomy, and adjuvant radiotherapy can only be considered in the specific situations described above. The results of recently published clinical studies indicate an improvement in survival, both from the use in adjuvant therapy the immunotherapy with the immune checkpoint inhibitors and from the combination therapy with BRAF and MEK inhibitors, and it can be expected that such treatment will become a standard of care in the nearest future, as it happened in US [1–4].

Interferon

For many years, apart from interferon (IFN), no other agents has been effective in the treatment of high risk skin melanomas. Interferon (mainly IFN-a-2b, used only in monotherapy) in the adjuvant therapy of melanoma patients (for a selected group) in most studies resulted in prolongation (in a repetitive manner) of relapse-free survival (RFS) (Tab. I) [4, 9–13]. The evidence of improved overall survival (OS) as a result of the use of IFN is much weaker and more controversial. In 10 out of 17 evaluated studies an improvement in RFS was observed, with the latest meta-analyses showing a reduction in the risk of relapse by 17–18% [relative risk (HR hazard ratio) 0.82–0.83; $p < 0.0001$] when using IFN in adjuvant therapy. The evidence for OS improvement comes mainly from meta-analyses and it is reflected in the improvement of OS by about 3% over 5 years in the whole group of patients. The use of adjuvant IFN treatment in all high-risk melanoma patients is therefore not justified (especially considering its high toxicity) and remains optional only for selected patients. Interferon a-2b (IFN a-2b) in high doses was registered in the United States and the European Union for IIB–III stage melanomas on the basis of a positive result of one of three studies of the Eastern Cooperative Oncology Group (ECOG) — ECOG 1684, while this drug was registered in low doses in Europe for II stage patients. The basis for registration was a significant increase in the overall survival time during the period of about 7 years of observation, which, however, after a longer period (12 years) was not confirmed. The results of meta-analyses indicate that the basic group of patients benefiting from IFN adjuvant therapy are those with ulcerated primary melanoma, especially in the subgroup of patients with clinically undetectable metastases in the sentinel node (formerly known as micro-metastases), and not with clinically diagnosed metastases found in swollen (palpable) lymph nodes (formerly known as macro-metastases) [11, 12]. Results of a study by the European Organisation for Research and Treatment of Cancer 18081 (EORTC 18081) are currently expected; its aim is to assess the use of pegylated IFN in the treatment of patients after primary ulcerated cutaneous melanoma resection without metastases to regional lymph nodes (interrupted study recruitment). The most common side effects are parainfluenza symptoms, fever, weakness, neutropenia, hepatotoxicity and depression. Part of the IFN toxicity profile changes during therapy. Along the course of treatment, parainfluenza symptoms decrease, while other reported side effects remain the same or even increase with the duration of treatment (mainly fatigue, anorexia, symptoms of depression/anxiety).

Immunotherapy with immune checkpoint inhibitors

In 2015, preliminary results of a study on the use of adjuvant treatment with anti-CTLA-4 antibodies (ipilimumab) after lymphadenectomy due to metastases to regional lymph nodes (stage III) were published. The study included 951 patients who were randomly allocated to the ipilimumab high-dose group at 10 mg/kg body weight every 3 weeks and then every 3 months up to 3 years (n = 476) or placebo (n = 476). With a median of the observation time being 2.7 years, 234 events were reported with reference to RFS in ipilimumab-treated group compared to 294 for placebo-treated group; the median RFS was 26.1 months compared to 17.1 months ($p = 0.0013$), respectively. The improvement of RFS referred to patients with both macro- and micro-metastases (definitions according to then valid 7th revision of TNM staging system) to lymph nodes; the result of adjuvant therapy was more important at the ulceration of the primary lesion. In the ipilimumab-treated group, 54% of patients had side effects with 3–4 toxicity levels compared to 25% in the placebo-treated group. Due to complications connected with ipilimumab administration, 5 patients (1%) died. Side effects led to permanent discontinuation of treatment in 52% of patients entering ipilimumab treatment [14]. The results of this study, presented in 2016 with a median follow-up time at 5.3 years, show a significant improvement in the use of ipilimumab adjuvant therapy in high doses for both RFS as well as distant metastasis free survival and OS. The percentage of 5-year OS in the group receiving ipilimumab was 65.4% compared to 54.4% in the group receiving placebo (hazard ratio for death 0.72, 95.1% CI 0.58–0.88; $p = 0.001$) [15]. Preliminary results of a subsequent E1609 study showed similar efficacy of a lower dose

Table I. Summary of the results of the most important clinical trials on adjuvant therapy with interferon (INF). Bold typeface distinguishes the studies where a significant benefit was obtained from INF therapy [acc. to 13]

Study	Study period/ INF type	Melanoma stage	RFS	OS
Very low doses of interferon, 0.5–1 million IU				
EORTC 18871/DKG-80	1 year/ INF-α-2b	IIB, III	**p = 0.02**	p = 0.18
Low doses of interferon, 3 million IU				
Austria	1 year/ INF-α-2a	IIB, III	**p = 0.02**	p = 0.6
France	18 months/ INF-α-2a	IIB, III	**Benefit** (p = 0.035)	p = 0.06
WHO-16	3 years/ INF-α-2a	III	p = 0.5	p = 0.7
E1690	2 years/ INF-α-2b	IIB, III	p = 0.17	p = 0.81
Scotland	6 months/ INF-α-2b	IIB, III	p = 0.051	p = 0.4
Germany	2 years/ INF-α-2a	III	**p = 0.0045**	**p = 0.018**
UKCCCR	2 years/ INF-α-2a	IIB, III	p = 0.3	p = 0.6
Intermediate doses of interferon, 10 million IU				
EORTC 18952	13 months/ INF-α-2b	IIB, III	**Benefit** only in subgroup IIB	No benefit
	25 months/ INF-α-2b	IIB, III	**Benefit** only in the IIB subgroup or in the group of patients with micro-metastases after a positive sentinel lymph node biopsy	No benefit
High doses of interferon, 20 million IU/m^2 vs observation				
E1684	52 weeks/ INF-α-2b	IIB, III	**p = 0.02**	**p = 0.01**
E1690	52 weeks/ INF-α-2b	IIB, III	No benefit	No benefit
NCCTG 83707	3 months/ INF-α-2a	IIA, IIB, III	p = 0.24	p = 0.53
Sunbelt Melanoma Trial	52 weeks/ INF-α-2b	IIIA	No benefit	No benefit
High doses of interferon, 20 million IU/m^2 vs vaccine				
E1694	96 weeks/ INF-α-2b vs GMK vaccine	IIB, III	**p = 0.0015**	**p = 0.009**
Long-term administration of pegylated interferon vs observation				
EORTC 18991			**p = 0.01**; improvement by 6.7%	p = 0.78

RFS — relapse-free survival; OS — overall survival

of ipilimumab (3 mg/kg) with less toxicity. The EORTC 18071 study has led to the registration of ipilimumab in the United States as an adjuvant therapy for melanoma patients after lymphadenectomy due to metastases to regional lymph nodes, however, its practical application is limited due to its high toxicity and more favourable test results with anti-PD-1 antibodies (nivolumab and pembrolizumab) and kinase inhibitors.

Nivolumab in a randomized clinical trial (CheckMate 238) in patients after resection of metastases at stage IIIB, IIIC and IV showed a 10% improvement in relapse-free survival if compared with ipilimumab at a lower toxicity (18-month RFS: 65% vs 53%). This is the only study where patients after the resection of distant metastases were also included. The improvement of distant metastases free survival (DMFS) was also demonstrated (HR 0.73). Adverse events associated with treatment at stage III or IV were reported

Table II. Summary of recent clinical studies on adjuvant therapy after melanoma resection with a high relapse risk

	EORTC 18071 **Ipilimumab vs placebo**	**BRIM-8** **Vemurafenib vs placebo**	**COMBI-AD** **Dabrafenib + trametinib vs placebo**	**Checkmate 238** **IPI vs NIVO**	**EORTC 1325/Keynote 054** **Pembrolizumab vs placebo**
Author	Eggermont 2015 Eggermont 2016	Lewis 2017	Long 2017	Weber 2017	Eggermont 2018
Population	IIIA (> 1 mm), IIIB, IIIC	IIC, IIIA, IIIB, IIIC	IIIA (> 1 mm), IIIB, IIIC	IIIB, IIIC, IV	IIIA (> 1 mm), IIIB, IIIC
BRAF mutation	?	100%	100%	41% / 43%	
RFS	**41% vs 30% (5 years)**	**82% vs 63% (12 months)** **62% vs 53% (24 months)** **79% vs 58% (12 months)** **46% vs 47% (24 months) IIIC** **84% vs 66% (12 months)** **72% vs 56% (24 months) IIC–IIIB**	**67% vs 44% (2 years)** **HR = 0.47** **58% vs 39% (3 years)**	**66% vs 53% (18 months)** **62,6% vs 50.2% (24 months)** **HR 0.66 vs HR 0.65**	**HR 0.57; difference after 18 months** **18.2%: 71.4% vs 53.2%**
OS	65% vs 54% (5 years) HR = 0.72	NDA	**91% vs 83% (2 years)** **86% vs 77% (3 years)** **HR = 0.57**	NDA	

OS — overall survival, RFS — relapse-free survival, NDA — no data available

in 14.4% of patients receiving nivolumab as compared to 45.9% in the ipilimumab-treated group [16]. Updated data from 2018, with a longer period of observation, confirm the beneficial effect of nivolumab in adjuvant therapy for one year, regardless of the PD-L1 expression status and *BRAF* mutation with respect to RFS (HR 0.66) and DMFS (HR 0.76) [17]. Nivolumab is currently registered for adjuvant therapy in the United States and the European Union.

Preliminary results of Keynote-054/EORTC 1325 trial in 1019 patients also indicate a reduction in the risk of relapse (HR for RFS 0.57) and DMFS using pembrolizumab adjuvant therapy for one year compared to placebo in the group of patients with resection stage III with a higher risk (IIIA with micro-metastasis size > 1 mm, IIIB and IIIC) [18]. A study comparing the use of nivolumab in adjuvant therapy with a combination of nivolumab and ipilimumab is currently under way (CheckMate 915).

Molecularly targeted treatment

Adjuvant therapy using dabrafenib with trametinib in patients with high risk *BRAF* mutation level III showed improvement in RFS (HR 0.47), DMFS (HR 0.51; 91% vs 70% after 1 year, 77% vs 60% after 2 years and 71% vs 57% after 3 years) and OS (HR 0.57) compared to placebo. In this study (COMBI-AD) dabrafenib with tramethinib were used for 1 year compared to placebo (stage IIIA with a metastasis di meter > 1 mm, IIIB/C) [19]. This study is the only one apart from the study with ipilimumab discussed above that has shown a significant improvement in overall survival rate. The safety profile of dabrafenib with tramethinib was consistent with that observed in the study, which included patients with melanoma at the IV stage of development. Dabrafenib with trametinib are currently approved for adjuvant therapy in the United States and the European Union. The formally 'positive' clinical trial BRIM-8 [20] also included the use of vemurafenib monotherapy in adjuvant therapy for one year as compared to placebo in patients with melanoma after stage IIC–III resection (the only study to date covering patients at stage II). The median disease-free survival (DFS) was 23.1 months in the vemurafenib-treated group compared to 15.4 months in the placebo group (HR 0.8; p = 0.026), but this effect was limited only to the IIC–IIIA–IIIB subgroup, and was not visible to more advanced patients at stage IIIC. At the same time, it is known from the current practice at patients with metastatic melanoma that monotherapy with BRAF inhibitors is not optimal if compared to the combined treatment of patients with the presence of *BRAF* mutations with BRAF and MEK inhibitors.

Summary

The results of systemic adjuvant therapy with immunotherapy after high-risk melanoma resection are summarised in Table II. Other immunotherapy methods (e.g. interleukin-2), vaccines or drugs with cytotoxic effects have no practical use in adjuvant postoperative therapy [1, 4, 5, 21].

In summary, adjuvant therapy with anti-PD-1 immunotherapy (ninolumab or pembrolizumab) or combined treatment with BRAF and MEK inhibitors (dabrafenib with tramethinib for populations with *BRAF* mutations) is becoming a new standard of care after melanoma resection with high risk of relapse (resection stages IIIA–IV) according to American and Polish recommendations [2, 4, 22]. This, in turn, means that the treatment of all patients with melanomas with stages from IIIA to IV should be discussed at multi-specialist team meetings in order to ensure optimal, modern and as effective a treatment as possible. In addition, it is important to ensure that high risk melanoma patients are included in prospective clinical trials of new adjuvant therapy where possible.

