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Original article

Cancer prevention and public health

The incidence and economic impact of dual smoking by office workers in Poland

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Introduction. Smoking tobacco is the first cause of deaths of men and second cause of deaths of women in Poland. The financial consequences reach 92 billion PLN annually. The new tobacco products gain their popularity especially among young adults, challenging public health and economy.

Material and methods. An anonymous questionnaire has been conducted in two weeks of March 2024 among office workers in Poland. The survey was conducted using CAWI method. Participation was voluntary.

Results. Two statistically significant differences were observed. The incident of smoking heated tobacco and dual smoking decreased with age. There was no statistically significant difference between sexes and choice of tobacco product.

Conclusions. The studied population chose HTPs and dual smoking on a larger scale than in other studies. The workplace plays a significant role in a health promotion and should address the rising trend of smoking new tobacco products as well as dual smoking.

Keywords: tobacco, cost, promotion, workplace, economic

Introduction

Smoking tobacco is the primary cause of death among men and second cause of deaths among women in Poland [1]. It leads to a heavy burden on the healthcare system as well as the budget, resulting in lost lives, lost years in health, lost productivity, and the significant costs of disease treatment. According to the research, a smoker's life is 10 years shorter than in case of non-smoker [2]. The percentage of lost years in health is 20.1% for men and 11.7% for women [2]. The financial consequences reach 92 billion PLN annually which exceeds by 4 times revenue from the sin tax [3]. The direct cost of smokers' treatment from the National Health Fund's budget is 50 billion PLN. Moreover, there is almost 42 billion PLN of indirect costs, for example due to employee sick leave as well as lost working hours due to breaks taken by employees [4].

Giving the above, activities aimed at tobacco limitation and cessation, including the ones at work, should continue to be a priority. The World Health Organization identifies smoking tobacco as one of the main public health issues and risk factors responsible for premature mortality from non-communicable diseases. Despite continuous efforts aimed at education, limitation of sale, legal regulations (for example prohibition of smoking in public places) and significant progress in this area, countries face new challenges due to the introduction of products with heated tobacco (HTPs) and e-cigarettes. The new products have gained popularity [5] especially among young adults, who are susceptible to manipulation from the ubiquitous advertising in their surrounds [6]. The competition between legal regulations and the tobacco industry increases the seriousness of this issue [7].

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Table I. Data of participants: sex, overweight and obesity

		Women	Men	Undeclared	Total
Sex	N	304	156	6	466
	[%]	65.24%	33.48%	1.29%	100%
Overweight	N	59	64	1	124
	[%]	12.66%	13.73%	0.21%	26.61%
Obesity	N	25	16	1	41
	[%]	5.36%	3.43%	0.21%	8.80%

Heated tobacco products and e-cigarettes have been introduced as an alternative to traditional (combustible) cigarettes, but their impact on health is still not fully known. However, there are reports about the impact of HTPs on acute respiratory and cardiovascular health [8].

These alternative products have been considered to support the cessation of smoking traditional cigarettes, practiced by 13% of users, but their effectiveness is still inconclusive [9]. Yet another even more concerning trend has appeared — dual smoking [10] which is when one person smokes two types of tobacco product (for example a combustible cigarette and HTP).

Material and methods

An anonymous, original questionnaire was conducted over two weeks in March 2024 (March 4–March 18) among office workers of the selected company operating in Warsaw, Poland. The survey included questions related to lifestyle choices, inter alia smoking, which is the subject of this article. The questions received by employees were as follows:

1. "How often do you smoke traditional cigarettes?"
2. "How often do you reach out for heated tobacco?"

Each of those questions provided four-stage answers to choose:

a) 1–4 cigarettes/sticks daily;
b) More than 5 cigarettes/sticks daily;
c) Less than 1 cigarette/stick daily — occasionally;
d) Never.

The survey was conducted using the computer-assisted web interviewing (CAWI) method. It was sent through internal communication to 2070 office workers. The work is performed in front of a screen monitor, and for some, it also includes decision-making positions and driving company car, which is defined as occupational exposure according to the local regulations. Participation in the survey was voluntary.

Statistics

The participation rate was 25% (466). Among respondents 90% were Polish-speaking employees and 10% were English-speaking. The majority of respondents were women (65.24%), while 33.48% were men and 1.29% did not declare their sex. The average age was 34 years and the average weight was 72 kg (67 kg for women and 83 kg for men). Based on the body mass index (BMI) calculations, almost 27% (124) of the employees participating in the survey were overweighed and almost 9% (41) were obese. Data are presented in Table I.

For the purposes of assessing the correlation between the preferred tobacco product, including dual smoking, and sex as well as age, a series of $\chi 2$ and Spearman correlation tests were performed. The group of employees who did not declare their sex (8 people) were excluded from the analysis, therefore the research group consisted of 458 employees.

Results

The majority of all respondents across both sexes declared that they never smoke cigarettes and never smoke heated tobacco — both 87.55% (401).

In total, nearly 17% (76) of employees participating in the survey declared smoking: 8.3% (38) smoke combustible cigarettes, 8.3% (38) HTPs and 4.15% (19) smoke both. Among smokers, the proportions are as follows: 40% used traditional cigarettes and 40% used heated tobacco products. It was also noted that 20% of smokers used both tobacco products simultaneously with different frequencies. The assumption of a minimum of 5 observations in each field was met, so the χ^2 test was applied and didn't show a statistically significant difference between the sexes. However it is noted that women in this group more frequently reached out for traditional cigarettes and were dual smokers, than men. The results are presented in Table II.

In the next step it was analyzed whether the age of smokers is correlated to the chosen tobacco product as well as dual smoking. Two statistically significant differences were observed. The incident of smoking heated tobacco (first observation) and dual smoking (second observation) decreased with age. The results are presented in Table III.

Discussion

The study provides a view on dual smoking among office workers in Poland (combustible cigarettes and heated tobacco

Table II. Correlations between sex and choice of tobacco product: traditional cigarettes, heated tobacco or both

		Women (1)	Men (2)	Total	(1) and (2)
Traditional cigarettes	N	26	12	38	$\chi^2 = 1.099$ $p = 0.577$
	[%]	**42.62%**	35.29%	40.00%	
Heated tobacco	N	22	16	38	
	[%]	36.07 %	47.06%	40.00%	
Traditional cigarettes and heated tobacco simultaneously	N	13	6	19	
	[%]	**21.31%**	17.65%	**20.00%**	
Total		61	34	95	

Table III. Correlation between age and choice of tobacco product: traditional cigarettes, heated tobacco or both

			Age
Traditional cigarettes	N	Rho Spearman	–0.078
	[%]	p	0.094
Heated tobacco	N	Rho Spearman	**–0.145**
	[%]	p	0.002
Traditional cigarettes and heated tobacco simultaneously	N	Rho Spearman	**–0.098**
	[%]	p	0.036

products). Although the results did not show statistically significant differences between sexes, there was a statistically significant correlation between smoking and age, which showed that reaching out for heated tobacco as well as dual smoking decreased with age. Studies on the whole population showed that 28.8% of adults in Poland smoke on a daily basis, with 27.1% being women and 30.8% men [1], and the tendency is growing comparing to the previous years. When it comes to the working population, 26% of professionally active men and 16% of women are smokers [11]. The research on office workers presented in this article showed a lower rate of smoking employees *vs.* population (17% *vs.* 28,8%), however there was higher rate of HTPs users (8.26% *vs.* 4%) [12]. Other research findings on the working population confirmed that smoking is more prevalent among physical employees (blue collar) [13], which can explain the lower smoking rate in this article's research group.

The conducted analysis showed a statistically significant correlation between smoking heated tobacco as well as dual smoking and age. The likelihood of smoking heated tobacco products decreased with age which is confirmed by other studies, showing that young adults prefer this type of tobacco over traditional cigarettes [13]. Dual smoking also decreased with age, which is reflected in research showing the behavior of young people and their motivations for smoking both types of tobacco [14]. This research also showed that 20% of smokers among employees responding to the survey declared dual smoking. This result is higher than figures from a nationwide study, which showed that 9.1% of smokers used cigarettes and heated tobacco products simultaneously [15]. Therefore the reasons behind dual smoking among employees need further research.

The population of the research in question are office employees in Poland. The workplace has a significant influence on employee health and is recognized as appropriate for the implementation of preventive and health promoting initiatives by both international organizations (WHO) and state organizations (Ministry of Health). In June 2022, a comprehensive study by the Prof. J. Nofer Institute of Occupational Medicine was devoted to the subject of health programs at work [16]. In this report, we can find literature proving the effectiveness of workplace health programs, references to absenteeism and presenteeism, as well as numerous recommendations to support employers in mitigating the effects of an aging and shrinking workforce. This study confirms the validity and importance of further activities in the area of health promotion at work.

Many of those initiatives are addressed to groups of employees and have an educational aspect (for example thorough webinars, training sessions). Two of the solutions proposed in a recently published report from the Nofer Institute are: creating online support groups and enhancing stress management [17]. There is also a large segment of solutions and products addressed to individuals, including digital

interventions through smart devices and mobile applications for the purposes of personalized healthcare. The primary goal of any health promotion, including that in the workplace, should be educating and increasing the health literacy of employees, who then skillfully reach out for and use the available solutions to suit their individual health needs, including personalized health care driven by technological innovations, which can be more interesting for young adults. This is important especially when targeting the younger population, which, as we can see from this and other studies, choose HTPs and practice dual smoking.

Tobacco smoking has significant financial, health, and social consequences on a wide scale. It affects the health of individuals, their own lives and those of their loved ones, as well as employers, the budget, and social security systems. The emergence of the new trend of dual smoking, especially among young people, is endangering their health and the future of a shrinking workforce, which has an impact on the whole economy.

It is noticeable from this research as well as from other published literature, that action is required to address the issue of dual smoking. Personalized health care is not without significance and can form a crucial part in managing those challenges, once employees are equipped with the proper knowledge and tools.

Limitations

This study has several limitations. The CAWI method which was used and its voluntary approach results in limited impact on responsiveness. The participants group was dominated by women and some fields have few responses. The original questionnaire allowed to research a wider scope of lifestyle behaviors for the employer's needs, but at the same time it limits the possibility of comparing the results with other studies using standard questionnaires.

Conclusions

This article provides data on the incidence of dual smoking by office workers in Poland. The studied population chose HTPs and dual smoking on a larger scale than in other studies. Further research is needed to evaluate motivations and facilitators behind dual smoking as well as health consequences. The workplace plays a significant role in health promotion, and should address the rising trend of smoking new tobacco products as well as dual smoking by young employees. Employers' initiatives should be adapted to young employees' needs, taking into considering their preferences to use innovative solutions.

Article information and declarations

Data availability statement

The data is in the possession of the author and can be provided on request.

Ethics statement

The survey used for the purposes of this research was anonymous and didn't include questions about personal nor sensitive data. The survey was not conducted among patients, only office workers, who agreed to participate and voluntarily and independently provided answers through the link received from the internal communication team at the workplace. Participants were informed that results will be a subject of further research. Data were gathered and kept in the internal system, safe in terms of GDPR.

Authors contributions

Agata Olearczyk — conceptualization, formal analysis, methodology, writing — original draft preparation.

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Conflicts of interest

The author declare no conflict of interest.

Supplementary material

None.

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Original article

Renal tumors

Outcomes of treatment, laboratory results, adverse effects, and tolerability of cancer treatment in patients with metastatic renal cell carcinoma treated with ipilimumab and nivolumab after cytoreductive nephrectomy

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Introduction. This publication aims to present the results of a retrospective analysis of the treatment outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with ipilimumab and nivolumab (IPI-NIVO) who underwent cytoreductive nephrectomy (CN), radical nephrectomy (RN) or nephron-sparing surgery (NSS) and in whom surgery was omitted.
Material and methods. The retrospective analysis includes the results of 34 patients treated and followed at the Institute of Oncology, Poznań University of Medical Sciences, from May 2022 to February 2024.
Results. Progression-free survival (PFS) was compared in two groups of patients — those who underwent CN (n = 8) and those who had no prior surgical treatment before IPI-NIVO (n = 12). There was a statistically significant difference in the length of PFS between the two groups compared in favour of patients who underwent CN before starting systemic treatment (p = 0.004). The majority of patients (n = 27) reported adverse events during IPI-NIVO treatment. There was no effect of CN performed before initiation of systemic treatment on the occurrence of adverse events during therapy (p = 0.677). The most common reasons for discontinuation of systemic treatment were the drugs adverse effects (n = 8) and disease progression (n = 7).
Conclusions. The results presented in the study suggest the important role of CN in the treatment of mRCC. Appropriate selection of patients suitable for CN is critical to achieving optimal treatment outcomes. Due to limited literature data, further studies are needed to evaluate the role and validity of performing CN in patients with mRCC treated with IPI-NIVO regimens.