Conflict of interest: none declared

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References

1. Rutkowski P (ed.). Złośliwe nowotwory skóry. Via Medica: Gdańsk 2014.
2. Rutkowski P, Wysocki PJ (ed.). Cutaneous melanoma. Guidelines for diagnostic and therapeutic management. *Oncology in Clinical Practice* 2017; 13: 241–258.
3. Dummer R, Hauschild A, Lindenblatt N et al. ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26 Suppl 5: v126–v132.
4. NCCN Guidelines. Melanoma, Version 3.2018.
5. Eggermont AMM, Dummer R. The 2017 complete overhaul of adjuvant therapies for high-risk melanoma and its consequences for staging and management of melanoma patients. *Eur J Cancer* 2017; 86: 101–105.
6. Ballo MT, Ang KK. Radiotherapy for cutaneous malignant melanoma: rationale and indications. *Oncology* 2004; 18: 99–107.
7. Burmeister BH, Henderson MA, Ainslie J et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol* 2012; 13: 589–597.
8. Henderson MA, Burmeister BH, Ainslie J et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. *Lancet Oncol* 2015; 16: 1049–1060.
9. Eggermont AM, Gore M. Randomized adjuvant therapy trials in melanoma: surgical and systemic. *Semin Oncol* 2007; 34: 509–515.
10. Sondak VK, Gonzalez RJ, Kudchadkar R. Adjuvant therapy for melanoma: a surgical perspective. *Surg Oncol Clin North Am* 2011; 20: 105–114.
11. Eggermont AM, Suciu S, Testori A et al. Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. *Eur J Cancer* 2012; 48: 218–225.
12. Ives NJ, Suciu S, Eggermont AM et al.; International Melanoma Meta-Analysis Collaborative Group (IMMCG). Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis. *Eur J Cancer* 2017; 82: 171–183.
13. Rutkowski P. Świtaj T. Immunoterapia czerniaków. In: *Immunoonkologia.* Wysocki P (ed.). Gdańsk: Via Medica, 2015.
14. Eggermont AM, Chiarion-Sileni V, Grob JJ et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma

(EORTC 18071): a randomised, double-blind, phase 3 trial. L*ancet Oncol* 2015; 16: 522–530.
15. Eggermont AMM, Chiarion-Sileni V, Grob JJ et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* 2016; 375: 1845–1855.
16. Weber J, Mandala M, Del Vecchio M et al.; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017; 377: 1824–1835.
17. Weber JS, Mandalà M, Del Vecchio M et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). *J Clin Oncol* 2018; 36 (Suppl; abstr 9502). ASCO Annual Meeting.
18. Eggermont AMM, Blank CU, Mandala M et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018; 378: 1789–1801.
19. Long GV, Hauschild A, Santinami M et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med* 2017; 377: 1813–1823.
20. Maio M, Lewis K, Demidov L et al.; BRIM8 Investigators. Adjuvant vemurafenib in resected, BRAFV600 mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2018; 19: 510–520.
21. Dreno B, Thompson JF, Smithers BM et al. MAGE-A3 immunotherapeutic as adjuvant therapy for patients with resected, MAGE-A3-positive, stage III melanoma (DERMA): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018; 19: 916–929.
22. Bello DM, Ariyan CE. Adjuvant therapy in the treatment of melanoma. *Ann Surg Oncol* 2018; 25: 1807–1813.

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Case report

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The efficacy of tapentadol prolonged release in the treatment of mixed cancer pain

Elwira Góraj

Pain can be experienced at every stage of cancer and its treatment (50% to 90%); about 19–39.1% of patients suffer from neuropathic pain and 75% from mixed pain. Due to different treatment strategy a proper diagnosis of pain is of high importance. Opioids with a pure agonist effect are used to treat moderate and severe nociceptive pain and adjuvant drugs in the first line treatment of neuropathic pain.

Tapentadol is the only centrally acting opioid that combines two mechanisms of action — mu-opioid receptor (MOR)-agonist and norepinephrine reuptake inhibitor (NRI) activities. This specificity of action particularly predisposes tapentadol for use in mixed pain as well as in the therapy of various pain syndromes, both in the mechanism of receptor and neuropathic pain. The indication for the use of tapentadol is the treatment of chronic pain of high severity in adults, which can be properly controlled only after the use of opioid analgesics.

In experimental and clinical studies, the efficacy and good safety profile of tapentadol was proofed, both in acute (somatic and visceral) and chronic pain syndromes, including neuropathic pain.

Most of the studies concern chronic non-cancer pain. In the present case, the aspect of the occurrence of mixed cancer pain in course of pancreatic cancer with coexisting chemotherapy-induced neuropathy (treated with gabapentin) is emphasized. Due to the lack of good visceral control the combined method was used with opioids i.e. fentanyl TTS and oxycodone. Neurolysis of the celiac plexus was performed, followed by followed by main opioid rotation for tapentadol PR, resulting in a reduction in basic (visceral and neuropathic pain), and a reduction in the severity of breakthrough pain episodes, which were controlled by rapid-acting transmucosal fentanyl.

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Key words: cancer pain, neuropathic pain, opioids, chemotherapy-induced polyneuropathy, tapentadol PR

Introduction

Pain can be experienced at every stage of cancer and its treatment. The early implementation of appropriate analgesics and adjuvant drugs in accordance with recommendations of WHO analgesic ladder and the guidelines of panel of expert scientific societies allows to sufficiently control pain in most cases. In moderate to severe pain, opioids are used. When choosing the right opioid, one should take into account the mechanism and intensity of pain, the patient's age, metabolism and confounding factors, co-morbidities, medication, psychological status, reaction to the previously used opioid and the history of drug abuse.

Potent opioids are usually classified by affinity for opioid receptors and divided into full agonists, partial agonists and agonist-antagonists.

The most frequently used are opioids from the group of pure agonists that do not have a definite maximum dose. Opioids that are partial agonists or agonist-antagonists have so-called ceiling effect. In Poland, the most commonly used partial agonist is buprenorphine (a partial agonist of the μ and δ opioid receptors and the κ receptor antagonist) which, when used in therapeutic doses, acts like a pure agonist without a ceiling effect for analgesia.

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In contrast to other opioids, buprenorphine has a beneficial effect from the safety perspective of therapy (e.g. the risk of opioid overdose), a ceiling effect for respiratory depression. The maximum recommended dose of transdermal buprenorphine is 140 mcg/h.

Buprenorphine is a partial agonist with low intrinsic activity. Opioids included in agonist-antagonists (butorphanol, nalbuphine, pentazocine) act agonistically on one of the receptors (mainly μ) and antagonistically on others. None of these is currently used in the treatment of acute and chronic pain [1, 2].

The pure mu-opioid receptor (MOR) agonists are classified according to the number of Ki, determining the degree of affinity for the receptor (binding strength).

Opioids were divided into three groups due to the K value:

— K(i) > 100 nM tramadol, codeine, meperidine, propoxyphene, pentazocine;
— K(i) = 1–100 nM hydrocodone, oxycodone, diphenoxylate, alfentanil, methadone, nalbuphine, fentanyl, morphine;
— K(i) < 1 nM butorphanol, levorphanol, oxymorphone, hydromorphone, buprenorphine, sufentanil [3].

The smaller the Ki value, the greater the affinity for the μ receptor.

The most common in the treatment of cancer pain are drugs with a pure agonist action in relation to the known types of opioid receptors (strong affinity for μ receptors and weak in relation to the κ and δ receptor).

Morphine and fentanyl are characterized by a similar profile of interaction with major classes of receptors. Methadone is characterized by a strong interaction of the μ and δ receptors. Oxycodone shows the strongest affinity for κ receptors [1, 2, 4, 5].

The duration of action may be pharmacologically determined (receptor binding mode), e.g. levorphanol and methadone, or pharmaceutically (tablet structure, patch) in sustained release formulations such as SR morphine, oxycodone, tapentadol PR, transdermal fentanyl, transdermal buprenorphine.

The side effects of opioids, which are most often clinically observed: nausea, sedation, constipation, respiratory depression, are the effect of activation of opioid receptors. Less common side effects, such as myoclonus, hallucinations and disorientation, are not reversed after administration of pure antagonists. Treatment of these symptoms requires a reduction of the opioid dose or a change of preparation (rotation). Quetiapine, haloperidol, olanzapine and chlorpromazine are also used in the treatment of hallucinations and myoclonus. Symptoms usually increase proportionally to the opioid dose, and partial or total rotation is usually necessary. Deciding on rotation, metabolic causes of symptoms, such as hyponatremia, hypercalcemia or metastases to CNS should be excluded.

Nausea and vomiting may occur in 10–40% of patients at the initial stage of treatment. Most patients develop tolerance to this symptom, some require periodic administration of antiemetics.

Constipation remains a persistent problem during the treatment with opioids. Therefore, the disorder does not develop the phenomenon of tolerance. In many cases of opioid-induced constipation an effective solution is partial or complete change to a preparation with a proven lower risk of this side effect. The solution to the problem may be the conversion of a hydrophilic opioid to a lipophilic opioid, e.g. buprenorphine, fentanyl. In persistent cases, a combination of an agonist and antagonist (acting locally at intestinal level) should be used — oxycodone with naloxone. The lack of an opioid with a favorable profile of side effects encourages the search for new analgesics, preferably with a different mechanism of action and high analgesic efficacy, while not exacerbating unpleasant side effects [1, 6–8].

Tapentadol

Tapentadol is the latest opioid preparation introduced for the treatment of chronic pain as a strong opioid of the third step of analgesic ladder. Originally, a fast-acting form was created, and then a long-acting (prolonged release, PR) formula was developed. Currently available in Poland doses of tapentadol PR are 50 mg, 100 mg, 150 mg, 200 mg and 250 mg.

Tapentadol, a centrally acting opioid with strong analgesic effect due to the dual mechanism of action contained in one molecule. The binding strength is K(i) 0.1 M. It is a mu-receptor agonist that simultaneously blocks the reuptake of norepinephrine (NRI — noradrenaline reuptake inhibitor). The affinity for the μ-receptor is 50 times weaker than in the case of morphine [1, 9, 10].

The affinity for the other opioid receptors (opioid receptor — κ, opioid receptor δ, ORL1 — opioid receptor-like receptor) is lower than for the MOR receptor. The degree of inhibition of serotonin reuptake is considered to be negligible and neglected in the characteristics of drug action [10].

It is highly probable (studies on animal models) that in cases of acute pain an agonistic activity on MOR receptor predominates in relation to the inhibitory effect of NRI.

Similarly, rats and mice *in vivo* experiments show a strong effect of tapentadol (which is 2–3 times weaker than morphine) in acute nociceptive pain. It is believed that the NRI mechanism synergistically contributes to the overall analgesic effect of tapentadol. The NA inhibitory effect is probably more important in chronic pain [9].

In relation to oral morphine, the conversion rate 1:3.3 is most commonly used [1].

Tapentadol is mainly metabolized in the liver, in the glucuronidation process, to inactive glucuronides or sulphates, primarily to glucuronyl-O-tapentadol (55%). Tapentadol and

its metabolites are mainly excreted by the kidneys (99%) and 1% of the drug is excreted in the faeces. It is very limited metabolism with the involvement of cytochrome P450 isoenzymes, which limits the potential of interactions of tapentadol with other drugs. It is most metabolized by CYP2C9, CYP2C19, CYP2D6. Tapentadol does not inhibit or excite any of the CYP isoforms [11].

Tapentadol exhibits *in vivo* efficacy in heat-induced hyperalgesia models with a minimum effective dose ED50. Its action in diabetic neuropathy is well-established.

It is believed that the total analgesic effect in cases of neuropathic pain results from the simultaneous activation of both mechanisms: MOR and NRI.

The antinociceptive effect of tapentadol is partially reversed by naloxone (the opioid portion of MOR), and the effect of the non-nociceptive mechanism can be reduced by administration of yohimbine, a α (alpha) 2-adrenergic blocker, affecting the sympathetic nervous system [9].

Inhibition of NA reuptake enhances the downstream pain-inhibiting pathway through α2-adrenergic receptors [10].

The moderate affinity to MOR opioid receptor and the demonstrated opioid-saving effect suggest that tapentadol should elicit less side effects associated with the use of opioid drugs compared to classical agonists. Indeed, in the comparative studies of morphine-tapentadol, oxycodone-tapentadol, fentanyl-tapentadol, it was shown that tapentadol to a lesser extent induces nausea and vomiting, as well as the duration of these symptoms is significantly shorter. Adverse symptoms occur at higher doses and the threshold for triggering symptoms is 100 times higher for tapentadol than for morphine.

Tapentadol has a weaker inhibitory effect on intestinal peristalsis than the equivalent dose of morphine (assessed by means of intestinal transit time labeled with carbon) [12]. A lower risk of causing adverse reactions was confirmed in the Merker study (2012). In the meta-analysis, the incidence of vomiting and constipation was significantly lower in the group of patients receiving tapentadol compared to the oxycodone group [7], while tapentadol to a greater extent promotes the occurrence of dryness in the mouth. Similar data were obtained by Mercadante, investigating the efficacy and tolerance of the drug among patients with cancer pain who had never received opioids (so-called *opioid naive*) [13].

According to available evidence, tapentadol inhibits the uptake of serotonin to a negligible extent, so it also has no side effects (constipation, nausea, vomiting, diarrhea) resulting from an increase in serotonin in the central and intestinal nervous system [10].

Neuropathic pain in the course of cancer

The latest definition of neuropathic pain accepted by the Committee on the Taxonomy of the International Association for the Study of Pain (IASP) states that neuropathic pain is pain caused by injury or illness of the somatosensory part of the nervous system. It is estimated that 50% to 90% of cancer patients experience pain during their lifetime [14]. Among them 19–39.1% suffer from neuropathic pain [15]. Early diagnosis of symptoms is particularly important due to a different treatment strategy as compare to nociceptive pain. Among numerous causes of neuropathic pain in the course of neoplastic disease, factors related to tumor growth as well as treatment methods are mentioned, for example radiation-induced plexopathy (RIP) or chemotherapy-induced peripheral polyneuropathy (CIPN). There are less frequent reports of neuropathic pain in the abdominal cavity, which is why they are not recognized early enough. Mechanical causes include biliary obstruction, impaired intestinal obstruction, organ perforation, advanced colorectal cancer, intraperitoneal chemotherapy. In cases of sympathetic plexus disorders, bladder dysfunction or orthostatic hypotension appear [14–16].

Pain in the course of pancreatic cancer may be visceral, somatic or neuropathic. It results from tissue damage, local inflammation, infiltration or mechanical obstacles. The signals are conducted by sympathetic fibers constituting the innervation of the visceral plexus from the level of Th12-L2 [17]. Feeling of paroxysmal stabbing or burning pain is sometimes confused with incidents of breakthrough pain. Pain intensifies at night, disrupts daytime activity and hinders basic functions such as dressing, washing, combing and rest at night. The relationship between clinically occurring symptoms and etiology is not always clear [14].

Case report

The patient aged 62 was treated for 6 months due to inoperable pancreatic cancer (adenocarcinoma ductale pancreatis G2) and received palliative chemotherapy. The patient was given 12 courses according to the FOLFIRNOX protocol: fluorouracil + calcium folinate + oxaliplatin + irinotecan. There were co-existing problems: arterial hypertension, hyperlipidemia, history of two prior myocardial infarctions (2011 and 2014) and coronary angioplasty. During the subsequent courses of chemotherapy, the patient had grade I neutropenia.

Common side effects of FOLFIRNOX are: neutropenia, neutropenic fever, thrombocytopenia, sensory neuropathy (platinum derivatives), diarrhea.

The neoplastic lesion was located in the head of the pancreas. The patient reported epigastric pain radiating to the spine at Th10–12. In addition, there was a feeling of numbness and tingling in the hands and feet (greater in feet). Symptoms began to intensify after the eighth cycle of chemotherapy. It was a mixed type of pain, with a distinct neuropathic component, described as pulsating, squeezing and radiating to the back. The patient was diagnosed with

two neuropathic pain: the first one as a pancreatic component, the second — peripheral polyneuropathy. Previous pharmacological treatment didn't sufficiently controlled the pain. The patient assessed his present pain intensity in the VAS scale (0–100) on 80–90, with periodic exacerbations up to 100.

The initial diagnosis was: visceral pain within the abdominal cavity in the course of pancreatic cancer, comorbid with pain of the nature of neuropathy in the hands and feet, with a feeling of numbness and tingling (complication after chemotherapy). The patient was referred by an oncologist to be qualified for interventional pain management (neurolysis of celiac plexus).

ECOG performance status was 2. The results of lab tests confirmed adequate liver and kidneys functions. Clinical symptoms of pre-cachexia have been observed, risk related to the nutritional status NRS (nutritional risk score) 2002 = 2.

Surgery was postponed due to the lack of sufficient assessment of the cardiac output — ejection fraction (EF). Heart failure is diagnosed below 50%, whereas with an EF of > 45%, there is a risk that the patient will have a fall in blood pressure following the expansion of the abdominal vascular bed.

The patient was admitted to establish analgesia. Drugs previously used were: oxycodone 60 mg b.i.d., fentanyl transdermal system 150 mcg/h every 3 days, morphine IR 20 mg PRN. Other medicines used: low molecular weight heparin 40 mg/0.4 1 amp. q.d. s.c., spironolactone 25 mg every other day, furosemide 40 mg q.d., metoprolol 25 mg q.d., pancreatin 25 thousand U q.d. with a main meal, alprazolam 0,25 mcg b.i.d., ketoprofen duo1 table PRN, ketoprofen forte 100 mg b.i.d.

To extent the diagnosis, a CT scan of the abdominal cavity was performed, which showed an advanced local cancer. In the area around the head of the pancreas, a solid-fluid lesion with approximate size 83 mm × 87 mm × 70 mm was visible. The lesion adhered to the aorta and duodenum and infiltrated the initial segments of the celiac trunk and upper mesenteric artery. The Wirsung duct distal to the lesion was widened to approx. 7 mm. The body and tail of the pancreas were normal. Enlarged peripancreatic lymph nodes and several lymph nodes along the aorta and inferior vena cava up to 36 mm × 25 mm were observed. The liver was normal, with no focal lesions. Bones without visible secondary lesions.

The dose of oxycodone was increased to 200 mg/day (below the calculated equivalent dose) with rotating within 3 days by 1/3 of daily dose. Fentanyl TTS was discontinued in two stages: reduction to 100 mcg/h and after another 3 days to 50 mcg/h.

Slow rotation allows better tolerance of treatment change. Salvage Rescue therapy with morphine IR 20 mg p.o. was used to titrate a requirement for strong opioid and achieve satisfactory pain control, and lactulose 3 × 20 ml as prevention of constipation. Gabapentin 100 mg t.i.d. as co-analgetic was added, gradually increasing to 300 mg t.i.d. due to the diagnosis of CIPN. A satisfactory analgesic effect was obtained, however, after 4 days the patient reported increasing constipation. Stool with a hard consistency appeared every 3–4 days, with flatulence, nausea and lack of appetite. In case of opioid-induced constipation constipation, conversion to another opioid with a lower risk of constipation should be considered. It was decided to convert a part dose of oxycodone daily dose (200 mg) to oxycodone with naloxone with the ratio 1/3 oxycodone with naloxone 60 mg/day and 2/3 oxycodone (140 mg/day). Instead of morphine IR INN-fentanyl buccal tablet should be considered, 400 mcg (after titration) was used to treat breakthrough pain, up to 4 times a day.

Lack of good analgesic effect, despite relatively high doses of opioid, may be caused by the increasing tolerance for a given opioid. The indication for conversion to another opioid is the development of tolerance, difficult to control adverse effects and unfavorable balance between analgesic effect and adverse effects.

Tolerance to opioids should be distinguished from the resistance of some types of pain to opioids (e.g. neuropathic pain). If the indication for rotation is the development of tolerance, or when the first opioid is used in high doses — treatment with the second opioid begins from 1/2–1/4 of the calculated equivalent dose. Tables with equivalent doses are only an example (guide) of how to calculate them, and they should be approached with caution.

Due to the lack of satisfactory pain control and increasing opioid-induced constipation — after obtaining a positive echocardiography result (EF 49%) — neurolysis of the celiac plexus was performed. Good analgesic effect was obtained.

In subsequent days, the dose of oxycodone was reduced every 3 days depending on the situation, without changing the dose of gabapentin (3 × 300 mg). Due to the duration of episodes of visceral pain INN-fentanyl buccal tablet (200 mcg) was maintained as a rescue medicine. The patient achieved a reduction in primary pain intensity up to 50 according to VAS scale.

Nausea and periodic vomiting appeared again. Abdominal X-ray revealed partial intestinal sub-obstruction. Conservative treatment was introduced: metoclopramide i.v., spasmolytic drugs i.v., dexamethasone i.v. Due to high dose of transdermal fentanyl previously taken (150 mcg/h) and lack of analgesic effect it seemed doubtful that the return to fentanyl TTS would be effective. In addition, due to peripheral edema and low molecular weight heparin taken, subcutaneous route would be associated with the formation of hematomas after injection and impaired absorption of the drug.

Over the next 4 days, analgesia was carried out with morphine i.v. in a PCA (patient controlled analgesia) pump. The pump was equipped with a button, triggering the supply of the programmed dose of rescue medication whenever was pressed by the patient. The conversion dose: oxycodone 200 mg = morphine 300 mg (conversion rate 1:1.5), 1/3 of the oral dose = 100 mg i.v. dose, which is 100 mg/24 h; and 4.1 mg/h as a continuous infusion. In addition, a PCA 1 mg bolus was programmed with lockout time 15 min.

After controlling nausea and vomiting, morphine i.v. was changed to tapentadol PR p.o. The choice of opioid was guided by the nature of the discomfort (mixed pain), partial occurrence of receptor (visceral) pain and partly neuropathic pain (peripheral polyneuropathy). Tapentadol also has a much more favorable profile of gastrointestinal side effects vs other potent opioids (e.g. oxycodone, morphine). The dose of tapentadol retard 200 mg b.i.d (less than equivalent) was included, keeping the INN-fentanyl buccal tablet 200 mgc as a rescue medicine. After the celiac plexus neurolysis and opioid re-rotation, the intensity of the basic pain stabilized at level 40 according to the VAS scale.

Final recommendations for pain management: tapentadol retard 200 mg b.i.d., INN-fentanyl buccal tablet 200 mcg/dose, not more than 4 times per day, gabapentin 3 × 200 mg t.i.d. for slow dose reduction and withdrawal.

It should be bear in mind that neuropathic pain, after controlling the dominant visceral pain, may be subjectively perceived as stronger (it begins to dominate) and reported as "more troublesome".

Discussion

In case of neuropathic pain, the plasticity of the nervous system causes pain to feel without a noticeable pain stimulus, so-called the phenomenon of spontaneous pain, or a painful response to the stimulus that does not usually provoke pain (allodynia), or increased pain from a stimulus that usually provokes pain and (hyperalgesia).

One of the mechanisms is sensitization at the level of the spinal cord and the upper levels of the CNS. Among the inhibitory mechanisms, the descending pathways, beginning in the midbrain and the medulla are important. They can inhibit or support the transmission of pain in the spinal cord. Serotonin and noradrenaline (NA) are important neurotransmitters. A painful stimulus may initiate a reversible reaction and the release of NA binding to alpha2 adrenergic receptors [14, 15].

The serotonergic pathway of the descending pain inhibition system can facilitate or inhibit impulses conduction across the various 5-HT receptor subtypes. Under normal conditions, constant descending and α2 adrenoceptor inhibition occurs.

At the time of nerve damage, conduction by descending path is increased. This phenomenon explains the lack of efficacy of selective serotonin reuptake inhibitor (SSRIs) in the treatment of chronic neuropathic pain. SSRIs indirectly cause simultaneous activation of inhibition as well as stimulation of 5-HT receptors [10].

Tapentadol (deprived of serotonin action), increasing the activity of descending noradrenergic pain inhibition pathways and simultaneously by activating opioid receptors inhibiting the ascending pathways of pain in the CNS, seems to be an interesting drug for the treatment of neuropathic pain syndromes [18]. The drug is slightly bound to plasma proteins, about 20%, which reduces the risk of interaction in the mechanism of protein binding. Inactive metabolites also do not cause adverse drug interactions. A small degree of microsomal metabolism through CYP enzymes minimizes the risk of interaction [11].

Neurolysis of the celiac plexus is performed mainly in cases of visceral pain located in the epigastrium caused by pancreatic, gastric and liver cancer and spread to the retroperitoneal lymph nodes. It is also performed in the case of pain related to chronic pancreatitis. The best effect is obtained if the tumor is located in the tail of the pancreas.

In the majority of patients, after the neurolysis procedure, the basic pain decreases or disappears, but the breakthrough pain remains in lower intensity. It is most often similar to primary pain and has an average of 2.7 points. Patients after neurolysis achieve better pain reduction, manifested by lower opioid consumption, reduced side effects of opioids and better quality of life [19].

In patients with nausea, vomiting or dysphagia, transdermal preparations of fentanyl and buprenorphine are an alternative to opioids administered s.c. or i.v. [1, 2].

Chemotherapy-induced polyneuropathy (CIPN) is a common side effect of chemotherapy. Oxaliplatin derivatives belong to the substance with the highest induction rate of polyneuropathy. Currently no consistent caring standard is available in the treatment of CIPN. Guidelines for the treatment of neuropathic pain should be followed. The drugs of choice according to currently available studies are: gabapentin, pregabalin, duloxetine, gels with baclofen (not available in Poland), amitriptyline [20]. The dual mechanism of action of tapentadol allows for consideration of the drug in CIPN therapy. The use of tapentadol is associated with low interaction risk. A good tolerance profile facilitates titration and rotation. Further research is needed to assess whether tapentadol may be considered as monotherapy or in combination with an adjuvant in the treatment of CIPN.

Summary

About 80% of patients with advanced pancreatic cancer suffer from severe and very severe pain, which requires intensive treatment. Pain in most cases is mixed in nature. Unrecognized neuropathic pain in the course of pancreatic diseases is a frequent cause of incorrect selection of drugs.

Achieving good pain control is one of the most important goals of palliative care. The administration of adequately high doses and the appropriate opioid (in the adjuvant setting) may be hindered by their poor tolerance and the inability to achieve an effective dose.

In case of no analgesic effect, it is recommended to replace one opioid to another (so-called rotation), in total or partial rage, adding another adjuvant drug, providing an effective method of relieving breakthrough pain (the right drug, the right dose and route of administration for a quick analgesic effect). Whenever the clinical situation requires, changing the route of drug administration from oral to parenteral s.c./i.v., TTS is recommended. Opioid pharmacology is complex, and the individual effect is the resultant of many factors. If pharmacological methods are not sufficiently effective, one should use interventional (procedure) methods of pain management [1, 2, 4].

Neurolysis of the celiac plexus does not always completely reduce pain. It causes a significant reduction in the intensity of basic pain, helping to reduce opioid doses, reducing the intensity of side effects and improving patients quality of life. The analgesic effect lasts about 2–3 months.

The treatment does not prevent the occurrence of breakthrough pains which require separate treatment [17, 19].

Most cancer patients experience mixed pain (74%) as the disease progresses. Taking into account the different mechanisms of nociceptive and neuropathic pain, μ agonists and drugs blocking the secondary uptake of NA are used in the treatment [5].

Tapentadol is the only centrally acting opioid that combines these two mechanisms of action — mi receptor agonists (MORs) and norepinephrine reuptake inhibitors (NRIs). The specificity of tapentadol makes it highly effective in the treatment of severe mixed pain as well as neuropathic pain syndromes. Its use also results in the possibility of opioid saving (opioid-sparing effect). The simultaneous action of MOR and NRI mechanism contributes to the final analgesic effect, allowing the use of lower doses to achieve a given level of analgesia [10]. The double mechanism provides effective antinociceptive action and alleviation of hyperalgesia and allodynia [9].

Tapentadol has a more favorable profile of side effects. Significantly less gastrointestinal adverse events were observed in the conducted studies compared to fentanyl, morphine and oxycodone. A favorable pharmacokinetic profile contributes to a small number of discontinuations due to poor tolerability or side effects. Because tapentadol does not show significant serotonergic activity, there is no risk of side effects typical for SSRI, including serotonin syndrome [6].

Long-term use of tapentadol has a slower effect on tolerability compared to morphine [8]. A synergistic, dual mechanism of action and the effect of saving opioids can increase the effectiveness of treatment by improving compliance (regularity of use) [8]. The efficacy of tapentadol in the treatment of mixed and neuropathic cancer pain, including CIPN, requires further investigation.