Keywords: metastatic renal cell carcinoma, immune checkpoint inhibitors, ipilimumab, nivolumab, cytoreductive nephrectomy

Introduction

Renal cell carcinoma (RCC) is a heterogeneous disease with several histological subtypes identified. The most common subtype is clear cell carcinoma, accounting for over 80% of all renal cancer cases [1]. Despite significant advances in the diagnosis and treatment of cancer, advanced-stage RCC, i.e.,

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with distant metastases (metastatic renal cell carcinoma, mRCC), remains a common clinical problem. Despite increasing access to diagnostic tools, such as ultrasound and computed tomography, it is estimated that approximately 25% of patients with RCC have metastases at the time of diagnosis. Statistically, only 8% of patients survive 5 years after diagnosis [2, 3].

Due to the lack of satisfactory response of mRCC to conventional chemotherapy and radiotherapy, effective systemic treatment of this cancer has been sought for many years [4]. Immunotherapies based on cytokines, such as interleukin-2 and interferon-alpha (IFN-α), were used for many years in the systemic therapy of mRCC until the introduction of molecularly targeted drugs [5, 6]. Immune checkpoint inhibitors (ICIs), such as ipilimumab and nivolumab (IPI-NIVO), have been used for several years and show high efficacy in the treatment of patients with mRCC. Ipilimumab and nivolumab are monoclonal antibodies that bind to the immune checkpoints CTLA-4 and PD-1, respectively. Studies have shown that the effect of IPI-NIVO at different stages of the immune response (CTLA-4 and PD-1 checkpoints) increases the efficacy of oncological treatment [7, 8].

For many years, the validity of cytoreductive nephrectomy (CN) has remained a controversial issue among urologists and oncologists treating metastatic renal cell carcinoma (mRCC). Cytoreductive nephrectomy is a surgical intervention that involves the non-radical removal of a cancer-affected kidney with the goal of reducing tumor mass and ultimately improving systemic treatment outcomes. The aim of CN is to remove as much cancerous tissue as possible, though not necessarily the entire tumor. Often, part of the tumor is left behind, especially if other organs are involved. Cytoreductive nephrectomy is often performed in patients with mRCC when a complete cure for the cancer is not possible [9]. Radical nephrectomy (RN), on the other hand, is a procedure in which the entire kidney is removed along with the surrounding adipose tissue, part of the ureter, and — in some cases — the lymph nodes. The main goal of RN is to completely remove the tumor when it is confined to the kidney, and there is no evidence of metastasis to other organs. It is a treatment with radical intent, i.e., to cure the patient completely [10]. In some patients, it is possible to perform nephron-sparing surgery (NSS), which is the surgical removal of a kidney tumor while preserving as much healthy kidney tissue as possible. Nephron-sparing surgery is the preferred treatment for patients with small-diameter RCC, typically less than 4 cm, but it may also be performed in selected cases of larger tumors [11, 12].

There is still limited data in the literature regarding the efficacy of treatment in patients with mRCC treated with IPI-NIVO who have undergone CN, and in whom CN was omitted. Therefore, it was decided to conduct a scientific study to evaluate the role of CN in mRCC patients treated with IPI-NIVO.

Material and methods

This article presents the results of a retrospective analysis of the treatment of patients with mRCC (stage IV according to the TNM classification). The study included patients treated systemically with IPI-NIVO therapy who underwent surgery (CN, RN, or NSS) prior to systemic treatment, and patients who did not undergo surgery prior to systemic therapy (Fig. 1). A detailed analysis was conducted on the outcomes of patients treated with IPI-NIVO who underwent CN, comparing them to the outcomes of patients who did not undergo surgical treatment. The retrospective analysis includes the results of 34 patients treated and followed at the Institute of Oncology, Poznań University of Medical Sciences, from May 2022 to February 2024. Prior to the start of the study, the Bioethics Committee of the Poznań University of Medical Sciences issued an opinion that the study did not have the characteristics of a medical experiment.

Statistical analysis was performed using software by Dell Inc. (2016), Dell Statistica (data analysis software system) version 13, and Cytel Studio version 11.1.0. The normality of the distribution of the variables studied was tested using the Shapiro-Wilk test. Student's t-test, Mann-Whitney, and Wilcoxon tests for dependent samples were used to compare individual statistical data. Categorical parameters were described as n (%). The statistical significance of the relationships examined was tested at the level of $\alpha = 0.05$.

Results

Among the 34 patients included in the study, 64.71% (n = 22) were men and 35.29% (n = 12) were women. The mean age of patients at the start of IPI-NIVO treatment was 64.85 years (range: 44 to 80 years). The mean age of the women enrolled in the study was 67.33 years, while the mean age of the men was 63.50 years. The tumor was more frequently located in the right kidney (n = 19, 55.88%) and less frequently in the left kidney (n = 15, 44.12%). 64.71% of patients underwent surgery prior to systemic treatment (n = 22), of which RN was the most common (n = 12, 54.55%), CN less common (n = 8, 36.36%), and NSS the least common (n = 2, 9.09%). Some patients (n = 8, 23.53%) underwent tumor embolization before the start of treatment, of which 2 patients underwent surgical treatment after embolization (CN in 1 patient, RN in 1 patient), and 6 patients were not eligible for surgical treatment after embolization due to advanced neoplastic process. Histopathologically, the most frequently diagnosed tumor was clear cell carcinoma (n = 30, 88.24%), while clear cell carcinoma with a sarcomatoid component was diagnosed in 4 patients (11.76%). In most histopathological diagnoses, the grade of malignancy on the Fuhrman scale was G2 (n = 21, 61.76%), Fuhrman G3 (n = 8, 23.53%), Fuhrman G4 (n = 3, 8.82%), and Fuhrman G1 (n = 2, 5.89%). All patients included in the study (n = 34, 100%) had distant metastases

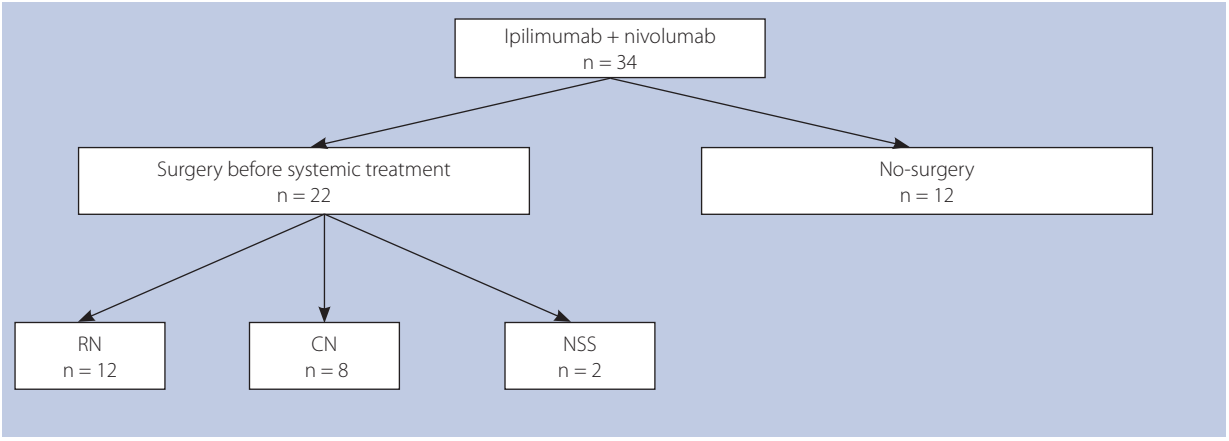

Figure 1. Distribution of patients included in the study; CN — cytoreductive nephrectomy; NSS — nephron-sparing surgery; RN — radical nephrectomy

at the time of treatment initiation. Distant metastases were found in more than one organ in 70.59% of patients (n = 24) and in only one organ in 29.41% of patients (n = 10). Metastases were most commonly found in the lungs (n = 23, 67.65%), less commonly in the adrenal glands (n = 11, 32.35%), liver (n = 9, 26.47%), bones (n = 5, 14.71%), pancreas (n = 4, 11.76%), central nervous system (n = 2, 5.88%), and other organs (n = 7, 20.59%). Metastases in the surrounding lymph nodes were found in 58.82% of patients (n = 20). Some patients (n = 14, 41.18%) were eligible for additional metastatic treatment with surgery, radiotherapy, or a combination of both. Surgical treatment of metastases was used in 6 patients (42.86%), radiotherapy was performed in 4 patients (28.57%), and a combination of surgery and radiotherapy was used in 4 patients (28.57%). All patients included in the study were graded according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) scale and classified into individual prognostic groups. The study included patients with intermediate (1–2 risk factors) and poor prognosis (3 or more risk factors), according to the IMDC. 58.82% of patients (n = 20) were in the intermediate prognosis group, while 41.18% (n = 14) were in the poor prognosis group, according to IMDC. The performance status of the patients was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale. The performance status of 44.12% of patients (n = 15) was ECOG 1, 38.24% (n = 13) was ECOG 0, and 17.64% (n = 6) was ECOG 2. The study did not include patients with ECOG 3 or higher. Patients in the study were also assessed using the Karnofsky Performance Status Scale. 38.24% of patients (n = 13) scored 100 points on the Karnofsky scale, 23.53% of patients (n = 8) scored 70 points on the Karnofsky scale, 20.59% of patients (n = 7) scored 80 points on the Karnofsky scale, and 17.64% of patients (n = 6) scored 90 points on the Karnofsky scale. The study did not include patients whose performance status was 60 or less on the Karnofsky scale.

The mean time from surgery (RN, CN, or NSS) to initiation of systemic treatment was 1703.55 days. The longest time from surgical treatment to systemic treatment occurred in patients who had previously undergone RN, averaging 2605.75 days. In patients who had previously undergone NSS, the mean time from procedure to initiation of systemic treatment was 2523.50 days, while in patients who had previously undergone CN, the mean time from procedure to initiation of systemic treatment was 145.25 days.

The mean duration of treatment with the IPI-NIVO regimen was 195.71 days. The mean number of cycles a patient received was 7.03 cycles. For patients who underwent RN prior to systemic treatment, the mean duration of treatment with the IPI-NIVO regimen was 226.75 days (mean of 8.17 cycles). For patients who underwent NSS prior to systemic treatment, the mean duration of treatment with the IPI-NIVO regimen was 259 days (mean of 9 cycles). For patients who underwent CN prior to systemic treatment, the mean duration of treatment with the IPI-NIVO regimen was 236.13 days (mean of 8.50 cycles). There were no significant statistical differences in the duration of systemic treatment with the IPI-NIVO regimen and the number of treatment cycles among patients who underwent RN, NSS, or CN prior to systemic treatment.

Treatment was discontinued in the combination phase of the IPI-NIVO cycle in 52.94% of patients (n = 18), while 47.06% of patients (n = 16) continued nivolumab therapy in the monotherapy phase. 55.88% of patients included in the study (n = 19) completed systemic treatment with the IPI-NIVO regimen and 44.12% of patients (n = 15) continued treatment after completion of the study. The most common reasons for discontinuation of systemic treatment were drug adverse effects (n = 8, 42.11%), disease progression (n = 7, 36.84%), death due to unrelated causes (n = 2, 10.53%), and other causes (n = 2, 10.53%). Due to treatment discontinuation before the first control point (i.e., after completion of the IPI-NIVO combination phase), 32.35% of patients (n = 11) had no radiological

assessment of treatment response. Radiological diagnostics and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response assessments were successfully completed for 67.65% of patients (23 out of 34). Progression after radiological evaluation was observed in 7 patients (20.59%), stable disease in 6 patients (17.65%), partial response in 8 patients (23.53%), and complete remission in 2 patients (5.88%). After completing treatment with the IPI-NIVO regimen, 23.53% of patients (n = 8) were eligible for subsequent lines of treatment (including cabozantinib).