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References

1. *Opioids therapy in the 21st century*. Smith HS (ed.). New York: Oxford University Press, 2013.
2. Portnoy R, Ahmed E. Principles of opioid use in cancer pain. *J Clin Oncol* 2014; 32: 1662–1670.
3. Volpe DA, McMahon Tobin GA, Mellon RD et al. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. *Regul Toxicol Pharmacol* 2011; 59: 385–390.
4. Fallon MT, Laird BJ. A systematic review of combination step III opioid therapy in cancer pain: an EPCRC opioid guideline project. *Palliat Med* 2011; 25: 597–603.
5. Leppert W. Rola analgetyków opioidowych w leczeniu bólu neuropatycznego u chorych na nowotwory. *Medycyna Paliatywna w Praktyce* 2014; 8: 81–84.
6. Riemsma R, Forbes C, Harker J et al. Systematic review of tapentadol in chronic severe pain. *Curr Med Res Opin* 2011; 27: 1907–1930.
7. Merker M, Dinges G, Koch T et al. Undesired side effects of tapentadol in comparison to oxycodone. A meta-analysis of randomized controlled comparative studies. *Schmerz* 2012; 26: 16–26.
8. Ahlbeck K. Opioids: a two-faced Janus. *Curr Med Res Opin* 2011; 27: 439–448.
9. Schroder W, Tzschentke TM, Terlinden R et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. *J Pharmacol Exp Ther* 2011; 337: 312–320.
10. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? *Eur J of Pain* 2010; 14: 781–783.
11. Dzierżanowski T, Ciałkowska-Rysz A. Tapentadol w leczeniu przewlekłego bólu związanego z nowotworem. *Medycyna Paliatywna* 2016; 8: 157–163.
12. Tzschentke TM, Christoph T, Kögel B et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther* 2007; 323: 265–276.
13. Mercadante S, Porzio G, Ferrera P et al. Tapentadol in cancer pain management: a prospective open-label study. *Curr Med Res Opin* 2012; 28: 1775–1779.
14. Esin E, Yalcin S. Neuropathic cancer pain: what we are dealing with? How to manage it? *Onco Targets Ther* 2014; 7: 599–618.
15. Bennett MI, Rayment C, Hjermstad M et al. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain* 2012; 153: 359–365.
16. Fallon M T. Neuropathic pain in cancer. *Br J Anaesth* 2013; 111: 105–111.
17. Hameed M, Hameed H, Erdek M. Pain management in pancreatic cancer. *Cancers (Basel)* 2010; 3: 43–60.
18. Schikowski A, Krings D, Schwenke K. Tapentadol prolonged release for severe chronic cancer-related pain: effectiveness, tolerability, and influence on quality of life of the patients. *J Pain Res* 2014; 8: 1–8. doi: 10.2147/JPR.S72150. eCollection 2015.
19. Góraj E. Zastosowanie neuroliz w leczeniu bólu nowotworowego. *Medycyna Paliatywna* 2012; 4: 13–23.
20. Hershman DL, Lacchetti C, Dworkin RH et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; 32: 1941–1967.

VIA MEDICA

Short review

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Adjuvant chemotherapy in the patients with rectal cancer after neoadjuvant chemoradiotherapy and radical resection — YES

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At the moment there are some scientific data supporting the use of adjuvant chemotherapy in patients with rectal cancer after neoadjuvant chemoradiotherapy and surgical treatment. The paper below presents some arguments for the use of adjuvant chemotherapy in the above clinical situation. The majority of deaths in patients with rectal cancer are caused by the presence of distant metastases, therefore there are significant grounds for the use of adjuvant chemotherapy in this group of patients. Summarising, there is no clear or scientific evidence against the use of adjuvant chemotherapy in patients with rectal cancer after preoperative chemoradiotherapy. In order to make a conclusive statement about the lack of any benefits from adjuvant therapy, it is necessary to carry out randomised studies on a homogeneous and standardised group of patients. Therefore, it seems appropriate to apply this therapy especially for patients with the N (+) features (with a tumour location between 10 cm and 15 cm), similar to colon cancer cases.

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Key words: rectal cancer, preoperative chemoradiotherapy, surgical treatment, adjuvant chemotherapy

Currently there is some scientific evidence supporting the use of adjuvant chemotherapy in patients with rectal cancer after neoadjuvant chemoradiotherapy and surgical treatment. The arguments for the usage of adjuvant therapy in such clinical conditions are presented below.

The majority of deaths in patients with rectal cancer are caused by the presence of distant metastases [1], therefore there are some essential grounds for the use of adjuvant chemotherapy in this group of patients. The task of adjuvant chemotherapy is to destroy micro-metastatic lesions, which remain invisible in imaging diagnostics.

Both surgical treatment and radiotherapy are solely the methods of local treatment, so their purpose is not the "liquidation" of the distant metastases. Fluoropyrimidines, in combination with radiotherapy, in neoadjuvant treatment are not used in doses which are systematically active (two courses are administered in the first and the fifth week of radiotherapy or three courses according to the de Gramont regimen as a consolidation therapy after a "short" radiotherapy) [1], that is why adjuvant chemotherapy should be used especially in patients with cancer dissemination risk factors, such as the presence of "positive" lymph nodes (N+ stage) or T4 stage.

A significant improvement in the efficiency of adjuvant chemotherapy in the third stage of colon cancer was obtained by adding oxaliplatin to the 2-drug regimen (5-fluorouracil and folinic acid). In the "MOSAIC" trial (André et al. 2015) the 10-year OS (overall survival) was 67.1% for the patient group treated with the chemotherapy with oxaliplatin regimen (FOLFOX 4) compared to 59.0% for the group of patients treated solely with 5-fluorouracil and folinic ac id) (HR = 0.80; p = 0.016) [2]. We have to remember that this was a colon cancer whose treatment method differs significantly from that applied for rectal cancer, yet with the proper patient selection (the third disease stage) and with the use of the more effective chemotherapy regimen (based on oxaliplatin), a significant and desired objective can be achieved, i.e. the improvement of survival factors.

In the EORTC 22921 randomised trial (Bosset et al. 2014), 1011 patients with rectal cancer were randomly distributed

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into 4 groups: the first two were treated with preoperative radiotherapy or radio-chemotherapy, whilst the next two groups received adjuvant chemotherapy, after neoadjuvant therapy and after surgical intervention. No statistically significant improvement was obtained with regards to DFS (disease-free survival), or to OS; the 10-year DFS was 47.0% in the patient group treated with adjuvant chemotherapy as compared with 43.7% in the group of patients undergoing observation alone (HR = 0.91; 95% CI 0.77–1.08; p = 0.29), whilst the 10-year OS was 51.8% as compared with 48.4% respectively (HR = 0.91; 95% CI 0.77–1.09, p = 0.32). It must be stressed that the evaluation of the efficiency of the applied adjuvant chemotherapy in patients with rectal cancer undergoing previously neoadjuvant radiotherapy or chemoradiotherapy, did not comprise the analysis of the subjects with N (+) stage (statistical analysis of the patients was based solely on the T stage), whereas this is precisely the group which might benefit most from the adjuvant treatment, like in the case of colon cancer patients; also here a suboptimal chemotherapy was used (without oxaliplatin), which is normally used in the adjuvant treatment of the colon cancer patients [2, 3]. The lack of efficiency of the adjuvant chemotherapy applied after preoperative chemoradiotherapy and after surgical intervention was presented in another third phase randomised clinical trial (Aldo et al. 2014). The patients (655 patients) were randomly distributed to the two study arms: arm A comprised patients treated preoperatively with chemoradiotherapy and then under observation alone, whilst arm B were patients who additionally received 6 courses of adjuvant chemotherapy according to the regimen: 5-fluorouracil with folinic acid. No significant differences between A and B groups were achieved with regards to the 5-year DFS and 5-year OS: 62.8% vs 65.3% (p = 08.82) and 70% vs 69.1% (p = 0.772) respectively. In spite of the definite results of the study, a number of doubts linger: a significantly lower rate of patients in the N(+) stage were included in the study, but they are the most important target group for the use of adjuvant chemotherapy and, what is more these patients were included into the specific study arms in different manners: in arm A there were 24.5% patients, whereas in arm B 34.6% (29.7% of the total entire patient population). Some other doubts concern the lack of important clinical and pathomorphological data — in 13.2% patients, the N stage was marked as Nx. This would mean that in spite of a poorer prognosis in arm B (a higher rate of patients in the N+ stage) similar results in survival were obtained. The lack of significant improvement in both DFS and OS could also be the outcome of the application of a suboptimal chemotherapy regimen: 5-fluorouracil with folinic acid (without oxaliplatin) [4].

Another third-phase randomised clinical trial, prepared by the Dutch group, "PROCTOR-SCRIPT" (Breugom et al. 2015), in which 437 patients were included (221 subjects in the observation group and 216 patients treated with adjuvant chemotherapy), also failed to confirm the efficiency of adjuvant chemotherapy. The 5-year OS for the group undergoing observation alone was 79.2% vs 80.4% in the group treated with adjuvant chemotherapy (HR = 0.93; 95% CI 0.62–1.39; p = 0.73; HR for DFS was 0.80; 95% CI 0.60–1.07; p = 0,13), whilst the 5-year cumulative frequency of loco-regional relapse was 7.8% for both groups and the 5-year cumulative frequency of distant metastases was 38.5% vs 34.7% respectively (p = 0.39). Nevertheless, in the analysis of the patient characteristics, it must be emphasised that the rate of patients who received neoadjuvant chemotherapy before the adjuvant chemotherapy was only 14.0% for both groups (12.7% in the group with observation alone and 15.3% in the group treated with adjuvant chemotherapy), which makes it impossible to draw reliable conclusions in this group of patients. Moreover, chemotherapy was based on 5-fluorouracil or capecitabin, without oxaliplatin [5].

The benefit in the use of adjuvant chemotherapy (Hong et al. 2014) was obtained in the second-phase clinical trial, "ADORE" ("ADjuvant Oxaliplatin in REctal cancer"). The study comprised 321 rectal cancer patients in the second and third stage (ypT3–4N0 or any ypT, N1–2 in screening) after neoadjuvant chemotherapy. Adjuvant chemotherapy consisted of a 2-drug regimen: 5-fluorouracil with folinic acid or the FOLFOX regimen in the second group. Some improvement with regards to the 3-year DFS was obtained for the patient group receiving chemotherapy based on the FOLFOX regimen in comparison with the patient group treated with 5-fluorouracil with folinic acid (71.6% vs 62.9%; HR = 0.657; 95% CI 0.434–0.994; p = 0.047). Some particular benefit with regards to the 3-year DFS was obtained in the group of patients with the third stage disease in comparison with patients with the second stage (66.6% vs 57.3%; HR = 0.602; 95% CI 0.371–0.977; p = 0.040) and (81.6% vs 71.3%; HR = 0,744, 95% CI 0,334–1,657; p = 0,47) respectively. The 3-year OS also turned out to be better in the group of patients receiving the chemotherapy regimen based on oxaliplatin in comparison with the group of patients treated with the 2-drug regimen (95.0% vs 85.7%; HR = 0.456, 95% CI 0.215–0.970; p = 0.036). Summing up this study, it must be stressed that the largest benefit in adjuvant treatment was gained by the patients with the third stage disease, which correlates with the results of adjuvant treatment in colon cancer [6].

The metanalysis which shows the lack of any benefit in such a course of treatment is that which is presented by Breugom et al. in 2015, which comprised 4 third-phase randomised clinical trials (1198 rectal cancer patient in total: "I-CNR-RT", "PROCTOR-SCRIPT", "EORTC 2292", "CHRONICLE"), in which adjuvant treatment consisted in a chemotherapy regimen based on 5-fluorouracil (3 trials), capecitabine (1 study) or XELOX regimen (1 study). No significant benefit was

shown in the entire patient population with regards to the OS with the use of adjuvant chemotherapy after a preoperative neoadjuvant chemoradiotherapy (HR = 0.97; 95% CI 0.81–1.17; p = 0.775). However, in the subgroup analysis, a significant improvement in DFS and remote recurrence was obtained in patients with the location of the primary tumour between 10 cm and 15 cm from the edge of the anus (HR = 0.59; 95% CI 0.40–0.85; p = 0.005 and HR = 0.61, 95% CI 0.40–0.94; p = 0.025 respectively). In the discussion of the metanalysis, the heterogenicity (the lack of homogeneity of the results) of the studies qualified for evaluation. In spite of the lack of proof with regards to significant differences to the heterogenicity of the qualified studies, some significant incompliances concerned, among others, different chemotherapy regimens applied in the adjuvant treatment, various regimens of preoperative therapy, taking into consideration the rate of the patients who were undergoing radiotherapy alone (2 studies), the diverse moment of the randomisation of the patients (randomisation before or after surgical treatment) or different standards of surgical intervention (total mesorectal excision and radical surgical intervention). Taking into consideration the doubts presented above, one cannot draw definite conclusions concerning the lack of efficiency of adjuvant chemotherapy in rectal cancer patients after preoperative treatment combined with chemoradiotherapy [7].

In another metanalysis (5 randomised clinical trials, 2398 patients), there was no statistically significant benefit in the use of adjuvant chemotherapy in comparison with the group undergoing observation alone among the rectal cancer patients after preoperative radiotherapy or radio--chemotherapy (Bujko et al. 2015). The differences both in OS and DFS were not statistically significant between the group with chemotherapy and the group of patients without adjuvant treatment (HR = 0.95; 95% CI 0.82–1.10; p = 0.49 and HR = 0.92; 95% CI 0.80–1.04; p = 0.19) respectively. Also no statistically significant difference was obtained with regards to DFS (4 randomised clinical trials, 2710 patients) between the group on chemotherapy based on oxaliplatin and the group of patients without oxaliplatin (HR = 0.84, 95% CI 0.66–1.06; p = 0.15) in spite of the fact that in two of four analysed trials there was a statistically significant difference in DFS to the advantage of the patients treated in chemotherapy with oxaliplatin.

Similarly as in the case of other clinical trials or metanalyses, a number of doubts arise, concerning the limited population of patients included into specific clinical trials, which makes it impossible to catch differences smaller than 3–5% with respect to the 5-year OS (type II error), suboptimal methodology (e.g. randomisation before preoperative treatment which decreases the possibilities of observing the effect of post-operative chemotherapy), diverse patient groups included into the trials and metanalyses (e.g. preoperative radiotherapy, varied disease stages without N+ a stage or even ypT0N0 stage or the first stage of disease), and also the fact in 3 of 9 studies in the metanalysis, only abstracts were available (no reviews, which always present the discussion of the obtained results) [8].

In a systematic review and metanalysis (in total 4 randomised clinical trials: "CAO/ARO/ AIO-04", "PETACC-6", "ADORE" and "CHRONICLE") published by Zhao L et al. (2016), the final analysis concerned 2793 rectal cancer patients in the second or third disease stage, who, after preliminary treatment with chemoradiotherapy followed by a surgical intervention, received adjuvant treatment consisting in chemotherapy regimens composed of capecitabine/5-fluorouracil/5-fluorouracil with folinic acid or underwent observation alone (one group) or chemotherapy regimens containing oxaliplatin in connection with 5-fluorouracil and folinic acid or capecitabine (the second group). In the group of patients treated according to chemotherapy regimens containing oxaliplatin, in comparison with the chemotherapy regimens without this drug, a statistically significant prolongation of DFS as the primary endpoint was obtained (HR = 0.85; 95% CI 0.73–0.98; p = 0.03), but no OS prolongation was obtained — and this was the secondary study endpoint (HR = 0.64; 95% CI 0.35–1.17; p = 0.15). In the presented metanalysis, the qualified studies differed significantly from each other, among others by the chemotherapy regimens (oxaliplatin was used in preoperative treatment only in two studies) and the planned recruitment was not completed ("CHRONICLE" study). Moreover, in three trials, adjuvant chemotherapy comprised patients with complete pathological remission after the ypCR treatment (ypT0N0M0) or the first disease stage (the group of patients who do not benefit from adjuvant therapy). In three trials, the rate of patients who completed the planned treatment in total or who received the majority of the chemotherapy courses totalled 43% to 55% (the group of patients with adjuvant treatment of chemotherapy based on 5-fluorouracil) and, most importantly, the group of patients solely with the third pathological disease stage was not evaluated separately whist this is the group of patients who may benefit from such a course of treatment the most. Similarly, as in the previous metanalysis, the differences and doubts shown by the authors do not allow for any definite conclusions [9]. The summary of the discussed studies and metanalyses is presented in Table I.

In conclusion, as of the current moment, there is no definite scientific evidence providing grounds for the use of adjuvant chemotherapy in rectal cancer patients after preoperative chemoradiotherapy. It is necessary to carry out a randomised study, yet it should concern a homogenous and standardised group of patients with respect to their treatment in order to determine definite opinions concerning the lack of benefits in adjuvant therapy. That is why currently, such therapy seems to be justified especially in

Table I. The presentation of the studies and metanalyses

Author/year	The number of subjects	Type of study	DFS improvement	OS improvement
Bosset et al. 2014 "EORTC 22921"	1011	The third-phase randomised clinical study	NO	NO
Aldo et al. 2014	655	The third-phase randomised clinical study	NO	NO
Breugom et al. 2015 "PROCTOR-SCRIPT"	437	The third-phase randomised clinical study	NO	NO
Hong et. al. 2014 "ADORE"	321	The second-phase randomised clinical study	YES	YES
Breugom et al. 2015	1198	The metanalysis of 4 studies: "I-CNR-RT", "PROCTOR-SCRIPT", "EORTC 2292", CHRONICLE"	YES With the primary tumour location between 10 and 15 cm	NO
Bujko et al. 2015	2398	The metanalysis of 5 studies: "EORTC 22921", "Italian trial", "PROCTOR/ SCRIPT", "CHRONICLE", "QUASAR"	NO	NO
		The metanalysis of 4 studies: "PETACC-6", "CAO/ARO/AIO-04", "ADORE", "ECOG E3201"		
	2710		NO	----------
Zhao L et al. 2016	2973	The metanalysis of 4 studies: "CAO/ARO/ AIO-04", "PETACC-6", "ADORE", "CHRONICLE"	YES	NO

DFS — disease-free survival, OS — overall survival

the group of patients with the N (+) stage (at least with the tumour location between 10 cm and 15 cm), similar to colon cancer; especially as there are no significant differences between colon cancer and rectal cancer as for their genetics and response to the palliative treatment [8].

Response

In the agreed recommendations concerning the controversies in the primary treatment of rectal cancer, 77% of "panellists" opted for the use of adjuvant chemotherapy in the case of confirmed "positive" lymph nodes after neoadjuvant chemotherapy (ypN+). To sum up this subchapter of these recommendations concerning adjuvant treatment, the authors pointed to the use of adjuvant chemotherapy which should be considered the standard treatment in rectal cancer patients with the tumour location between 10 cm and 15 cm from the edge of the anus, with the presence of "involved" lymph nodes before neoadjuvant treatment (cN+) or after its completion (ypN+), and the chemotherapy regimen should contain oxaliplatin (47% votes for "yes", 16% for "no", 37% abstentions [1].

A similar sentiment was also seen in the most recent ESMO guidelines concerning the treatment of rectal cancer (Glynne-Jones et al. 2017), whose authors recommend considering the use of adjuvant treatment with chemotherapy in the third and second pathological disease stage ("yp") with the presence of risk factors ("high-risk" group) after preoperative radiotherapy or chemoradiotherapy [10].

Also the NCCN recommendations (The National Comprehensive Cancer Network, version 4.2017) are definite with regards to the indications connected with the use of adjuvant chemotherapy after neoadjuvant chemotherapy. In patients with the T3N0 or (N+) or T4 stages and/or a non resectable tumour, after the neoadjuvant treatment with radiotherapy or chemoradiotherapy and surgical intervention, it is recommended to use adjuvant chemotherapy based on oxaliplatin (regimens such as: FOLFOX or CAPOX, or 5-fluorouracil with folinic acid or capecitabine), and the entire perioperative systemic treatment should last 6 months in total [11].

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References (the most significant publications)

1. Lutz MP, Zalcberg JR, Glynne-Jones R et al. Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer. *Eur J Cancer* 2016; 63: 11–24.
2. André T, de Gramont A, Vernerey D et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to braf mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol* 2015; 33: 4176–4187.
3. Bosset JF, Calais G, Mineur L et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; 15: 184–190.
4. Sainato A, Cernusco Luna Nunzia V, Valentini V et al. No benefit of adjuvant fluorouracil leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; 113: 223–229.
5. Breugom AJ, van Gijn W, Muller EW et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomised phase III trial. *Ann Oncol* 2015; 26: 696–701.
6. Hong YS, Nam BH, Kim KP et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014; 15: 1245–1253.
7. Breugom AJ, Swets M, Bosset JF et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Onco*l 2015; 16: 200–207.
8. Bujko K, Glimelius B, Valentini V. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery +/– fluoropyrimidine and surgery + a fluoropyrimidine +/– oxaliplatin. *Eur J Surg Oncol* 2015; 41: 713–723.
9. Zhao L, Liu R, Zhang Z et al. Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadiuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials. *Colorectal Dis* 2016; 18: 763–772.
10. Glynne-Jones R, Wyrwicz L, Tiret E et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28 (Suppl 4): iv22–iv40.
11. NCCN Clinical Practice Guidelines in Oncology: NCCN Guidelines® Rectal Cancer Version 4.2017 — January 18, 2018; NCCN.org.

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Short review

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Is adjuvant chemotherapy justified in rectal cancer patients after radio-chemotherapy and radical resection?

Krzysztof Bujko

Recommendations for the application of post-operative adjuvant chemotherapy in patients who received preoperative radio-chemotherapy are not consistent. Some of them advise post-operative chemotherapy, whilst others follow-up without any adjuvant treatment. The objective of this paper is to undertake an overview of the randomised studies evaluating whether the administration of adjuvant chemotherapy can be justified with clinical evidence. A systematic overview of the publications shows 5 randomised trials in which only the patients after pre-operative radio-chemotherapy were enrolled, whilst randomisation concerned adjuvant therapy vs follow-up without adjuvant therapy. None of the studies showed any improvement after post-operative chemotherapy with regards to both the overall survival and disease-free survival rate. Moreover, 3 randomised studies were found in which post-operative chemotherapy with fluoropyrimidine was compared with post-operative chemotherapy with fluoropyrimidine with the addition of oxaliplatin. One of these studies showed an improvement in the overall survival rate after the use of post-operative chemotherapy, whereas in two others the difference was statistically insignificant. Two studies showed a slight improvement after chemotherapy with regards to disease-free survival rates, whilst no such effect was observed in the third. A meta-analysis of the studies comparing the results after the administration of post-operative chemotherapy with the results after the chemotherapy-free follow-up did not demonstrate any positive effect of the chemotherapy on the overall and disease-free survival rate. A meta-analysis of randomised studies in which post-operative chemotherapy with fluoropyrimidine was compared with post-operative chemotherapy with fluoropyrimidine with the addition of oxaliplatin did not show any improvement in disease-free survival rates in patients receiving oxaliplatin. The overall survival was not analysed because of the lack of appropriate data at the moment the meta-analysis was made. The above overview of the randomised trials points to a lack of any strong evidence justifying the administration of post-operative chemotherapy.

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Key words: rectal cancer, post-operative chemotherapy, preoperative chemotherapy

Introduction

This paper deals solely with patients diagnosed with advanced rectal cancer who received pre-operative radio-chemotherapy. Recommendations concerning the administration of post-operative adjuvant chemotherapy in these patients are not consistent. The guidelines of the National Comprehensive Cancer Network recommend administration in the patients with clinical stage II–III of the disease, irrespectively of the tumour's response to irradiation [1]. The guidelines of the Medical Society for Medical Oncology restrict the administration of adjuvant chemotherapy to patients with pathological stage III of the disease, and to the patients with stage II if the recurrence of risk is very high [2]. In contrast to the above guidelines, Dutch and Norwegian recommendations do not advise the administration of chemotherapy [3]. The difference of opinion concerning the advisability of the administration of post-operative chemotherapy is also observed among European experts [4]. The differences are also seen in routine practice: for example a Swedish population study showed that, depending on

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the region, among the patients with stage III of the disease, the rate of those receiving adjuvant chemotherapy varied between 13% and 77% [5]. This paper is an overview of randomisation studies with an objective to evaluate whether the administration of adjuvant chemotherapy is justified by clinical evidence.

The overview of randomised trials comparing post-operative chemotherapy with observation

A systematic overview of publications [6], revealed 5 randomised trials which fulfilled the following criteria:

1. Only patients after pre-operative radio-chemotherapy were included,
2. Patients were randomised for adjuvant chemotherapy or for a observation without adjuvant chemotherapy [7–13].

The total number of patients included in all these 5 studies was 2398. In 4 studies, 5-fu was administered [7–10, 12, 13], whilst in the fifth — oxaliplatin was added to 5-fu [11]. None of these 5 studies saw any improvement after post-operative chemotherapy with regards either to overall survival and to disease-free survival. A detailed discussion of these studies is presented below.

In the EORTC 22921 study (n [number of patients] = 1011) the patients were randomly allocated to 4 study arms, and randomisation was used twice — for pre-operative radio-chemotherapy vs pre-operative radiotherapy and also post-operative chemotherapy vs follow-up [7, 8]. The 10-year overall survival rate was 51.8% in the patient group with post-operative chemotherapy and 48.4% in those patients undergoing a follow-up without post-operative chemotherapy, hazard ratio (HR) 0.91 (95% confidence interval [CI] 0.77–1.09), p = 0.32. The respective values for disease-free survival were 47.0% and 43,7%; HR = 0.91 (95% CI 0.77–1.08), p = 0.29.

An Italian study (n = 643) showed a 5-year overall survival rate of 66.9% in the patient group with post-operative chemotherapy and 67.9% in the control group, p = 0.88 [9]. The respective values for disease-free survival were 63.8% and 60.8%, p = 0.42.

In the PROCTOR/SCRIPT study (n = 437), a 5-year overall survival was observed in 79.2% of patients in the group receiving post-operative chemotherapy and 79.2% in the control group, HR = 0.93 (95% CI 0.62–1.39), p = 0.73 [10]. The respective values for disease-free survival were 62.7% and 55.4%, HR = 0.80 (95% CI 0.02–1.07), p = 0.13.

The CHRONICLE study was discontinued due to a poor accrual after the inclusion of merely 113 patients [11]. The median of the follow-up period was short — 3.6 years. 3-year overall survival amounted to 89% in patients receiving post-operative chemotherapy and 88% in the control group, HR = 1.18 (95% CI 0.43–3.26), p = 0.75. The respective values for disease-free survival were 78% and 71%, HR = 0.80 (95% CI 0.38–1.69), p = 0.56.

The QUASAR study comprised patients with stage II of the disease, with both rectal and colon cancers [12, 13]. In the rectal cancer patients, an improvement of overall survival was observed after 5 years with borderline statistical significance; 78% — in patients with post-operative chemotherapy and 74% in the group with observation only, HR = 0.77 (95% CI 0.54–1.00), p = 0,05. Yet in the subgroup which received pre-operative radiotherapy (n = 203), the difference was not significant, HR = 0.44 (95% CI 0.25–1.10).

An overview of randomised studies comparing post-operative chemotherapy with fluoropyrimidine with and without oxaliplatin

A systematic overview of publications [6] showed 3 randomised studies in a total number of 2675 patients in whom post-operative chemotherapy with fluoropyrimidine was compared with post-operative chemotherapy with fluoropyrimidine with the addition of oxaliplatin [14–16]. One of these studies showed an improvement of overall survival rates after the administration of post-operative chemotherapy [16]; in the two remaining studies, the difference was not statistically significant. Two studies showed some improvement after chemotherapy with respect to disease-free survival rates [14, 16], whilst in the third one, no effect was seen [15]. In two studies, randomisation was performed before pre-operative radio-chemotherapy in the patients with clinical stage II or III of the disease [14, 15], whereas in the third study the randomisation was carried out after surgery only in patients with pathological stage III [16]. These studies are discussed in detail below.

In the German CAO/ARO/AIO-04 study, (n = 1265) after a median follow-up period of 50 months, the overall survival rates after 3 years were 88.7% in those patients receiving oxaliplatin and 88.0% in the patients treated only with 5-Fu; HR = 0.96 (95% CI 0.72–1.26) [14]. No 'p' value was presented, yet the 95% confidence interval for the hazard ratio (HR) shows that the difference was not statistically significant. The 3-year disease-free survival rate amounted to 75.9% and 71.2% respectively; HR 0.79 (95% CI 0.64–0.98), p = 0.03. A limitation for the interpretation of the results of this study consisted in the difference in the administration of 5-fu between two randomised groups: in patients in the group with the addition of oxaliplatin, this medication was administered in continuous infusion, whilst in the control group — only in a bolus.