The age of patients whose tumors progressed during treatment with the IPI-NIVO regimen was compared to the age of patients whose tumors did not progress. The mean age of patients at the start of systemic treatment who experienced tumor progression during treatment with the IPI-NIVO regimen was 55.14 years (range: 46 to 63 years), while the mean age of patients at the start of treatment who did not experience tumor progression during treatment with the IPI-NIVO regimen was 67.37 years (range: 44 to 80 years). A statistically higher incidence of tumor progression was observed in younger patients compared to older patients ($p < 0.001$).

The majority of patients (n = 27, 79.41%) reported adverse events during treatment with the IPI-NIVO regimen, and 19 patients (55.88%) reported more than one adverse event. The most common grade 1 and 2 adverse events on the Common Terminology Criteria for Adverse Events (CTCAE) scale were weakness and fatigue (n = 14, 41.18%), less frequently observed were gastrointestinal toxicity (n = 12, 35.29%), thyroid dysfunction in the form of hypothyroidism or hyperthyroidism (n = 10, 29.41%), hepatic toxicity (n = 8, 23.53%), skin and mucous membrane toxicity (n = 6, 17.65%), renal toxicity (n = 4, 11.76%), significant weight loss (n = 4, 11.76%), cardiac disorders (n = 3, 8.82%), and others (n = 2, 5.88%). The most common CTCAE grade 3 and 4 adverse events included hepatic toxicity (n = 3, 8.82%), cardiac complications (n = 2, 5.88%), gastrointestinal toxicity (n = 1, 2.94%), blood count abnormalities (n = 1, 2.94%), and anaphylactic shock (n = 1, 2.94%). There was no effect of CN performed before initiation of systemic treatment on the occurrence of adverse events during systemic treatment ($p = 0.677$). 41.18% of patients (n = 14) required a delay of the next cycle due to adverse events (n = 11, 78.57%) or random events (n = 3, 21.43%). However, it should be noted that 58.82% of patients (n = 20) did not require an extension of the interval between IPI-NIVO cycles. Importantly, there was no effect of extending the interval between IPI-NIVO cycles on the risk of cancer progression ($p = 0.410$).

The study analyzed the results of basic laboratory tests and body weight at baseline and at the end of treatment with the IPI-NIVO regimen (Tab. 1). Notably, there was a statistically significant increase in liver parameters — alanine aminotransferase (ALT; $p = 0.032$) and total bilirubin ($p = 0.001$) in patients who completed treatment with the IPI-NIVO regimen compared to baseline. There were no statistically significant differences in other laboratory values or body weight between the baseline and the end of treatment with the IPI-NIVO regimen.

The influence of CN prior to systemic treatment on the efficacy of the IPI-NIVO regimen was analyzed in detail. Progression-free survival (PFS) was compared in two groups of patients – those who underwent CN (treatment group, n = 8) and those who had no prior surgical treatment (control group, n = 12). Patients who underwent CN prior to systemic treatment had a mean PFS of 381.38 days (range: 182 days to 696 days), while patients who were not eligible for CN had a mean PFS of 127.17 days (range: 20 days to 529 days). There was a statistically significant difference in the length of PFS between the two groups compared in favour of patients who underwent CN prior to starting treatment with the IPI-NIVO regimen ($p = 0.004$). The number of treatment cycles with the IPI-NIVO regimen was also compared between patients who underwent CN and those who did not. Patients in the treatment group received an average of 8.50 cycles of IPI-NIVO, while patients in the control group received an average of 4.58 cycles of the IPI-NIVO regimen ($p = 0.149$). The influence of CN prior to systemic treatment on the presence or absence of tumor progression during treatment with the IPI-NIVO regimen was also compared. There was no statistically significant effect of CN on the presence or absence of tumor progression during treatment ($p = 0.619$).

The influence of CN before the start of systemic treatment on the occurrence of adverse events during treatment with the IPI-NIVO regimen was analyzed. No effect of CN prior to systemic treatment was found on the occurrence of adverse events during treatment with the IPI-NIVO regimen ($p = 0.629$). The effect of CN on the need to extend the interval between IPI-NIVO cycles was also analyzed. There was no statistically significant effect of CN on the need to extend the interval between IPI-NIVO cycles ($p = 1.00$).

Discussion

Survival outcomes for patients with mRCC have improved significantly in recent years, and combination treatment regimens based on immunotherapy (i.e., a combination of ipilimumab with nivolumab) prolong survival compared to single-drug targeted therapies (e.g. sunitinib) [13]. The IPI-NIVO regimen has become the gold standard in many countries, including Poland, from 2022, when it was reimbursed for the systemic treatment of mRCC in patients with intermediate and poor prognosis, according to IMDC. The impact of CN on the results of oncological treatment of patients with mRCC has been the subject of extensive scientific discussion for many years. From antiangiogenic drugs (e.g., sunitinib) to immunological drugs (e.g., ipilimumab and nivolumab), the role of CN in the treatment of mRCC remains unclear, which is why in the modern era of immunotherapy, many ongoing clinical trials are investigating this issue in detail [14].

Table 1. Laboratory test results at baseline and at the end of ipilimumab and nivolumab (IPI-NIVO) treatment

	N	Mean	Median	Minimum	Maximum	SD	P-value
Body weight (start of treatment) [kg]	34	77.24	79.00	43.00	126.00	17.09	0.502
Body weight (end of treatment) [kg]	34	77.91	76.50	43.00	125.00	17.66	
Hemoglobin (start of treatment) [mmol/L]	34	7.69	7.70	5.20	11.1	1.06	0.456
Hemoglobin (end of treatment) [mmol/L]	34	7.59	7.70	4.60	10.80	1.30	
Hematocrit (start of treatment) [L/L]	34	0.38	0.38	0.28	0.54	0.05	0.696
Hematocrit (end of treatment) [L/L]	34	0.38	0.39	0.26	0.50	0.06	
Platelets (start of treatment) [10'9/L]	34	291.47	275.50	177.00	689.00	107.95	0.242
Platelets (end of treatment) [10'9/L]	34	280.41	250.50	128.00	593.00	116.26	
Neutrophils (start of treatment) [10'9/L]	34	5.59	5.17	1.92	13.56	2.21	0.675
Neutrophils (end of treatment) [10'9/L]	34	5.55	5.55	1.41	13.67	2.06	
Creatinine (start of treatment) [umol/L]	34	126.85	107.00	67.00	761.00	116.85	0.888
Creatinine (end of treatment) [umol/L]	34	119.56	104.00	62.00	387.00	62.83	
ALT (start of treatment) [U/L]	34	19.71	15.00	7.00	52.00	11.67	**0.032**
ALT (end of treatment) [U/L]	34	30.94	18.50	7.00	180.00	36.69	
AST (start of treatment) [U/L]	34	20.74	18.00	8.00	44.00	8.80	0.085
AST (end of treatment) [U/L]	34	28.38	20.50	10.00	181.00	31.48	
Bilirubin (start of treatment) [umol/L]	34	8.88	7.98	4.29	21.00	4.14	**0.001**
Bilirubin (end of treatment) [umol/L]	34	9.40	8.92	3.00	25.72	4.86	
TSH (start of treatment) [uIU/mL]	34	1.67	1.53	0.62	3.70	0.84	0.321
TSH (end of treatment) [uIU/mL]	34	2.26	1.74	0.02	17.69	2.97	
FT3 (start of treatment) [pg/mL]	34	3.52	3.24	1.32	15.31	2.17	0.584
FT3 (end of treatment) [pg/mL]	34	3.67	3.22	2.00	13.63	2.27	
FT4 (start of treatment) [ng/dL]	34	1.41	1.24	0.34	5.17	0.75	0.084
FT4 (end of treatment) [ng/dL]	34	1.60	1.31	0.96	5.65	1.02	

ALT — alanine aminotransferase; AST — aspartate aminotransferase; FT3 — free triiodothyronine; FT4 — free thyroxine; SD — standard deviation; TSH — thyroid-stimulating hormone

The results presented in the study suggest the important role CN plays in the treatment of mRCC. A statistically significant prolongation of PFS was observed in patients who underwent CN prior to IPI-NIVO treatment compared to patients who did not undergo CN. The above results are consistent with other scientific studies. Kumada et al. [15] also showed that performing CN prior to systemic treatment significantly prolonged PFS. A total of 137 patients with mRCC were included in the retrospective analysis. In the group of patients who did not undergo CN before systemic treatment (group I), the median PFS was 5 months, while in the group of patients who underwent CN before systemic treatment (group II), the median PFS was 13 months ($p = 0.006$).

The study showed no effect of CN on the incidence of adverse events during systemic treatment ($p = 0.629$). This means that CN does not reduce the quality of life of patients with mRCC who underwent CN compared to patients who did not undergo surgical treatment. There are few literature reports describing the impact of CN on the quality of life of patients with mRCC. Larcher et al. [16] analyzed the treatment history of 317 patients with mRCC between 1988 and 2019. It was shown that 43% of patients who underwent CN reported complete relief of symptoms, and 71% of patients reported an improvement in their overall health after the procedure [16]. To draw reliable conclusions about the impact of CN on patients' quality of life, a prospective assessment is needed immediately after the procedure and several weeks and months after surgery.

Renal cancer is an important source of antigens that can stimulate the immune system, thereby increasing the efficacy of immune checkpoint inhibitors (such as IPI-NIVO). Studies have shown that renal cancer is highly immunogenic, meaning it has a high ability to induce an immune response due to

the presence of multiple tumor-specific antigens. These antigens can activate immune cells and increase their ability to target and destroy cancer cells. The presence of tumor-associated antigens can lead to increased infiltration of immune cells, such as T-cells, which are key to the anti-tumor response. This immune activation is further modulated by immune checkpoints such as PD-1/PD-L1, which can be targeted by immune checkpoint inhibitors (such as IPI-NIVO) to enhance the immune response against the tumor [17, 18]. The above arguments argue against performing CN in patients treated with IPI-NIVO because the presence of the tumor as a source of antigens is crucial for stimulating the immune system, and improving the results of treatment with IPI-NIVO in the treatment of mRCC.

Patients diagnosed at a younger age had a statistically higher rate of mRCC progression during treatment compared to patients diagnosed at an older age ($p < 0.001$). Due to the small number of patients included in the study, these results should be interpreted with caution. Literature reports show that the prognosis of older patients with mRCC is worse compared to younger patients, mainly due to more frequent comorbidities, poorer physical condition, as well as potentially higher toxicity of drugs used in older patients [19, 20]. Clarification of the issue of age in the context of treatment planning seems to be a very important aspect. Perhaps the age of patients should become an independent prognostic factor on which the qualification for certain systemic therapies should depend. This requires further prospective and randomized scientific analyses. Further research is needed to refine therapeutic strategies and improve survival rates in different age groups of patients eligible for systemic treatment of mRCC.

The results obtained in this study are promising, but need to be continued in order to draw more precise conclusions. Due to limited literature data, further studies are needed to evaluate the role and validity of performing CN in patients with mRCC treated with the IPI-NIVO regimen. From a clinical point of view, it is also important to find the best time to perform CN (before or after starting IPI-NIVO therapy). If it is determined that systemic therapy prior to CN is optimal, the duration of systemic therapy prior to CN needs to be determined. This will allow for further prospective randomized trials to evaluate the role of CN in the treatment of patients with mRCC.

The conducted study is not without limitations. The main limitation is its retrospective nature and the small number of patients included in the study. In addition, all patients were treated at a single center, which also reduces the scientific value of the study. What is more, there was no comparative analysis between patients who underwent CN prior to systemic treatment and patients who underwent CN after initiation of systemic treatment with IPI-NIVO.