In the PETACC-6 study (n = 1090) after a median follow-up period of 68 months, overall survival rates after 5 years was 83.1% in patients receiving capecitabin alone and 80.1% in patients treated with oxaliplatin with capecitabin; H = 1.17 (95% CI 0.89–1.54), p = 0.25 [15]. The respective values for disease-free survivals were 71.3% and 70.5%, HR = 1.02 (95% CI 0.82–1.28) p = 0.84.

In the Korean phase II study (ADORE) with randomisation of the patients (n = 321) with pathological stage II and

III after preoperative radio-chemotherapy with the use of 5-fu and leucovorin and after tumour resection, the subjects were randomised into two regimens of post-operative chemotherapy: FOLFOX and 5-fu in a bolus with leucovorin [16]. The median age was only 54. After a median follow-up period of 38.2 months, better outcomes were observed in patients treated with the addition of oxaliplatin, both in 3-year disease-free survival rates (71.6% vs 62.9%; HR = 0.66, p = 0.047) and in overall survival rates (95.0% and 85.7%; HR = 0.46, p = 0.036). Similarly to the German study, the limitation of the interpretation of the results of the Korean study was the difference in the administration of 5-fu between the two randomised groups: in the group receiving oxaliplatin, the medication was administered in continuous infusion, whilst in the control group only in a bolus.

Meta-analyses

Breugom et al. [17] published a meta-analysis with the use of individual data of the patients with pathological stage II and III [7–11]. The meta-analysis comprised 4 out of 5 of the above mentioned studies comparing the results after the administration of post-operative chemotherapy with the results of the observation without chemotherapy. The median observation period was 7 years. No improvements in overall survival rates after the administration of chemotherapy in comparison with observation was seen; HR = 0.97 (95% CI 0.81–1.17). No improvement in disease-free survival rates was observed either; HR = 0.91 (95% CI 0.77–1.07). In the subgroup analysis, only in patients with the rectal cancer located 10–15 cm from the edge of the rectum, was there some improvement observed in disease-free survival rates after chemotherapy; HR = 0.59 (95% CI 0.40–0.85), p = 0.005, yet without any improvement of overall survival rates. In other subgroups, such as pathological stage II or III, ypN0, ypN1 or ypN3, patients after an anterior resection or after an abdominoperineal resection (APR), after preoperative irradiation 5 × 5 Gy or traditionally fractionated radiotherapy or radio-chemotherapy, no improvement after chemotherapy was seen both with regards to overall survival rates and disease-free survivals.

Another meta-analysis [6], made on the basis of the published data concerning all the above listed 5 studies, comparing the results after the administration of post-operative chemotherapy with the results after observation only without chemotherapy [7–13], also showed a lack of any improvement after post-operative chemotherapy with respect to overall survivals and disease-free survivals: 0.95 (95% CI 0.82–1.10), p = 0.49 and 0.92 (95% CI 0.80–1.04), p = 0.19. The lack of any improvement after chemotherapy was observed both in the subgroups with ypT0–2 stage and in the subgroup with metastases to the lymph nodes. When the meta-analysis was made separately for the studies in which randomisation was carried out after the surgery and those in which randomisation was carried out before the commencement of preoperative irradiation, it turned out that in the first case, better disease-free survival rates were observed after the administration of post-operative chemotherapy: HR = 0.79 (95% CI 0.62–1.00), p = 0.047, yet without any improvement in the overall survival rates. In the latter type of randomisation, no positive effect from post-operative chemotherapy was observed in the evaluation of overall and disease-free survival rates.

Also a meta-analysis of [6] 3 of the above mentioned randomised studies was carried out; in this meta-analysis, post-operative chemotherapy with fluoropyrimidine only was compared with post-operative chemotherapy with fluoropyrimidine plus the addition of oxaliplatin [14–16]. The addition of oxaliplatin did not cause any improvement of disease-free survival rates; HR = 0.84 (95% CI 0.66–1.06), p = 0.15. Overall survival rates were not analysed because of the lack of appropriate data at the moment the meta-analysis was carried out.

Discussion

The meta-analyses of the randomised studies did not show any positive effect of post-operative chemotherapy on overall survival rates in patients who previously received pre-operative irradiation. The lack of any improvement was observed both in the cancer subgroup which responded to radiotherapy, i.e., those patients with stage ypT0–2, and in the patients with stage III of the disease where the largest effect could have been expected. Therefore, no strong evidence points to the advisability of post-operative chemotherapy.

It is worth pointing out, however, that an improvement of disease-free survival rates (yet without any improvement in overall survival rates) was observed in the meta-analysis of the studies in which randomisation was carried out after surgery [6]. The moment of randomisation overlaps with the moment when routinely the decision whether to administer chemotherapy or not is taken. In the studies in which randomisation was carried out before surgery, many patients did not begin previously planned post-operative chemotherapy as a result of post-operative complications, lack of further consent of the patient, or disease progression. These patients had to be included into the analysis with regards to the intention-to-treat principle. However, with regards to the poor prognoses of these patients, chances for observing treatment benefits decreased. That is why randomisation before surgery is suboptimal. The improvement of disease-free survival rates (yet with a lack of improvement in overall survival rates) after surgery in the randomised studies points to the minor influence of post-operative chemotherapy. Thus a question arises whether this benefit outweighs the toxicity of chemotherapy.

The toxicity of chemotherapy lessens the quality of life of patients during treatment [18]. Post-operative chemothe-

rapy with fluoropyridines leads to acute toxicity consisting of diarrhoeas, nausea, vomiting and fatigue as well as pain resulting from stomatitis and loss of appetite [18]. In rare cases, complications may be life-threatening or might require hospitalisation. Toxic deaths occur in about 1% of patients, affecting mainly the elderly [19]. The rate of III+ complications was observed in 36–40% of patients receiving chemotherapy with oxaliplatin [11, 16]. Closure of the colostomy is deferred till the moment chemotherapy is completed. The administration of post-operative chemotherapy is connected with the larger costs of treatment. Post-operative chemotherapy causes not only acute complications, but also delayed ones.

The above mentioned EORTC randomised study after a median observation period of 4.6 years showed that statistically more patients reported pain, diarrhoea, weaker physical activity and difficulties in everyday activities after the administration of post-operative chemotherapy than in the control group [20, 21]. Oxaliplatin causes chronic neuropathy, the intensification of which can lead to a lower quality of life [22].

The controversies concerning the administration of post-operative chemotherapy described in this paper point to the fact that a patient should be informed about its doubtful efficacy and possible complications. An evaluation as to whether the benefits from the use of chemotherapy exceed its toxic side-effects is subjective and should be left to the patient who must be adequately informed about the arguments for and against. It was observed that many patients prefer observation without chemotherapy when its beneficial effect is only minor [23].

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References

1. Rectal Cancer, NCCN Clinical Practice Guidelines in Oncology, http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Electronic Citation (access: August 2018).
2. Glynne-Jones R, Wyrwicz L, Tiret E et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28 (suppl 4): iv22–iv40.
3. Poulsen LØ, Qvortrup C, Pfeiffer P et al. Review on adjuvant chemotherapy for rectal cancer — why do treatment guidelines differ so much? *Acta Oncol* 2015; 54: 437–446.
4. van de Velde CJ, Boelens PG, Borras JM et al. EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum. *Eur J Cancer* 2014; 50: e1– e34.
5. Tiselius C, Gunnarsson U, Smedh K et al. Patients with rectal cancer receiving adjuvant chemotherapy have an increased survival: a population-based longitudinal study. *Ann Oncol* 2013; 24: 160–165.
6. Bujko K, Glimelius B, Valentini V et al. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo) therapy: A meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. *Eur J Surg Oncol* 2015; 41: 713–723.
7. Bosset JF, Calais G, Mineur L et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; 15: 184–190.
8. Bosset JF, Collette L. Adjuvant chemotherapy for rectal cancer — authors' reply. *Lancet Oncol* 2014; 15: 197–198.
9. Sainato A, Cernusco Luna Nunzia V, Valentini V et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; 113: 223–229.
10. Breugom AJ, van Gijn W, Muller EW et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol* 2015; 26: 696–701.
11. Glynne-Jones R, Counsell N, Quirke P et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; 25: 1356–1362.
12. QUASAR Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; 370: 2020–2029.
13. Gray R, McConkey C. Adjuvant chemotherapy for rectal cancer? Authors' reply. *Lancet* 2008; 371: 1503.
14. Rödel C, Graeven U, Fietkau R et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015; 16: 979–989.
15. Schmoll HJ, Haustermans K, Price TJ et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/– oxaliplatine in locally advanced rectal cancer: final results of the PETACC-6 trial. *J Clin Oncol* 2018; 36 (suppl; abstract 3500).
16. Hong YS, Nam BH, Kim KP et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014; 15: 1245–1253.
17. Breugom AJ, Swets M, Bosset JF et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; 16: 200–207.
18. Chau I, Norman AR, Cunningham D et al. Longitudinal quality of life and quality adjusted survival in a randomised controlled trial comparing six months of bolus fluorouracil/leucovorin vs twelve weeks of protracted venous infusion fluorouracil as adjuvant chemotherapy for colorectal cancer. *Eur J Cancer* 2005; 41: 1551–1559.
19. Benson AB 3rd, Schrag D, Somerfield MR et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004; 22: 3408–3419.
20. Tiv M, Puyraveau M, Mineur L et al. Long-term quality of life in patients with rectal cancer treated with preoperative (chemo)-radiotherapy within a randomized trial. *Cancer Radiother* 2010; 14: 530–534.
21. Mercier M, Pasquet P, Puyraveau M et al. Evaluation of the sphincter function and quality of life in French patients with rectal cancer who entered the EORTC 22921 study. *Eur J Cancer* 2005; 41 (3 Suppl): 171.
22. Mols F, Beijers T, Lemmens V et al. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. *J Clin Oncol* 2013; 31: 2699–707.
23. Harrison JD, Solomon MJ, Young JM et al. Patient and physician preferences for surgical and adjuvant treatment options for rectal cancer. *Arch Surg* 2008; 143: 389–394.

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William James Morton (1845–1920). Author of America's first X-ray textbook

Richard F. Mould

William James Morton (1845–1920) was the son of a famous father and by supporting his father is linked to the story of ether anaesthesia. Ether and the dentist William Thomas Green Morton (1819–1868) has far outlasted any medical/scientific contributions made by the electrotherapist/radiologist William James Morton. It is also noticeable that several of his obituaries make no mention of any of his contributions with X-ray work. In later life he served a prison sentence for fraud relating to non-existing silver mines. The X-ray textbook written by William James Morton, in association with Edwin Hammer, was published in September 1896 and was the first X-ray textbook to be published in the USA. Several X-ray images made by William James Morton are included in this brief biography.

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Introduction

Both William James Morton (1845–1920) and his father were involved in various controversies during their lifetimes: for the elder Morton these were linked to the priority claim for the use of ether as an anaesthetic [1–5]. The younger Morton was drawn into these controversies by supporting his father. William James Morton was also convicted for fraud later on in his life, in 1912, relating to non-existent silver mines in Canada. Several of his obituaries fail to mention his contribution to X-ray knowledge in 1896 and this brief biography redresses this to a certain extent, including five X-ray images dating from 1896. As well as being the author of the first X-ray textbook in the USA [6], William James also published the world's first whole body radiography taken as a single image: as distinct from a whole body radiograph being made of two or three sections. The most detailed of his biographies [7] is that found in the book *Trail of the Invisible Ligh*t by E.R.N. Grigg. Although this reference does not include a selection of Morton's radiographs.

Morton family genealogy

The Morton family were originally from Scotland with Robert Morton an immigrant to the USA. William Thomas Green Morton was Robert's great-grandson. The 1870 USA census entry shows William James Morton as a 25-year old medical student living with his mother and three of his four siblings (Edward, Elizabeth & Nathanial) in Needham, Norfolk, Massachusetts. A decade later in 1880 William James (Fig. 1) is living in New York City with his first wife, Elizabeth Lee, and her family. By 1900 his home was in Manhattan and he was described as a physician. In 1910 he was still living in Manhattan but described as a physician-general practice. However, by 1920 he had moved with his 2nd wife (who was much younger than him) to Miami, Florida. He had no children with either wife and died in 1920 of heart disease.

William Thomas Green Morton

William Thomas Green Morton (1819–1868) is famous for being the first to publicly demonstrate, in September 1846,

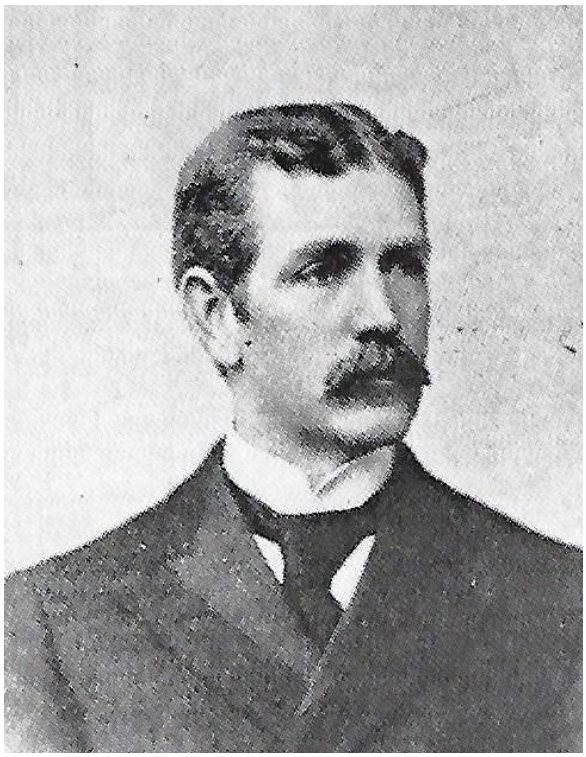

Figure 1. William James Morton in the 1880s

that inhaled ether could be used as a surgical anaesthetic. This was for a tooth extraction. He claimed throughout his life that he was the discoverer of anaesthesia and it became his obsession to obtain exclusive patent rights for the use of ether anaesthesia. He was to give up his thriving dental practice, became involved in much litigation, and died deeply in debt.