Conclusions

There is no clear effect of CN on the course of mRCC treatment. The decision to perform CN should always be made by a multidisciplinary oncology team, including a urologist, oncologist, and radiation therapist, after discussing the potential benefits and risks of the procedure with the patient. Appropriate selection of patients suitable for CN is critical to achieving optimal outcomes of cancer treatment.

The results obtained in this study are promising, but need to be continued in order to draw more precise conclusions. Due to limited literature data, further studies are needed to evaluate the role and validity of performing CN in patients with mRCC treated with the IPI-NIVO regimen. From a clinical point of view, it is also important to find the best time to perform CN (before or after starting IPI-NIVO therapy). If it is determined that systemic therapy prior to CN is optimal, the duration of systemic therapy prior to CN needs to be determined. This will allow for further prospective randomized trials to evaluate the role of CN in the treatment of patients with mRCC.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author, Maciej Michalak.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. The opinion of the Ethics Committee was obtained that there were no features of a medical experiment.

Author contributions

Maciej Michalak — conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing — original draft preparation.

Anna Kopczyńska — conceptualization, formal analysis, methodology, writing — original draft preparation.

Andrzej Antczak — conceptualization, formal analysis, investigation, supervision, writing — review & editing.

Tomasz Milecki — formal analysis, methodology, writing — original draft preparation.

Piotr Tomczak — conceptualization, formal analysis, investigation, methodology, project administration, supervision, writing — review & editing.

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Conflict of interest

None declared.

Supplementary material

None.

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Review article

Colorectal cancer

The role of transanal total mesorectal excision (TaTME) in the surgical treatment of rectal cancer

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Transanal total mesorectal excision (TaTME) is an innovative surgical approach for treating mid- and low-rectal cancers. The method offers several distinct advantages that make it superior to traditional techniques, with the principal benefits being better visualization and improved access to the lower pelvis. In this paper, we review the general assumptions of this method, with particular emphasis on the two-team (Cecil) approach. We also summarize our own experiences with the use of TaTME. Our experiences suggest that TaTME provides satisfactory oncological outcomes similar to those obtained with other commonly recognized surgical techniques. Moreover, TaTME is widely accepted by patients, especially those wishing to preserve their anal sphincters. However, more multicenter studies are needed to define objective indications for TaTME and to ultimately standardize the surgical technique, as published evidence suggests that many aspects of this procedure vary substantially from center to center.

Keywords: rectal cancer, TaTME, surgical technique

Introduction

Rectal cancer remains a challenge for oncology surgeons. The dynamic development of surgical techniques observed within the last 40 years, after Heald introduced the principles of total mesorectal excision (TME), has not ended. Newly emerged surgical procedures have many supporters but also some opponents. Treatment outcomes obtained with these methods can be verified objectively with multicenter studies, which results in the introduction of new surgical treatment standards. Attempts to verify the outcomes of rectal cancer treatment were also undertaken in Poland [1, 2]. During the previous decade, a new technique for rectal cancer surgery, the transanal total mesorectal excision (TaTME) proposed by Lacy, has been the subject of an ongoing debate within the Polish surgical community. Below, we present the general assumptions of this method and our own experiences with the use of TaTME at the Lower Silesian Oncology, Pulmonology and Hematology Center in Wroclaw (Poland).

Benefits of TaTME

Transanal total mesorectal excision has emerged as an innovative surgical approach for the treatment of mid- and low-rectal cancers. The method offers several distinct advantages that make it superior to traditional techniques, such as laparoscopic or open TME. One of the key benefits of TaTME is its ability to provide enhanced visualization and access to the lower pelvis. Approaching the rectum transanally, surgeons gain a direct view into the mesorectum from below, which is particularly advantageous in patients with challenging pelvic anatomy, i.e. those with a narrow pelvis, obesity, or bulky tumors. The improved access offered by TaTME facilitates a more accurate dissection of the distal rectum, with the resultant improvement

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in the quality of the mesorectal excision and clearer circumferential and distal margins [3]. As a result, TaTME is associated with lower rates of incomplete resections and positive circumferential resection margins — two factors that are crucial for minimizing local recurrence of rectal cancer [4, 5].

Aside from the oncological benefits mentioned above, TaTME has demonstrated superior outcomes in sphincter preservation. Due to its accuracy, the transanal approach allows the surgeon to dissect tumors located in close proximity to the anal canal more carefully, thus reducing the demand for a permanent colostomy. This benefit is particularly important in the case of patients with low-rectal tumors, in whom traditional approaches might necessitate a more radical surgery, such as abdominoperineal resection (APR) [6]. Preserving the sphincter, TaTME contributes to better postoperative functional outcomes, particularly in terms of continence and overall quality of life [7].

Furthermore, TaTME has been associated with lower conversion rates to open surgery than conventional laparoscopic approaches. The minimally invasive nature of TaTME reduces the need for conversion and contributes to shorter recovery times, decreased postoperative pain, and reduced duration of hospital stay [3]. A combination of transanal and transabdominal techniques allows for a more comprehensive and accurate resection, minimizing the risk of complications and wound infections [4].

In patients with locally advanced rectal cancers, TaTME offers an opportunity for a tailored approach, adjusted for complex pelvic anatomy and challenging tumor location. The ability to address tumors in the deep pelvis or those involving adjacent structures makes TaTME a versatile option in complex oncological cases [3]. Overall, the advantages of TaTME, such as improved access, higher rates of sphincter preservation, reduced conversion to open surgery, and faster recovery, make it an increasingly preferred option in the surgical treatment of rectal cancer.

Indications and contraindications for TaTME

Indications

Transanal total mesorectal excision is primarily indicated for the surgical management of rectal cancer, particularly in patients who present with the following characteristics:

1) mid- to low-rectal cancer:
— TaTME is highly suitable for patients with rectal cancers located in the mid to distal rectum (within 10 cm from the anal verge). The technique allows for superior visualization and accurate dissection in this anatomically confined space [4, 6];
2) challenging pelvic anatomy:
— patients with a narrow pelvis, obesity, or male sex can present a technical challenge in the case of conventional laparoscopic or open surgery. Transanal total mesorectal excision offers improved access to the lower rectum, making it a preferable option in such cases [4, 5];
3) locally advanced rectal cancer:
— patients with stage II or III rectal cancer who require neoadjuvant chemoradiotherapy prior to surgery can benefit from TaTME. This approach allows for better mesorectal excision with negative resection margins, both crucial determinants of outcome in advanced cases [3, 4];
4) patients requiring sphincter-sparing surgery:
— in patients with low-rectal cancer who are candidates for sphincter-sparing surgery, TaTME allows for more accurate dissection of the rectum in close proximity to the anal canal, increasing the likelihood of preserving continence and avoiding a permanent colostomy [6, 7];
5) multidisciplinary cancer care:
— TaTME is often employed as part of a multimodal treatment plan involving neoadjuvant therapy, multidisciplinary discussion, and careful patient selection to maximize oncological outcomes [8].

The role of anorectal manometry

While anorectal manometry is not a primary indication for TaTME, it can be an essential tool in the preoperative assessment of patients, especially those with low-rectal cancers considered for sphincter-preserving surgery. In such cases, anorectal manometry is used to evaluate the function of the anal sphincters, rectal sensitivity and coordination — crucial factors for maintaining postoperative continence.

Key scenarios in which manometry is useful:

1) sphincter-sparing surgery:
— in patients with low-rectal tumors located close to the anal canal who desire sphincter preservation, manometry is helpful in assessing sphincter integrity and function. In patients with poor sphincter function (e.g. low anal resting pressure or weak squeeze pressures), the risk of postoperative incontinence may be high. Therefore, if the patient presents with poor sphincter function, a more radical surgery, such as APR, might be recommended instead of TaTME to avoid complications related to impaired continence [6, 7];
2) preoperative evaluation of functional outcomes:
— manometry can guide the surgical decision-making process, providing information about baseline anorectal function, especially in patients with pre-existing anorectal dysfunction. Manometry is helpful in identifying patients with potentially increased risk of poor functional outcomes after TaTME, such as fecal incontinence, and allows the surgical team to adjust the treatment plan accordingly [5];
3) non-oncological indications (functional disorders):
— in rare instances, TaTME may be considered a treatment option in complex benign conditions, such as recurrent rectal prolapse. In such cases, anorectal manometry can help assess sphincter competence and anorectal function to determine whether the procedure would be beneficial or should be replaced by an alternative approach [3].

Contraindications

Despite its previously discussed advantages, TaTME is contraindicated in several clinical scenarios in which the risks may outweigh the benefits:

1) locally unresectable tumors:
— tumors that have invaded adjacent organs or structures, e.g. the bladder, prostate, or sacrum, are not amenable to TaTME, as the approach does not provide sufficient access for multivisceral resections required in such cases [4];
2) high-rectal tumors:
— tumors located in the upper rectum (more than 10 cm from the anal verge) are generally managed better with conventional laparoscopic or open TME. As mentioned before, the advantages of TaTME are primarily limited to tumors located in the mid and low rectum [5, 6];
3) severe comorbidities or poor surgical candidates:
— patients with significant cardiovascular and respiratory comorbidities or other systemic conditions that severely limit their ability to tolerate surgery should not undergo TaTME. While as minimally invasive as it may be, TaTME is still a complex procedure that requires prolonged anesthesia and meticulous postoperative management [7];
4) previous extensive pelvic surgery or radiation:
— patients with extensive adhesions from previous surgeries or those with a history of multiple rounds of pelvic radiation may not be ideal candidates for TaTME. Scar tissue formation and fibrosis can significantly limit the technical advantages of the transanal approach in such cases, increasing the risk of complications [8];
5) advanced anastomotic techniques required:
— when performing an anastomosis involves a high degree of complexity (e.g., intersphincteric resection), alternative approaches may be more applicable, as TaTME does not always facilitate an optimal anastomotic technique in such challenging cases [3].

The two-team approach (Cecil approach) — a collaborative surgical revolution

In the ever-evolving field of rectal cancer surgery, TaTME has redefined the way surgeons approach complex pelvic anatomy. At the heart of this innovation is the two-team approach, also referred to as the Cecil approach, where two surgical teams, one working abdominally and another working transanally, collaborate in real-time to optimize the outcomes. The Cecil approach has been gaining widespread attention not only for its efficiency but also for the precision and finesse it brings to the operating table.

The two-team approach is very demanding logistically and requires excellent coordination of work between both teams, the one operating from the bottom and the one operating from the abdominal side (Fig. 1).

Two surgical teams operate in coordination, with their efforts converging on the tumor from both the abdominal and transanal approaches. The abdominal team carefully navigates the upper rectum and colon, releasing tissues and managing blood supply. Meanwhile, the transanal team works from below, meticulously dissecting the rectum near the tumor to obtain clean, safe resection margins. This synchronized choreography allows for a dual approach to tackling rectal cancer, and the results have been transformative.

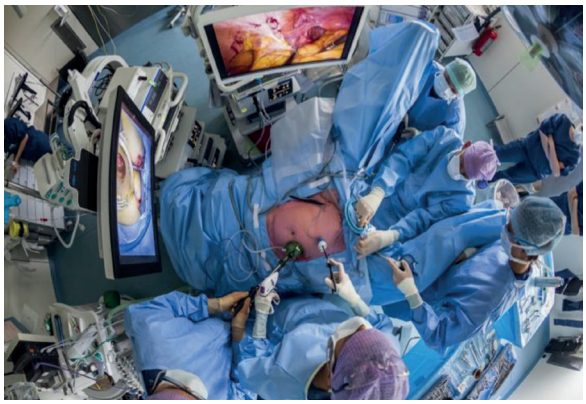

Figure 1. Transanal total mesorectal excision (TaTME) using the two-team (Cecil) approach

The efficiency of two hands over one

The most striking benefit of the two-team approach is its impact on operation time. During a conventional surgery, one team performs the procedure in a step-by-step manner, whereas in the Cecil approach, both teams operate simultaneously. This significantly reduces the overall duration of the surgery, which is beneficial both for the surgical team and for the patient who spends less time under anesthesia [4]. Shorter time in the operating room corresponds also to fewer risks and faster recovery. Using the two-team approach, surgeons can achieve the same goals in a markedly shorter time without compromising the quality of the procedure.