Morton originally worked as a clerk, printer and salesman before entering Baltimore College of Dental Surgery in 1840 and qualified in 1842 when he left college to study with the dentist Horace Wells (1815–1848) in Hartford, Connecticut and for six months, became his business partner. In 1844 Morton entered Harvard Medical School and was present at the lectures of Charles Thomas Jackson (1805–1880) who introduced him to the anaesthetic properties of ether. Then in January 1845 he was present at Massachusetts General Hospital when Wells tried and failed to demonstrate the pain killing effects of nitrous oxide during surgery. It was on 30 September 1846 that Morton successfully demonstrated the use of ether as an anaesthetic during extraction of a tooth and on 16 October followed the success with a patient undergoing tumour surgery.

Morton attempted to obtain exclusive patent rights to the use of ether anaesthesia but completely failed over the succeeding years. For example, he unsuccessfully petitioned the United States Congress three times for recognition of his rights to enable him to receive subsequent profits. The truth concerning priority is that the Georgia surgeon Crawford Williamson Long (1815–1878) employed ether as an anaesthetic in March 1842 and demonstrated the use of ether several times before physician and surgeons in Georgia. However, Long did not publish his findings until 1849.

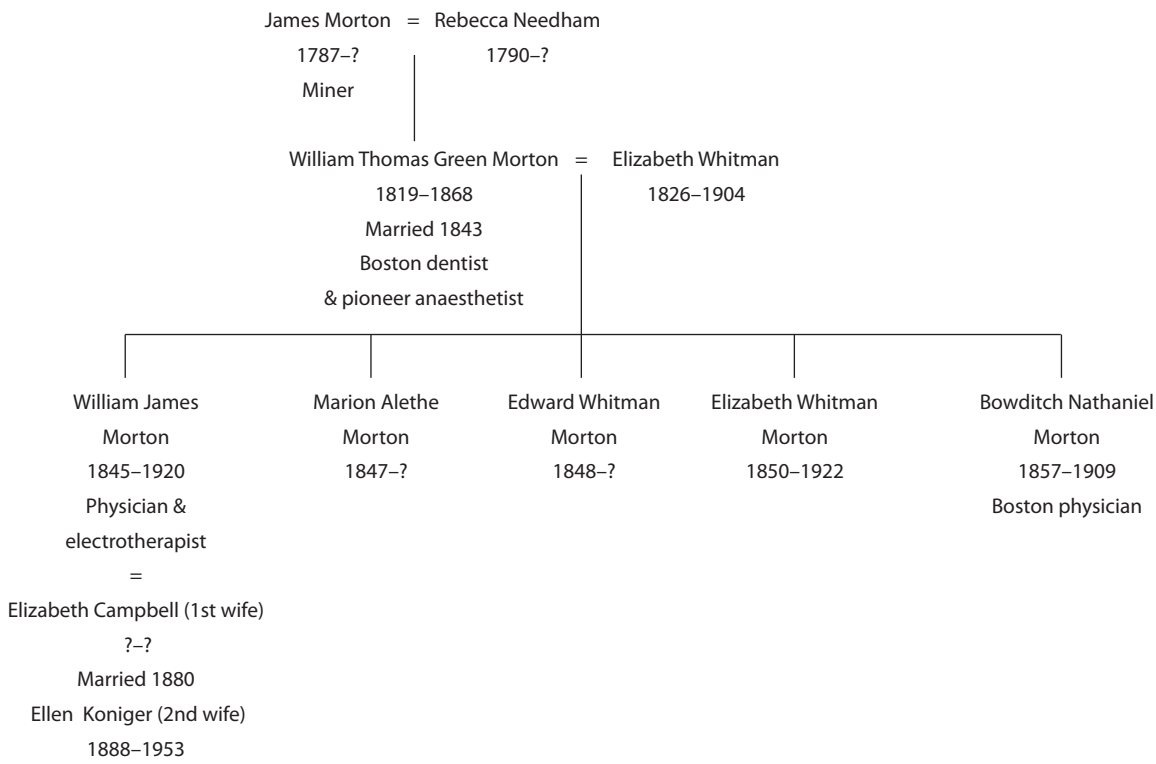

Figure 2. Morton family tree

In December 1846 and during 1849, 1851 and 1853 he made failed applications to the United States Congress for a 'national recompense' of US$ 100,000. All these applications failed. This failure was in part due to the claims of Jackson and Wells as the discoverers of ether.

In 1852 he received an honorary degree from Washington University of Medicine in Baltimore (later to become the College of Physicians & Surgeons). In 1862 he joined the Army of the Potomac as a volunteer surgeon and used ether on more than 2000 soldiers during the battles of Fredericksburg, Chancellorville and the Wilderness.

Just before his death he exhibited rather bizarre behaviour in July 1868 in that when riding in a carriage with his wife, he suddenly demanded the carriage stop, and he ran into the lake in Central Park 'to cool off'. This was because he had suffered a major stroke which proved fatal soon afterwards [1–5, 8].

Education & early years of William James Morton

William James Morton (1845–1920) attended the first established public school in the United States, the Boston Latin School. He entered Harvard in 1863 and obtained his M.A. in 1867. In 1867 he interrupted his Harvard studies and taught for a year at the Gardiner (Massachusetts) High School. He matriculated at Harvard Medical School following father's death in July 1868.

In 1869 he supported himself financially by being the resident medical officer in the Discharged Soldiers' Home and then as a junior doctor at Massachusetts General Hospital, becoming a House Surgeon in 1871. He graduated M.D. from Harvard in 1872 and later that year travelled to Europe. It was also in 1872 that he was awarded Harvard's Boylston Prize for his thesis about his father's work on *Anaesthetics*. Morton travelled first to Vienna, 1872–1874, and then to Kimberley, South Africa where he became the medical officer of a mining company (as well as establishing a profitable private practice). During this period to 1876 he hunted big game and staked his own diamond mining claims.

He returned to the USA at the end of 1876 via England, France and Germany. During his French visit he received teaching in Paris at the Salpêtrière Hospital from Jean-Martin Charcot (1825–1893). Morton spent time defending his father's work on anaesthesia [9–14] and undertook his own work using cocaine for local anaesthesia. However, he was to become better known as an electrotherapist and radiologist than an anaesthetist [5, 7, 15].

Professional life 1878–1895

Morton settled in 1878 in New York City, opening an office at 33 East 33rd Street and married in 1880. Following its purchase by Morton, he became the Editor of the *Journal of Nervous & Mental Disease* (which he sold in 1885 and then was no longer the Editor) and from 1882–1885 was adjunct Professor of Nervous Diseases at the New York Post-Graduate Medical School. He obtained full Professorship in 1890 and this remained his main academic title for the following 30 years. He served as a neurologist to the New York Infant Asylum 1887–1897. On the frontispiece of his X-ray textbook [6], following he listed several memberships (Table I).

The basis for his reputation as a famous electrotherapist was his design of apparatus for producing what he termed the 'Morton current'. This was a static machine with Leyden jars, a wet sponge electrode and a gun-shaped electrode [7, 16]. He specialised in neurology and with some 20 other physicians watched Daniel Smith Lamb (1843–1929) perform the autopsy on Charles Guiteau (1840–1882) the executed assassin of President Garfield. Morton himself reported on the examination of Guiteau's brain [17]. He published several papers on electrotherapeutics [*for example*, see 16, 18–23]. This period 1878–1895 predates the discovery of X-rays in November 1895 and of radioactivity in 1896 and radium in 1898. From 1899–1908 Morton again published on electrotherapeutics [24–34] as well as on X-rays.

X-rays 1896–1897

The electrotherapeutic apparatus available to Morton enabled him to immediately start experimenting with X-rays (Fig. 3) once the knowledge of their discovery reached the USA. In 1896, as well as his book [6], written with the electrical engineer Edwin Wesley Hammer (1867–1951), he also published several papers on X-rays [35–42].

Morton's textbook [6] is arranged in four parts I–IV with three appendices A–C. {I} Definitions. {II} Apparatus. {III} Operation. {IV} Surgical value of the X-ray. {A} A new form of radiation: the preliminary communication to the Würzburg Physico-Chemical Society by Professor Konrad Roentgen dated December 1895. {B} Experiments with Roentgen rays, Roentgen ray lamps and other experiments, Influence of temperature on X-ray effects by Thomas A. Edison. {C} The surviving hypothesis concerning the X rays by Oliver Lodge. Table II gives the eight subsections of Part IV.

Table I. Memberships held by William James Morton in 1896 [6]

- Professor of Diseases of the Mind & Nervous System and Electro-Therapeutics in the New York Post Graduate Medical School & Hospital
- Member of the Medical Society of the County of New York
- Permanent Member of the Medical Society of the State of New York
- Member of the New York Academy of Medicine
- American Electro-Therapeutic Association
- American Neurological Association
- Harvard Medical Society of New York City
- American Medical Association
- Societe Francaise d'Electrotherapie
- New York Electrical Society etc. etc.

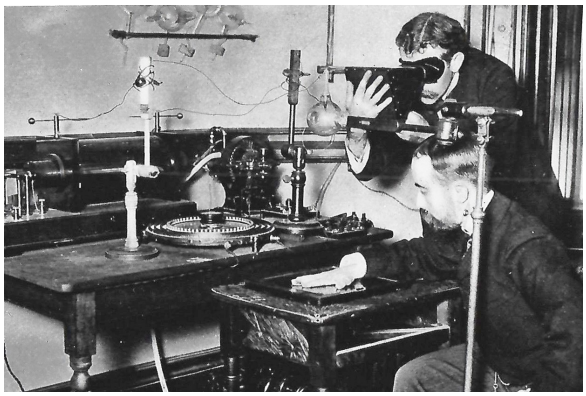

Figure 3. Morton's X-ray apparatus arranged for simultaneous radiography and fluoroscopy [6]

The subsection on curative action of the X-ray is produced here in full as it represents the start of thoughts on X-ray therapy and on X ray damage. "Much interest has been excited as to the influence of X-rays on bacteria. In February 1896, Dr Morton exposed cultures of the cholera vibrio of the bacillus colli communis, the bacillus of typhoid fever and of diphtheria to the X-rays for 30 minutes and for one hour. They were from time to time compared with other cultures kept under the same conditions except for the exposure to X rays in the usual manner. No differences could be determined at that time between the cultures which had been exposed to the X rays and those which had not been so exposed.

These experiments, however, were conducted in the early days of the X ray, when it was not by any means powerful, and yet it remains with the powerful X ray of today to determine whether or not in reality the X ray possesses a germicidal action.

In favour of an influence of the X rays upon tissue is the experience of the experimenter that after viewing a powerful X ray continuously through a fluoroscope, the eyes are frequently affected painfully. Inflammation of the eyelids, upper lips and of the skin of the face generally, somewhat if the nature of sunburn, has been recorded by more than one experimenter as the result of exposure to the X ray."

His publication of a whole body X-ray image was in 1897 [43] (Fig. 4) and in the same year he also published an image of the head [44]. The apparatus included a 12" induction coil whose primary was supplied from the 117 volt Edison current of the New York street mains. The distance of the tube to the X ray plate was 54" and the time taken including stoppages was 30 minutes.

At the end of Morton's book [6] is a list of radiographs which could be purchased from the American publisher of the book: American Technical Book Company of 45, Vesey

Table II. Surgical value of the X-ray

- Normal anatomy
- Fractures, Dislocations, Diseases of the Bones & Deformities
- Stiff joints (Ankylosis)
- The X-ray in Dentistry
- Foreign Objects in the Body
- Soft Tissues & Location of Organs
- Medico-Legal
- Curative Action of the X-ray

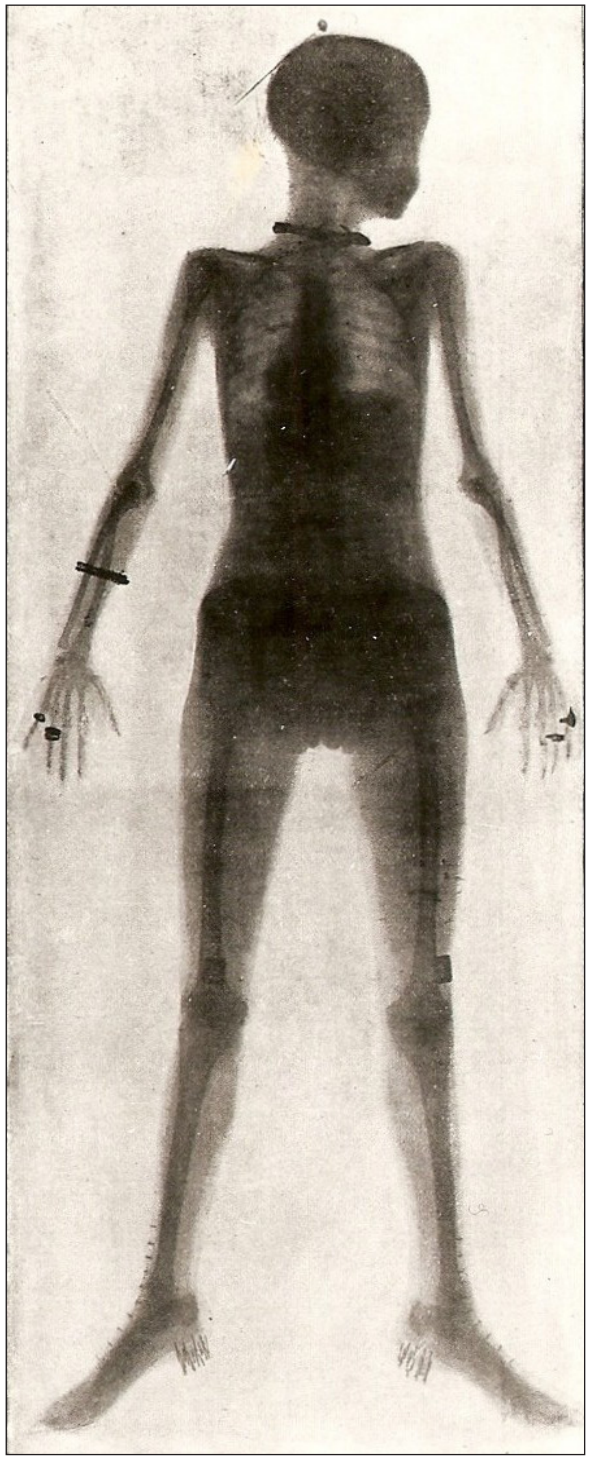

Figure 4. The world's first whole body radiograph taken in a single exposure [43, 44]

Street, New York. They are advertised as life size and handsomely mounted. Most cost 60 cents. Figures 5–8 are examples.