Enhanced visualization — two perspectives, one objective

Perhaps one of the greatest challenges in rectal surgery is the necessity of navigating within the confined space of the pelvis, especially in patients with complex anatomies, i.e. those with a narrow pelvis or suffering from obesity. The two-team approach provides surgeons with an unmatched view of the surgical field. While the abdominal team dissects the colon and upper rectum from above, the transanal team obtains unprecedented access to the lower rectum and mesorectum. This dual visualization reduces the risk of incomplete resections and increases the precision of the procedure, especially in patients with low-rectal tumors in whom achieving clear resection margins is of utmost importance [4, 6].

By approaching the tumor from both sides, surgeons can avoid "tunnel vision," a common problem during single-team

operations. Instead, the operators have access to a widely open surgical field, which allows them to perform a more comprehensive and controlled dissection of the tumor and surrounding tissues.

Oncological and functional mastery

One of the paramount concerns in rectal cancer surgery is achieving clear circumferential and distal margins, which is key to reducing the risk of local recurrence. The two-team approach, involving simultaneous abdominal and transanal dissection, and improves the accuracy of the resection margins. In particular, the ability of the transanal team to dissect tissues from below contributes to cleaner distal margins, a crucial factor for reducing cancer recurrence and improving long-term outcomes [7].

The use of the two-team approach also increases the likelihood of preserving anal sphincters in low-rectal tumors. In patients in whom sphincter-sparing surgery is an option, the transanal approach improves control and precision of dissection near the sphincters. This translates into better functional outcomes, particularly in terms of continence, allowing patients to avoid a permanent colostomy and improving their quality of life post-surgery [3, 7].

Tailoring surgery for complex cases

For patients with challenging pelvic anatomies, such as a narrow male pelvis, obesity, or the presence of bulky tumors, the two-team approach offers a strategic advantage. The simultaneous effort of both teams allows them to overcome the space constraints more easily. While the abdominal team creates a space and mobilizes tissues from above, the transanal team works meticulously from below to access and dissect tissues that would otherwise be difficult to reach [5]. This dual approach opens up the pelvis in a way that could not be achieved by a single team operating from just one side.

Relieving surgeon's fatigue — a collaborative benefit

The reduction of surgeon's fatigue is a frequently overlooked advantage of the two-team approach. Transanal total mesorectal excision is a technically demanding procedure that can last several hours when performed by a single team. With the Cecil approach, the workload is split between two teams. Surgeons working in tandem can maintain their concentration and precision for the duration of the procedure, which leads to better outcomes for the patient and less exhaustion for the operating team [3].

Two teams, one goal

The two-team (Cecil) approach in TaTME represents remarkable progress in rectal cancer surgery, whereby collaborative speed and precision translate into superior clinical outcomes. By allowing two teams to work in parallel, the Cecil approach reduces operating time, facilitates visualization, and improves oncological and functional outcomes. In patients with complex and challenging pelvic anatomies, the Cecil approach was demonstrated to be an innovative solution. It allows the surgeons to achieve their goals with greater efficiency yet without compromising the patient's safety.

With the two-team approach, rectal cancer patients are more likely to benefit from sphincter preservation, faster recovery, and, ultimately, cancer-free survival.

Surgical steps

Abdominal approach:

1) patient positioning:
— the patient is placed in a lithotomy position with legs raised, providing access to both the abdomen and the perineum;
2) pneumoperitoneum and trocar placement:
— the abdominal team creates a pneumoperitoneum (insufflation of the abdomen with CO_2) and inserts laparoscopic or robotic trocars for instrument access;
3) mobilization of the sigmoid colon:
— the abdominal team mobilizes the sigmoid colon by incising the lateral peritoneal attachments. this ensures adequate mobilization of the colon for later anastomosis;
4) ligation of the inferior mesenteric vessels:
— the inferior mesenteric artery and vein are identified and ligated to ensure proper blood supply to the remaining colon and to provide adequate mobility of the bowel;
5) dissection of the upper rectum and mesorectum:
— the abdominal team begins the dissection of the upper part of the rectum, releasing the mesorectum from the surrounding tissues while protecting critical structures, such as the hypogastric nerves and ureters;
6) division of the sigmoid colon:
— once sufficient mobilization is achieved, the sigmoid colon is divided using a surgical stapler, preparing it for eventual anastomosis.

Transanal approach:

1) placement of the transanal platform:
— a specialized transanal platform (e.g. GelPOINT or SILS port) is inserted into the anal canal, providing access for instruments and visualization;
2) circumferential mucosal incision:
— the transanal team makes a circumferential mucosal incision at the rectal level below the tumor (Fig. 2), to facilitate accurate dissection of the distal part of the tumor;
3) dissection of the mesorectum:
— the mesorectum is carefully dissected in a "bottom-up" approach. the transanal team works toward the abdominal team's dissection, ensuring a total mesorectal excision and maintaining clear resection margins;
4) transanal transection of the rectum:
— once the rectum is thoroughly dissected and mobilized, the transanal team transects the rectum below the tumor

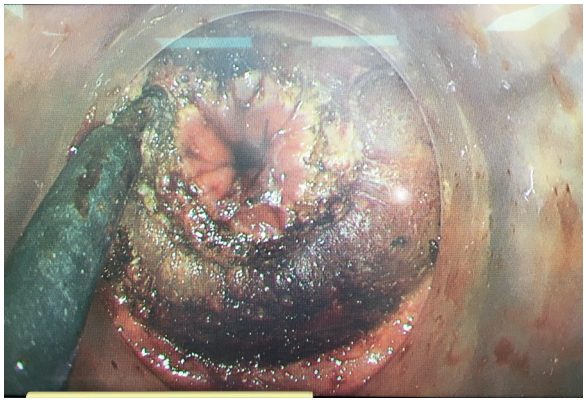

Figure 2. Circumferential mucosal incision at the rectal level performed by the transanal team during transanal total mesorectal excision (TaTME) using the two-team (Cecil) approach

using a surgical stapler or scalpel, depending on the tumor's location;

5) connection with abdominal dissection:

— the transanal and abdominal dissections meet in the middle, completing the full mobilization of the rectum and mesorectum;

6) extraction of the specimen:

— the tumor and the surrounding rectal tissue are typically removed transanally, minimizing trauma to the abdomen and reducing the size of any necessary incisions.

Final steps:

1) colorectal anastomosis:

— after the tumor is excised, the two teams work in coordination to create a colorectal anastomosis, often using a circular stapler, reconnecting the healthy ends of the colon to restore bowel continuity;

2) protective ileostomy (if needed):

— in some cases, a temporary diverting ileostomy is created to protect the anastomosis and to facilitate its appropriate healing, thus reducing the risk of complications;

3) closure:

— the transanal platform is removed, and the abdominal incisions are closed. the patient is then prepared for postoperative recovery.

Our own experiences with TaTME

In our material patients with rectal cancers located up to 6 cm from the anorectal junction (AJ) and normal sphincter function have been qualified for TaTME at the Department of Oncological Surgery, Lower Silesian Oncology, Pulmonology and Hematology Center in Wroclaw (Poland). Patients with tumors located more than 6 cm from the AJ were qualified for standard surgical techniques using the abdominal approach. In our opinion, extending the indications for TaTME to tumors in other locations and with non-malignant conditions, as reported at some centers abroad, is unnecessary.

The first TaTME at the Lower Silesian Oncology, Pulmonology and Hematology Center was performed on May 5, 2016. Until the end of September 2024, 237 TaTME procedures have been performed on 165 men (69.6%) and 72 women (30.4%) aged between 26 and 86.

The group of patients qualified for TaTME included 226 with rectal cancer, 7 with benign rectal polyps that could not be treated endoscopically, 3 with rectal neuroendocrine tumors (NET), and 1 with a submucosal tumor. The tumors represented groups I-III according to the Rullier classification [8]. The average distance of the tumor from the AJ was 2.92 cm, with a range from 0 cm to 6 cm.

Published evidence suggests that obese patients and men are the groups that benefit most from TaTME [9]. The average body mass index (BMI) of patients operated on using TaTME at our center was 26.58 kg/m^2, with a range from 17.75 kg/m^2 to 41.28 kg/m^2.

The qualification for preoperative treatment, conducted by a multidisciplinary team, was based on guidelines published by various scientific bodies, including the Polish Society of Clinical Oncology (PTOK), Polish Society of Surgical Oncology (PTChO), European Society for Medical Oncology (ESMO), and the European Society of Surgical Oncology (ESSO). Based on clinical data, 172 patients were qualified for preoperative treatment. The remaining patients were qualified directly for TaTME, either as a primary surgery (n = 50) or as a secondary procedure after an initial non-radical local excision of the rectal tumor (n = 15). Patients qualified for neoadjuvant treatment received standalone radiotherapy 5 × 5 Gy (n = 91), radiotherapy combined with chemotherapy (n = 79), or standalone chemotherapy (n = 2).

Early outcomes of TaTME in our group were similar to those obtained with classical TME performed either via open or laparoscopic techniques, which is consistent with the results published by other authors [10, 11]. Subradical resection (R1) was obtained in only 5 (2.1%) patients operated on using TaTME, with the remaining 232 (97.9%) patients satisfying the criteria of radical resection (R0).

Low anterior resection syndrome (LARS) appears to be an important clinical issue in patients subjected to TaTME. According to the literature, LARS may occur in up to 76% of patients operated on using TaTME, with the primary risk factor being the distance between the tumor and the AJ [12]. However, despite performing very low anterior rectal resections (with a mean distance between the anastomosis and AJ of 2.5 cm), we did not observe an increased incidence of LARS in our material. Thus, the true frequency and the exact causes of LARS as a potential frequent complication of TaTME should be addressed in detail in future studies.

Conclusions

Transanal total mesorectal excision is a valuable option for the surgical treatment of rectal cancers and extensive polyps

of the lower rectum. In selected cases of rectal cancer, TaTME may constitute an alternative to abdominosacral (ASAR) or perineal (APR) resection of the tumor. However, it needs to be emphasized that TaTME is a demanding, minimally invasive technique with a long learning curve. Our own experiences suggest that TaTME provides satisfactory oncological outcomes similar to those obtained with other commonly recognized surgical techniques. Moreover, TaTME is widely accepted by patients, especially those wishing to preserve their anal sphincters. Despite performing very low anterior rectal resections, we did not observe an increased incidence of LARS, which was reported by other authors as a common complication of TaTME. While TaTME is used in many clinics, the principles of patient qualification and many technical aspects vary from center to center. Thus, more multicenter studies are needed to define objective indications for TaTME and to ultimately standardize this surgical technique.

Article information and declarations

Data availability statement

The data have not been published in any other journal.

Ethics statement

The study was conducted with the approvalof the Bioethics Committee of the Wrocław Medical University.

Author contributions

Marek Bębenek — conceptualization, investigation, methodology, supervision, writing — original draft preparation, writing — review & editing.

Michał Kazanowski — data curation, investigation, methodology, writing — original draft preparation.

Bartosz Kapturkiewicz — formal analysis, investigation, resources, validation, writing — original draft preparation.

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Conflict of interest

None declared.

Supplementary material

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Review article

Tumor biology

The phenomenon of the *BRAF* and *TERTp* mutational duet in melanoma and other cancers

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The unique oncogenic duo of *BRAF* and *TERT* promoter (*TERT*p) variants was demonstrated to be associated with aggressiveness and poor prognosis in several different cancer types, including melanoma and thyroid cancer. It has been shown that the coexistence of *BRAF* and *TERT*p variants has a significantly more substantial impact on clinical outcomes than the presence of mutated *BRAF* or *TERT*p alone. At the same time, the co-occurrence of *BRAF* and *TERT*p variants may also be the Achilles Heel of cancer cells in the context of targeted therapies' effectiveness. This paper aims to summarize data from tumors in which clinically significant variants in *BRAF* and *TERT*p were documented as prognostic or predictive markers.

Keywords: *BRAF*, *TERT*p, melanoma, thyroid cancer, glioma

Introduction

Cutaneous melanoma (cuMM) represents only 4% of all skin cancers. However, it is responsible for 80% of all skin cancer deaths, which makes it the most lethal of all primary cutaneous neoplasm types. In the last few decades the cuMM incidence rate has risen steadily worldwide among light-skinned populations. The National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) database ranked melanoma of the skin in 5th place of frequency for 2024, estimating it will account for 5% of all new cancer cases in the United States [1]. In Poland, in turn, according to the World Health Organization (WHO) statistics, cuMM was the 16th most common cancer type in men and women in 2022 [2]. While increase of cuMM incidence is still substantial in most European countries, in several high-risk countries, like Australia, a decrease/stabilization in melanoma incidence has been reported, thanks to effective public health campaigns and increased sunscreen accessibility [3].

Early cuMM detection is critical since it gives a better prognosis. According to the SEER database, the 5-year relative survival rate for melanoma skin cancer is 100% when it is localized. However, the 5-year relative survival drops to 74% and 35% in regional and distant cuMM, respectively [1]. Until recently, cuMM was considered a cancer that is highly resistant to traditional treatment involving surgical resection of the lesion and adjuvant treatment (chemo- and radiotherapy). Nevertheless, a better understanding of the biology of melanoma and the introduction of targeted therapies and immunotherapy have significantly improved the effectiveness of therapeutic approaches in recent years. That said, there is a strong need for biomarker identification that would enable the usage of personalized medicine that can be individually tailored to the patient and/or tumor. An ideal solution would be to identify unique molecular markers that would improve patients' diagnostics and/or risk stratification and treatment. However, published data show that many oncogenic drivers

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are common for different tumor types and do not segregate by organ of tumor origin. These observations provide new opportunities in therapies by classifying cancers based on genomic aberrations and using similar molecular therapeutic approaches regardless of tumor histology. This has allowed the development of so-called tumor-agnostic targeted therapies that use the same drug to treat different cancer types with the same genetic variant detected [4]. To date, six molecular markers have achieved tissue-agnostic indications in patients with advanced solid tumors. Among them, there is a *BRAF* variant, NM_004333.6(*BRAF*):c.1799T>A (p.Val600Glu) (from now on referred to as the *BRAF* V600E variant), the presence of which is related to the possibility of applying a combination of BRAF and MEK inhibitors. This therapy is used primarily in melanoma and anaplastic thyroid cancer. The presence of *NTRK* fusions in solid tumors, in turn, allows the use of larotrectinib or entrectinib that targets TRK (tyrosine kinase domain). The other biomarkers mentioned above include *RET* fusions, mismatch repair deficiency (dMMR), HER2 overexpression, and TMB-high (tumor mutation burden) [4, 5].

In the following review, we will focus on two molecular markers that co-occur in different cancer types, including melanoma, and are used as diagnostic, prognostic, and predictive markers: *BRAF* V600 pathogenic variants with emphasis on the *BRAF* V600E one and *TERT* promoter (*TERT*p) pathogenic variants. These two genes are mutated in a variety of different cancer types and have been associated with aggressiveness and poor prognosis. However, even though their prognostic role in some cancers is beyond doubt, in others, it is still a matter of debate.

BRAF as an oncogene

BRAF is one of the most commonly mutated and best-known oncogenes in human tumorigenesis. BRAF kinase belongs to the RAF family of serine/threonine kinases, and is a part of the mitogen-activated kinase pathway (MAPK), altered in most cancers. Its activation results from a ligand binding to receptor tyrosine kinases (RTKs), followed by RTKs phosphorylation that leads to RAS GTPases activation and dimerization of RAF family members. Activated RAF kinases, including BRAF, trigger activation of MEK1/2 and ERK1/2 kinases, leading to direct and indirect regulation of transcription of genes involved in cell proliferation and survival [6].

Germline pathogenic variants in the *BRAF* gene are rarely observed and are associated with developmental syndromes termed RASopathies, like Noonan and LEOPARD syndromes, but mainly the cardiovascular-cutaneous (CFC) syndrome. *BRAF* germline activating variants are present in 50–75% of patients with CFC syndrome [7, 8]. It is a rare autosomal dominantly inherited disorder characterized by several birth defects, including a distinctive facial appearance, short stature, ectodermal tissue abnormalities, congenital heart defects, gastrointestinal motility disorders, and intellectual disability. There are isolated reports in the literature indicating a germline mutation of the V600 variant in CFC syndrome. Most observed germline variants of the *BRAF* gene typically involve codons other than V600, and are characterized by milder ERK/MAPK pathway activation. Analyses performed on cell lines show that germline *BRAF* variants present reduced transforming capability compared to the most frequent somatic *BRAF* V600E mutation, and have less potency in deregulating BRAF function [7]. In turn, somatic variants of the *BRAF* gene are strong oncogenic events reported in aggressive and indolent tumors — solid and liquid — in both children and adults. The frequency of *BRAF* oncogenic variants in human malignancies is reported at 6% [9]. These are the most prevalent molecular alterations in melanoma (40–60% of cases), hairy cell leukemia (circa 100% of patients), and papillary thyroid carcinoma (PTC; 29–83% of cases) [10–12]. *BRAF* V600 variants are reported to be present also in many other cancers, including cholangiocarcinoma, colorectal cancer, chronic lymphocytic leukemia, glioblastoma, GIST (gastrointestinal stromal tumors), lung cancer adenocarcinoma, ovarian cancer, kidney cancer, pancreatic cancers and others [13]. More than 200 *BRAF*-mutant alleles have been discovered, with 30 variants functionally characterized [14]. *BRAF* V600E is the most common one (accounts for 70–90% of all *BRAF* variants) and has the highest oncogenic potential. This alteration and other variants within the 600 codon belong to class 1 *BRAF* variants, which are RAS-independent and enable BRAF kinase to function as an active monomer [15]. Although *BRAF* V600E presence is usually related to a more aggressive course of cancer, it is not only present in malignant tumors. It has been reported in some benign lesions and neoplasms of low malignant potential, like endosalpingiosis [16], metanephric adenoma [17], Erdheim-Chester disease, and Langerhans cell histiocytosis [18] or papillary craniopharyngioma [19]. *BRAF* V600E is also present in about 80% of melanocytic nevi, suggesting that it is insufficient alone to drive oncogenesis [20]. It is well known that despite the mutated BRAF kinase activity, most melanocytic nevi remain harmless over the course of an individual's lifetime. It has been indicated that oncogenic *BRAF* plays a dual role: induce hyperproliferation and subsequent cell cycle arrest. This intriguing duality in the role of oncogenic *BRAF* adds a layer of complexity to our understanding of cancer biology. The prevalent theory explaining this phenomenon is oncogene-induced senescence (OIS), with elevated expression of p16INK4a and other cyclin-dependent-kinase inhibitors. However, the term "senescence", conventionally defined as permanent cell-cycle arrest, has been questioned for the proliferation arrest of melanocytic nevi because nevus recurrence and transformation to primary melanoma is associated with cell cycle re-entry. McNeal et al. [21] identified that *BRAF* V600E induces a reversible arrest in human melanocytes directed by MIR211-5p/MIR328-3p regulation of *AURKB* (aurora

kinase B) and conditional on the melanocyte differentiation state (differentiated melanocytes *vs.* melanocyte progenitor or stem cells). The Aurora B kinase, as an enzymatic component of the Chromosomal Passenger Complex, plays a critical role in cell division, but also cell cycle checkpoint, DNA damage response by interaction with p53, and normal physiological processes. Overexpression and amplification of Aurora B have been observed in several human cancers, including melanoma, and predict tumor recurrence and poor prognosis [22]. McNeal et al. [21] suggested that acquiring the *BRAF* V600E variant permits melanocytes to switch between hyperproliferation and mitotic arrest. Moreover, many studies have shown that in most tumors with *BRAF* variants, inactivation of tumor suppressor genes is essential for malignant transformation [23–25].

TERT as an oncogene

The *TERT* gene encodes the telomerase's catalytic subunit, which regulates telomeres' length. The telomerase activity is silenced in most normal cells, which is related to the shortening of telomeres in each round of cell division until a critical length is reached and the cell enters replicative senescence. The number of cell divisions before the senescence is known as the Hayflick limit [26–28]. Telomerase expression is maintained in selected cells, like stem-like cells and germ cells. In cancer cells, telomerase reactivation is a known hallmark of tumorigenesis, as more than 90% of all human cancers express this enzyme [29]. *TERT* induction leads to telomerase activation, which, by stabilizing the length of telomeres, gives cancer cells unlimited proliferative potential. Recent studies indicated additional telomere-independent, oncogenic TERT functions. These include the impact on non-telomeric DNA damage responses, promotion of cell growth and proliferation, control of mitochondrial integrity following oxidative stress, and participation in the transcriptional regulation of gene expression [30]. TERT was found to interact with β-catenin, which stimulates epithelial-mesenchymal transformation (EMT), stemness of cancer cells, and thereby cancer metastasis and recurrence [31]. Moreover, via interaction with NF-kappaB p65, TERT is involved in the up-regulation of metalloproteinases (MMPs) expression, contributing to cancer progression [32]. Those mentioned above and many more TERT molecular linkages and mechanisms of action indicate its strong involvement in multiple cancer hallmarks.

The reactivation of TERT in most tumors is mainly a consequence of *TERT*p variants and focal amplification/rearrangements [33]. The most common *TERT*p variants are C>T transitions, located at hot spots -124 bp and -146 bp from the transcription start site, referred to as NM_198253.3(*TERT*):c.-124C>T (from now on referred to as C228T variant) and NM_198253.3(*TERT*):c.-146C>T (from now on referred to as C250T variant), respectively. These variants were initially found in 2013 and reported in 71% of melanoma cases [34, 35]. It has been indicated that C228T and C250T affect *TERT* expression, telomerase activity, and telomere length. Both these alterations generate an 11 bp nucleotide fragment, "CCCGGAAGGGG", that provides a new binding site for E-twenty-six (ETS) family transcription factors [34, 36]. Not long after the discovery, *TERT*p variants were reported as frequent in several different tumor types, including 83% of glioblastoma [37], 66% of bladder cancer [38], and 47% of hepatocellular carcinoma (HCC) [39]. There is a clear separation in the frequency of *TERT*p alterations between tumors with high and low proliferative potential [36]. *TERT*p variants are more prevalent in tumors with low proliferative potential, like the melanoma mentioned above, glioblastoma, bladder cancers, and HCC, and less frequent in tumors that have high proliferative potential like breast cancer (0.9%) [40], testicular germ cell tumors (~3%) [41], and myeloid malignancies [42]. So far, *TERT*p variants have been reported in more than 50 distinct cancer types. These two hot spot alterations are believed to be a secondary genetic event following the deregulation of MAPK or Wnt signaling pathways [43]. Moreover, a recent study by Zarif et al. [44] demonstrated that the prevalence of *TERT*p variants varies among patients with different cancer types based on race and sex [44]. The authors observed a higher frequency of *TERT*p variants in melanomas of patients self-reported as White compared to melanomas of patients self-reported as Asian and Black. However, Asian patients had more often *TERT*p-mutated head and neck cancer than White patients. Regarding the association with sex, in males, *TERT*p variants were more frequent in melanoma, hepatobiliary, and thyroid cancers compared to females. In contrast, females were more enriched for *TERT*p variants than males for head and neck cancer.