Cancer 1902–1915

Morton not o nly published on X-ray diagnosis but also on X-ray therapy and radium therapy for cancer [45–56]. He was most productive up to 1908. His final publication was in 1915 [57].

Mining fraud & prison 1911–1913

Morton's earliest publications on mining were in 1877–1878 relating to the South African diamond fields [58, 59]. Many years later in 1911 a New York promoter, Albert Freeman, induced Morton's friend Julian Hawthorne (1846–1934), who was the son of the famous novelist Nathaniel Hawthorne (1804–1864), to participate in the organisation of four companies, created to operate mining properties in the Canadian cobalt region. The four companies were combined into the Hawthorne Iron & Silver Mines Company and a considerable amount of stock was issued. The Board of Directors included William James Morton, and the lawyer Josiah Quincy (1859–1919) who was a former mayor of Boston and former assistant United States Secretary of State. The advertising claims circulated in leaflets by the U.S. Mail were in fact false, but investors nevertheless subscribed over 3.5 million U.S. dollars as investment in the non-existing silver mine.

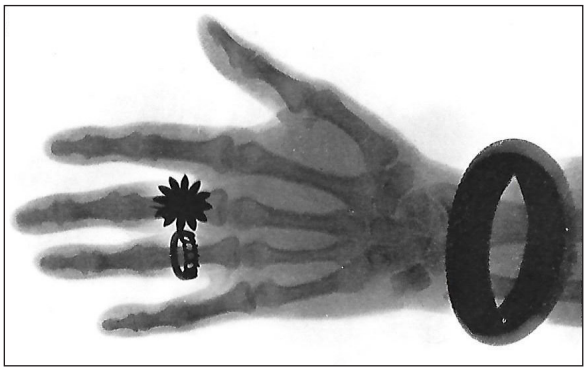

Figure 5. Gold rings & bracelet [6]

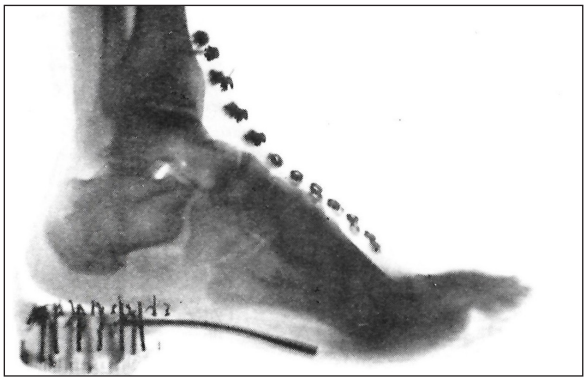

Figure 6. Illustration of bones in the foot [6]

Figure 7. Picture of a non-living subject: frontal view of skull showing not only the location of the teeth where concealed within their sockets but also the outlines of the cavities of the teeth themselves [6]

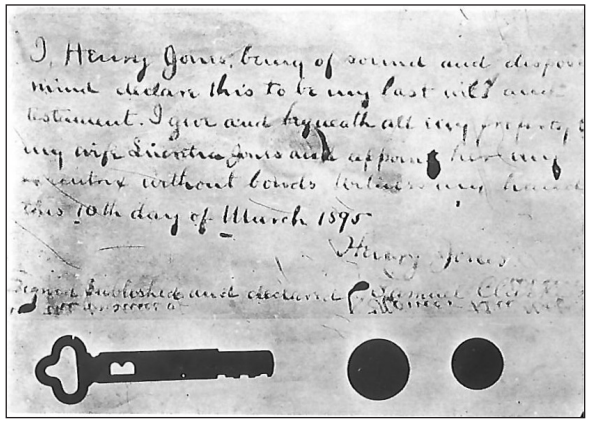

Figure 8. Handwriting, purporting to be a will, photographed as an experiment by the aid of the X ray in a sealed envelope [6]

Eventually the fraud was exposed and the Federal Government indicted Freeman, Hawthorne, Morton and Quincy on the charge of using the U.S. Mails in aid of a scheme to defraud. The proceedings opened on 28 November 1912 with 106 witnesses giving testimony during six weeks at a cost to the Government of U.S. $50,000. The jury deliberated for 28 hours and acquitted Quincy but found Freeman, Hawthorne and Morton guilty. Freeman was sentenced to five years in prison (Atlanta Federal Penitentiary) and Hawthorne and Morton to one year and one day.

They served six months. Hawthorne moved to California and became a successful writer. Morton on 13 December 1913 was granted a pardon by President Woodrow Wilson and on 26 June 1914 was reinstated as a practicing physician by the New York Board of Regents. After his prison term Morton returned to his old office at East 28th Street, New York, but he had lost his old stamina [7, 60, 61].

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References

1. Asbell MB. William Thomas Green Morton. *Worcester Medical News* 1970; 35: 15–18.
2. Vandam LD. The last days of William Thomas Green Morton. *J Clin Anesthesia* 1996; 8: 431–434.
3. Wolfe RJ. *Tarnished Idol: William Thomas Green Morton and the Introduction of Surgical Anaesthesia, a Chronicle of the Ether Controversy*. San Anselmo, CA: Norman Publishing, 2001.
4. Snow SJ. *Blessed Days of Anaesthesia: How Anaesthetics Changed the World*. Oxford: Oxford University Press, 2008.
5. Aponte-Feliciano A, Desai SP, Desai MS. William James Morton (1845–1920): like father, like son (?). *J Anesthesia History* 2013; 31: 18–20.
6. Morton WJ in collaboration with Hammer EW. *The X Ray or Photography of the Invisible and its Value in Surgery.* London: Simpkin, Marshall, Hamilton, Kent, 1896 and New York: American Technical Book Company, 1896.
7. Grigg ERN. William James Morton (1845–1940), first medical electro--radiologist in America. In: Grigg ERN. *The Trail of the Invisible Light*. Springfield: Illinois, 1965. Chapter 6, pp 778–799.
8. https://en.wikipedia.org/wiki/William_T._G._Morton (accessed 12 August 2018)
9. Morton WJ. The introduction of anaesthesia. *Med Record* 1892; 42: 719–720.
10. Morton WJ. Memoranda on the "Discovery of anaesthesia". New York 1895; Washington DC: National Library of Medicine.
11. Morton WJ. Origin of the term anaesthetic. *Med Record* 1894; 46: 799–800.
12. Morton WJ. Discovery of anaesthesia. *Hartford Times* 12 April 1895; 8: 1.
13. Morton WJ. Memoranda relating to the discovery of surgical anaesthesia and William T. G. Morton's relation to this event. *Postgraduate New York*; 1905: 20: 333–353.
14. Morton WJ. Geschichtliche Beitraege zur Entdeckung der Anaesthesie in der Chirurgie und ueberdie Beziehungen Dr. William T.G. Mortons zu derselben. Wiener med Presse 16 September 1906; 47: 1888–1897.
15. Aponte-Feliciano A, Desai SP, Desai MS. William James Morton, MD. His life and contributions to medicine. Abstract: Anethesiology 2011 conference October 2011.
16. Morton WJ. The Franklinic interrupted current, or, my new system of therapeutic administration of static electricity. *Med Record* 1891; 39: 97–104.
17. Morton WJ, Dana CL. Microscopical appearance of Guiteau's brain. *Med Record* 1882; 22: 134–135.
18. Morton WJ. On statical electrotherapeutics or treatment of disease by Franklinism. *Med Record* 1881; 19: 367–371, 395–398.
19. Morton WJ. Size and kind of Holtz machine adapted to medical uses. *Med Record* 1881; 19: 472.
20. Morton WJ. A new current of induction electricity; or, a new method of producing electrical nerve and muscle reaction. *Med Record* 1881; 20: 62–63.
21. Morton WJ. The place of static or frictional electricity in medicine. *Med Record* 1890; 37: 609–610.
22. Morton WJ. A brief glance at electricity in medicine. Lecture: Columbia College. *Tr Amer Inst Electrical Engineers* 1893; 10: 555–602.
23. Morton WJ. Electricity in medicine from a modern standpoint. Lecture: New York State Medical Society. *Tr Med Soc New York* 1895; 245–267.
24. Morton WJ. Cases of sciatic and brachial neuritis and neuralgia; treatment and cure by electrostatic currents. Cases compiled from records by W.B. Snow. *Med Record* 1899; 55: 521–527.
25. Morton EWJ. Electrostatic currents and the cure of locomotor ataxia, rheumatoid arthritis, neuritis, migraine, incontinence of urine, sexual impotence and uterine fibroids. *Med Record* 1899; 56: 845–849.
26. Morton WJ. Is static electricity a specific for organic and structural nervous disorders? *Med Record* 1900; 57: 43–44.
27. Morton WJ. The static induced current. *Med Record* 1900; 57: 520, 746–747.
28. Morton WJ. The use of electricity in chronic rheumatism. *Med Record* 1900; 57: 674–676.
29. Morton WJ. A case of multiple neuritis with atrophy, fibrillar twitchings, cramps and exaggerated reflexes: two years duration and recovery. *J Nervous & Mental Disease* 1900; 27: 605–608.
30. Morton WJ. Galvanisation. Properties of the Galvanic current. *Post Graduate, New York* 1905; 20: 35–41.
31. Morton WJ. Recent advances in electrotherapeutics. *New York Med J* 1905; 81: 634–637.
32. Morton WJ. New high potential high frequency 'cataphoric' electrode or phoric medicamental electrode. *Med Record* 1905; 68: 843.
33. Morton WJ. The wave current and high frequency currents. *J Advanced Therapeutics* 1908; 26: 227–239.
34. Morton WJ. Static electricity; its method of application and therapeutic value. *Post Graduate New York* 1908; 23; 331–343.
35. Morton WJ. Photography of the invisible without the aid of a Brookes {this is an error and should be Crookes} tube. *Elec Engineer* 5 February 1896; 21: 140–141.
36. Morton WJ. A Roentgen picture from a medical point of view. *New York Med Journal* 14 March 1896; 63: 333.
37. Morton WJ. A needle in the foot demonstrated by Roentgen rays. *Med Record* 14 March; 49: 371–372.
38. Morton WJ. The x-ray detection of deformity of bones. *New York Med Journal* 11 April 63: 479–480.
39. Morton WJ. A Roentgen picture of the bones of the wrist and hand. *New York Med Journal* 18 April 63: 516.
40. Morton WJ. A Roentgen picture of a marasmic infant. *New York Med Journal* 25 April 1896; 63: 540–541.
41. Morton WJ. The x-ray and its application in dentistry. *Dental Cosmos* June 1896; 38: 476–486.
42. Morton WJ. The x-ray and some of its applications in medicine; stereopticon views. *Med Record* 4 July 1896; 50: 9–11.
43. Morton WJ. X-ray picture of an adult by one exposure. *Elec Engineer* 19 May 1897; 23: 522, also in *Archives of the Roentgen Ray* July 1897; 2: 17.
44. Morton WJ. The x-ray picture of the living human head. *Items of Interest, New York* July 1897; 19: 313–315, also in *Amer X-ray Journal* October 1897; 1: 89–91.
45. Morton WJ. The treatment of malignant growths by the X ray with a provisional report on cases under treatment. *Med Record* March 1902; 61: 361–365.
46. Morton WJ. Radiotherapy for cancer and other diseases. *Med Record* May 1902; 61: 801–805.
47. Morton WJ. Primary and recurrent mammary carcinoma treated by the X ray. *Med Record* May 1903; 63: 845–851.
48. Morton WJ. The X and violet radiations in the treatment of cancer and other diseases. *Med Brief St. Louis* June 1903; 31: 842–844.
49. Morton WJ. Some cases treated by the X ray. Facial cancer, carbuncle, cheloid, acne, alopecia, areata, sychosis, fibroid tumor, psoriasis, lupus. *Med Record* July 1903; 64: 121–127.
50. Morton WJ. Treatment of cancer by the X ray, with remarks on the use of radium. *Int J Surgery* October 1903; 16: 289–294.
51. Morton WJ. Radiotherapy and surgery, with a plea for preoperative radiations. (Lecture before Harvard Medical Society) *Med Record* March 1905; 67: 443–447.
52. Morton WJ. Trypsin for the cure of cancer; with report of the microscopic examination of a cancer tumor of the breast, thus treated. *Med Record* December 1906; 70: 893–900.
53. Morton WJ. Trypsin for the cure of cancer. *Med Record* January 1907; 71: 110–111.
54. Morton WJ. A case of cancer treated by trypsin. *New York Med J* March 1907; 85: 443–444.
55. Morton WJ. Some problems in the chemotherapy of cancer. *New York Med J* March 1912; 95: 625–627.
56. Morton WJ. Imbedded radium tubes in the treatment of cancer. With a report of a case of sarcoma remaining cured nine years after treatment. *Med Record* November 1914; 86: 913–915.
57. Morton WJ. Radiochemicotherapy; the internal therapeutics of the radio-elements. *Med Record* March 1915; 87: 381–390.
58. Morton WJ. South African diamond fields, and a journey to the mines. *Bull Amer Geographic Soc* 1877; 9: 66–83.
59. Morton WJ. To South Africa for diamonds. *Scribner's Monthly* 1878; 16: 551–663, 662–675.
60. https://en.wikipedia.org/wiki/William_J._Morton (accessed 18 August 2018)
61. https://en.wikipedia.org/wiki/Julian_Hawthorne (accessed 18 August 2018)