BRAF and *TERT*p variants separately and as a molecular duet in cutaneous melanoma

Most *BRAF* variants in melanoma are missense ones determining amino acid substitution at valine 600. *BRAF* V600E accounts for 70–88% of all *BRAF* variants in melanoma, followed by variants: NM_004333.6(*BRAF*):c.1798_1799delinsAA (p.Val600Lys) (referred to V600K; 5-12%), and NM_004333.6(*BRAF*):c.1799_1800delinsAT (p.Val600Asp) (referred to V600D), which, together with the NM_004333.6(*BRAF*):c.1798_1799delinsAG (p.Val600Arg) variant (referred to V600R) account for ≤ 5% [45]. Detection of *BRAF* mutational status — post-chemotherapy — plays a crucial role in determining prognosis, together with other factors like age, gender, metastases, Eastern Cooperative Oncology Group (ECOG) scale, and lactate dehydrogenase (LDH) levels [46]. Shinozaki et al. [47] showed decreased overall survival (OS) in patients treated with bio-chemotherapy for melanoma when the *BRAF* variant was detected in ctDNA compared to patients in whom the *BRAF* variant was not found in serum (13 *vs.* 30.6 months). In a study by Ardekani et al. [48], higher *BRAF* expression was also associated with poor OS in primary melanoma patients, and a correlation between *BRAF* expression and both thickness and ulceration

of the tumor was demonstrated [48]. Nevertheless, the presence of the *BRAF* V600 variant is a predictive marker determining the targeted therapy choice. The first inhibitor of mutated BRAF approved by the U.S. Food & Drug Administration (FDA) was vemurafenib, and it showed objective response rates of ~50% in patients with metastatic melanoma and tumors positive for *BRAF* V600E [49, 50]. Melanomas treated with BRAF inhibitors only, develop mechanisms to reactivate MAPK/PI3K/Akt/alternative pathways in a short time, and resistance occurs. These pathways may be activated through mutations, copy-number alterations, and other mechanisms. The most frequent are *NRAS* variants and *MEK1/2* variants. Less frequently, PI3K/Akt pathway alterations are observed [51]. In order to overcome this resistance, a combination of BRAF and MEK inhibitors has been proposed. Compared to vemurafenib monotherapy, it provides improved OS and a more than 64% response rate [52]. At present, analysis of *BRAF* mutational status is recommended in tumors of cutaneous melanoma stage III or IV, and when a *BRAF* V600 variant is detected, a combined BRAF/MEK inhibitors therapy is advised (dabrafenib/trametinib; vemurafenib/ /cobimetinib; encorafenib/binimetinib). This targeted therapy may be applied as the first-line or after progression on immunotherapy with PD-1 inhibitors [53]. Nevertheless, the efficacy and effects of this combined therapy may be highly different. In some cases, it may result in tumor shrinkage or even complete tumor resolution; in others, drug resistance/tumor recurrence may be the effect [54, 55]. For this reason, new therapeutic strategies are being sought to combat resistance mechanisms, and attention has turned to other processes whose inhibition could aid in inhibiting cancer cell growth. Inhibition of mitotic cell division may be a goal. Targeting Aurora B, the kinase we mentioned earlier, with inhibitors is a promising therapeutic strategy for cancer treatment [56]. Nevertheless, at present, there are no markers that would support clinicians in predicting therapeutic responses of *BRAF*-altered cancers to BRAF/ /MEK inhibitors.

BRAF V600E was found to be associated with the presence of *TERT*p variants in human cancers, particularly in melanoma and thyroid cancers [57–59]. Moreover, this duet has also been reported in gliomas [60] and low-grade serous ovarian carcinoma [61]. Most *TERT*p variants in melanoma include two aforementioned hot spots — C228T and C250T — that have a UV signature with C>T nucleotide substitution [62]. *TERT*p variants were indicated as an independent marker of poor survival in patients with cutaneous melanoma [59]. Several studies have also demonstrated an association between *TERT*p variants and increased Breslow thickness, as well as tumor ulceration [59, 63, 64].

The frequency of *BRAF* V600 and *TERT*p variant co-occurrence in melanoma was reported at 20–25% [63, 65]. In a study concerning a selected *BRAF*-mutated melanoma cohort, 72% of cases were positive for *TERT*p alterations [66]. However, there are population-dependent differences in the *TERT*p variant's frequency. In the Asian population, for instance, the prevalence of *TERT*p C228T and C250T in melanoma was significantly lower compared to the Caucasian population, reported as 5.9% and 5.5%, respectively [67]. These differences may be due to the dominance of acral and mucosal melanomas in the Asian population. Similar to the Caucasian population, *TERT*p mutations were more commonly observed in *BRAF*-mutated tumors. The unique coexistence of these two genes' hot spot alterations is an important discovery due to its biological and clinical consequences since *BRAF* V600 and *TERT*p variants as a duet are a robust driver for the aggressiveness of human cancer. In cutaneous melanoma, this mutational duet was reported to be strongly correlated with adverse clinicopathological parameters, like thickness, high mitotic rate, sentinel node metastases, presence of ulceration, and absence of regression [63], and these correlations were not significant when each of these variants was analyzed alone (*BRAF* V600 and *TERT*p variants). This synergistic oncogenicity of *BRAF* V600E and *TERT*p alterations is associated with strong cooperation between these two oncogenes. The mechanism of *BRAF* V600E/ /MAPK pathway-dependent up-regulation of *TERT* expression is the following: the *BRAF* V600E/MAPK pathway promotes the expression of GABPB protein via FOS transcription factor phosphorylation and its binding to the GABPB promoter; increased GABPB expression leads to formation of the GABPA-GABPB complex, which selectively binds to the mutated *TERT* promoter and in consequence, strongly up-regulates its expression (Fig. 1) [65, 68]. Despite the strong negative impact of this molecular duo on the clinical course of melanoma, recent studies emphasize its simultaneous potential as a therapeutic target. Tan et al. [69] showed that the genetic duet of *BRAF* V600E and *TERT*p variants is the Achilles Heel of cancer cells, the most vulnerable therapeutic target. Using thyroid cancer, melanoma, and colon cancer cell models, the authors showed that dabrafenib and trametinib induced apoptosis of cancer cells harboring both variants. Yet, they displayed little proapoptotic effect in cells with only the *BRAF* variant. The same results were observed *in vivo*. What is more, after drug withdrawal, tumors harboring only the *BRAF* variant regrew rapidly in contrast to tumors with both alterations that remained hardly measurable. It has been hypothesized that cancer cells with these alterations evolve to rely on *BRAF* V600E-dependent high *TERT* expression, which results in apoptosis suppression. Therefore, using BRAF/MEK inhibitors may lead to apoptosis of cancer cells and tumor elimination. In a clinical setting, Thielmann et al. [66] also demonstrated better therapeutic responses in patients with melanoma harboring *BRAF*/*TERT*p variants with more prolonged progression-free survival (PFS) and OS compared to patients with only *BRAF*-positive melanoma. However, the authors did not observe a plateau of durable responses, as reported by Tan et al. [69] in an *in vitro* study.

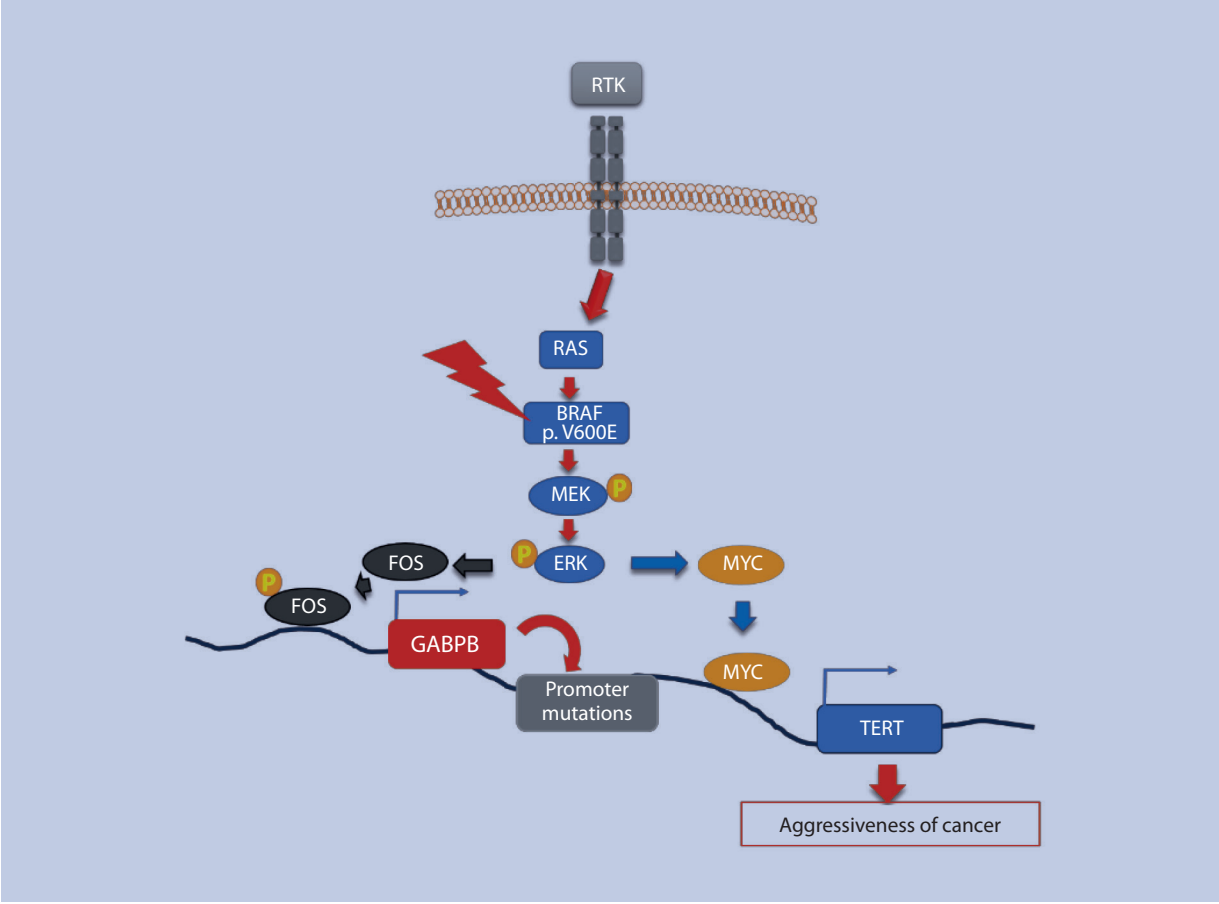

Figure 1. *BRAF* and *TERT* oncogenic cooperation mechanisms. The main model of *BRAF* V600E and *TERT*p variants' oncogenic cooperation is through the *BRAF* V600E-activated MAPK pathway — FOS phosphorylation — acting as a transcription factor of the *GABPB* gene. The GABPB, in turn, is part of the GABP complex that recognizes the ETS binding motif within the *TERT* gene promoter, created de novo due to either C228T or C250T variants. The *BRAF* V600E-activated MAPK pathway may also promote *TERT* expression via MYC. This model is *TERT*p variant independent

BRAF and *TERT*p variants as a molecular duet in other cancers

Thyroid cancers

Thyroid cancers (TC) are at the forefront in terms of *BRAF* V600E frequency, which plays a fundamental role in tumorigenesis and progression of TC, and papillary thyroid carcinoma (PTC) in particular. *TERT*p variants — C228T and C250T — are most common in more aggressive TCs with a frequency as follows: 11.3% in PTC, 17.1% in follicular thyroid carcinoma (FTC), 14.6% in Hurthle cell carcinoma (HCC), 43.2% in poorly differentiated carcinoma (PDTC), and 40.1% in anaplastic thyroid carcinoma (ATC) [57]. No *TERT*p variants were found in medullary thyroid carcinoma or benign thyroid tumors. Regarding the clinical impact of *BRAF* V600E and *TERT*p variants in TCs, mutated *BRAF* alone demonstrated associations with poor prognosis factors. However, the coexistence of *BRAF* V600E/*TERT*p variants showed a much more substantial negative impact in terms of clinical outcome. Shen et al. [70], in the analysis of the 388 PTC cohort (TCGA database), reported that *BRAF*/*TERT*p positive mutational status was associated with older patient age, extrathyroidal invasion, advanced disease stages III/IV, larger tumors, distant metastases, disease recurrence and patient mortality. *BRAF* V600E alone, in turn, was only associated with extrathyroidal invasion. In our study, although a smaller PTC cohort was analyzed, similar data were obtained supporting the meaning of the *BRAF* V600E/*TERT*p duet in the progression of PTC [71]. We reported a strong association of *BRAF* and *TERT*p alteration coexistence with gender, advanced age of patients, T3 and T4 stage of disease, lymph node metastases, larger tumor size, and infiltration of the tumor capsule. It was also demonstrated that these two alterations might play a role in the dedifferentiation of thyroid cancer, leading to TC formation with a status known as RAI (radioactive iodine)-refractory DTC (RAIR-DTC) [72]. Currently, multikinase inhibitors — sorafenib and lenvatinib — are recommended for treating patients with RAIR-DTC. Yet, these drugs are associated with significant adverse effects that lead to dose reduction and temporary or permanent discontinuation in many patients. Because of the positive effects of BRAF/MEK inhibitors in *BRAF*-mutated melanoma patients, their use was also studied in RAIR-DTC patients with promising results in some cases [73, 74]. However, the mutational status of *TERT*p was not considered in these studies. Su et al. [75] were

the first to report the effectiveness of anlotinib (a multitarget tyrosine kinase inhibitor) treatment in a patient with *BRAF*- and *TERT*p-mutated RAIR-DTC. The authors speculated that the presence of *BRAF* V600E/*TERT*p mutational duet might be a predictive marker for the beneficial effect of anlotinib therapy. More data is needed to confirm this hypothesis.

The interaction of mutated *BRAF* and *TERT*p on the molecular level in TCs may differ from mechanisms observed in melanoma, as reported by Song et al. [76]. The Authors demonstrated that GABP and ETS1 expression, previously associated with *BRAF* V600E/MAPK-dependent up-regulation of *TERT*, was not significantly affected by mutated *BRAF* in PTCs. Instead, *BRAF* V600E/MAPK activation triggered ETV1, ETV4, and ETV5 up-regulation in TCs. These ETS factors, induced by mutated *BRAF*, bind directly to the *TERT*p and activate it.

Gliomas

Gliomas represent the most common central nervous system (CNS) tumors. The prevalence of *BRAF* V600 variants in gliomas is reported as 15.4% in adults and 17.0% in pediatric patients [77]. *TERT*p variants, in turn, are present in 24.4%, 38.7%, and 44.9% of glioma cases with grades II, III, and IV (according to the WHO classification from 2016), respectively [78]. Discovery of *BRAF* alterations in CNS tumors opened new therapeutic possibilities for these patients [79]. Still, the efficacy of mutated BRAF inhibitors varies qualitatively by glioma histologic subtype. It has been demonstrated that additional molecular events, including loss of *CDKN2A* or telomerase reactivation, may significantly influence the clinical outcome in *BRAF*-mutated tumors [80, 81]. According to the latest WHO classification of CNS tumors, *TERT*p variants should be analyzed in patients with IDH-wild type diffuse glioma, and their presence is sufficient for diagnosing glioblastoma G4 [82]. The role of *TERT*p mutations in glioblastoma oncogenesis is beyond any doubt. Nevertheless, its prognostic impact remains controversial [83]. It has been indicated that the prognostic value of *TERT*p variants may depend on tumor grade and *IDH* mutational status [84]. The co-occurrence of *TERT*p and *IDH* variants in low-grade gliomas (LGG) was shown to be associated with better overall survival, similar to gliomas with *TERT*p, *IDH* variants, and 1p/19q co-deletion. However, patients without *TERT*p and *IDH* variants and those with 1p/19q co-deletion showed poor survival. The presence of *TERT*p variants only, in turn, seems to be associated with aggressive tumors and poor prognosis [85].

The coexistence of *BRAF* V600E and *TERT*p variants was observed to be enriched in more aggressive, high-grade tumors [81, 86]; still, it is not as common as in melanoma or PTC. The molecular mechanism of mutated *BRAF* and *TERT*p interaction in glioma is similar to that described in melanoma, and is based on the ETS1 up-regulation via the MAPK pathway and its binding to mutated *TERT*p, which leads to *TERT* activation [60].

Serous ovarian carcinoma

Serous carcinoma is a predominant type of epithelial ovarian cancer (EOC) and is classified into two main subtypes: high-grade serous carcinoma and less common low-grade serous carcinoma (LGSC). The frequency of the *BRAF* V600E variant varies from 2% to 38% in LGSC [87–89]. It is also found in up to 48% of serous borderline tumors [90]. There are studies showing an association between the presence of the *BRAF* V600E and early-stage disease and improved prognosis in LGSC [89]. Moujaber et al. [91], in turn, reported that most women with *BRAF*-mutated LGSC were diagnosed at an advanced stage. Moreover, recurrent *BRAF* V600E-positive LGCS was not responsive to chemotherapy. However, the use of a BRAF inhibitor, dabrafenib, gave a sustained response. The data about *BRAF/TERT*p mutational duet in ovarian cancer are scarce. Tavallaee et al. [61] first reported a case study of LGSC recurring as a carcinosarcoma in a lymph node with *BRAF* V600E and *TERT*p C228T alterations present in both primary and recurrent tumors. This case may support a hypothesis of the synergistic effect of this mutational duet in this patient's LGSC that led to an aggressive clinical course and high-grade transformation.

Soft tissue sarcoma

BRAF alterations are rare in soft tissue sarcoma (STS) cases, with a frequency of 1.2% and *BRAF* V600E presence between 0.3–0.6% [92]. Kobayashi et al. also showed that the most frequent variants accompanying *BRAF* V600E mutation in STS concerned the *CDKN2A* gene and *TERT*p. The percentage of *BRAF/TERT*p mutated STS is small, yet it should not be marginalized considering the clinical importance of these two molecular events' co-occurrence. Several case reports have documented the presence of the *BRAF* variant in various sarcoma subtypes, including malignant peripheral nerve sheath tumors (MPNST), clear cell sarcoma, synovial sarcoma GIST, undifferentiated pleomorphic sarcoma, and Ewing sarcoma. However, these cases exhibit significant differences in treatment approaches, such as the use of specific drugs and whether BRAF/MEK inhibition was combined or used as monotherapy [93–96].

Conclusions

There is no doubt that the *BRAF/TERT*p mutational duet plays an important role in tumorigenesis, progression, and the aggressiveness of cancer cells. It has also been demonstrated that the coexistence of these two alterations makes cancer cells more sensitive to BRAF and MEK inhibitors, as their survival becomes dependent on *BRAF* V600E-induced *TERT* up-regulation. Further studies are needed to elucidate the dual role of this molecular duet and its translation into targeted therapies that could be used in different types of cancer.

Article information and declarations

Authors contributions

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Review article

Tumor pathology

Discrepancies in dermatoscopy — pathology correlation of pigmented skin lesions

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Various dermatoscopic algorithms are used to diagnose skin lesions. There are specific dermatoscopic structures that suggest malignancy. Despite constant progress in dermatoscopy, the method has its limitations. There is a group of pigmented lesions that we cannot name in dermatoscopy, or even determine whether they are benign or malignant. Many benign lesions are excised. The article aims to explain the factors that may cause the discrepancies between dermatoscopic and histopathologic diagnoses of pigmented skin lesions. The reasons for the discrepancies are complex. Different structures are evaluated in dermatoscopy (pigment distribution) and histopathology (architecture and morphology of melanocytes). Every single dermatoscopic structure can be seen both in benign and malignant lesions. Some early melanomas lack specific dermatoscopic criteria. Finally, there is no consensus among pathologists regarding the final diagnosis in the group of melanocytic lesions. Despite its limitations, dermatoscopy significantly increased melanoma detection, especially in the early stages.

Keywords: dermatoscopy, pathology, correlation, melanoma

Introduction

Dermatoscopy is a noninvasive technique for diagnosing skin lesions. One of the applications is the diagnosis of pigmented skin lesions (PSL) and differentiation between melanoma and nevus. The meta-analysis of Vestergard et al. [1] showed that the relative diagnostic odds ratio for melanoma, for dermatoscopy *vs.* the naked eye examination, was 9.0 [95% confidence interval (CI) 1.5–54.6; p = 0.03] and 15.6 (95% CI 2.9–83.7; p = 0.016), (depending on studies included in the analysis). Moreover, the sensitivity for dermatoscopy was estimated as 0.9 (95% CI 0.8–0.95) — higher than the naked eye examination [0.71 (95% CI 0.59–0.82)] [1]. In the same study, the specificity of dermatoscopy was evaluated as 0.9 (95% CI 0.57–0.98) [1].

Over the decades, the approach to clinical, dermatoscopic, and pathological diagnosis of melanoma has evolved towards earlier recognition of cancer [2]. Medical training focused on *"how not to miss melanoma"*, which led to increased awareness, detection, and treatment of melanocytic tumors. The threshold for diagnosing melanoma has been lowered. Failure to recognize melanoma may have serious consequences for patients and doctors. The decision to excise the lesion is based mainly on dermatoscopy examination.

This narrative review aims to clarify the discrepancies between dermatoscopic and histopathologic diagnoses of PSL on non-facial non-acral skin. These discrepancies may explain, at least in part, why so many benign lesions are removed.

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Basic rules of dermatoscopy of pigmented skin lesions

Dermatoscopic criteria for PSL evolved over decades, which reflects the process of understanding the method and the need for simple algorithms that can be easily used in everyday practice. Different algorithms help to diagnose pigmented skin lesions, such as the ABCD rule, the 3-point checklist, the 7-point checklist, color, architecture, symmetry, and homogeneity (CASH), and chaos and clues [3]. One of the most widespread methods is an algorithmic system based on pattern analysis developed by Kittler et al. [4]. In short, the method uses basic elements (lines, dots, clods, circles, pseudopods) and colors to describe a lesion. The same elements form basic patterns (for example, reticular pattern, parallel pattern, pattern of dots). Colors depend on the type and distribution of pigment. The main pigment is melanin, followed by hemoglobin and keratin. Apart from patterns and colors, there are also clues to malignancy and specific diagnosis.

To sum up, patterns + colors + clues = diagnosis. The lesions could present many patterns and colors, distributed symmetrically or asymmetrically. Chaos is the asymmetry of structures, border abruptness, or colors [4]. The basic melanoma model includes more than one pattern or/and more than one color distributed asymmetrically with at least one clue to malignancy [5].

Discrepancies between dermatoscopic and histopathologic examination

The main difference between dermatoscopy and patomorphology of PSL is that dermatoscopy evaluates mainly the distribution and color of pigment (melanin), whereas histopathological examination is based on the architecture and cytomorphology of melanocytes. In dermatoscopy, structures are two-dimensional on a horizontal plane, and we cannot see the deeper parts of the lesion. With dermatoscopy, we can examine the whole lesion, compare it with the patient's other lesions, and follow it up. Histopathological examination remains the gold standard. We can assess the whole depth of the lesion and the cell morphology on vertical sections, but only about 2% of the lesion is examined [6]. It is crucial to understand that not every melanocytic lesion is pigmented, such as amelanotic melanomas and a group of dermal nevi. In such cases no pigment can be found in dermatoscopy, and other structures are evaluated (mainly the pattern of vessels). On the other hand, not every PSL has a melanocytic origin.

Melanin

The process of melanin synthesis is called melanogenesis. Melanocytes, localized in the basal layer of the epidermis, produce melanin in melanosomes. They contact up to 40 keratinocytes to form epidermal-melanin units. Melanin-loaded melanosomes concentrate at melanocytic dendrites and are transferred to keratinocytes. In keratinocytes, melanin forms caps upon the nuclei to protect against ultraviolet radiation (UV). Then, via a process called autophagy, the melanin is degraded upon keratinocyte terminal differentiation [7–9].

The accumulation of melanin is higher in the basal layer of the epidermis but can be in the upper layers, including the stratum corneum. Melanin granules could be found in the dermis, as well. They could fall from the epidermis or be released by melanocytes. Some melanin is phagocyted by macrophages called melanophages. To sum up, we can find melanin granules in 1) melanocytes, 2) keratinocytes, 3) macrophages (melanophages), or 4) lie free in the epidermis or dermis. Figure 1 shows irregular melanin deposits on different levels of the epidermis and the dermis. Figure 2 shows dermatoscopy and histopathology of lentigo simplex (A, B) and the melanocytic nevus with melanin deposits in stratum corneum (C, D).

Nonmelanocytic lesions classified as nevus or melanoma

Reticular lines are probably the most common pattern of melanocytic lesions. The formation of reticular lines comes from the skin structure. The dermo-epidermal junction is not a flat line but is wavy to form rete ridges and dermal papillae. In nonmelanocytic lesions in rete ridges, pigmented keratinocytes are grouped and look darker in dermatoscopy than keratinocytes over dermal papillae. In melanocytic lesions, the formation of reticular lines is more complex. When melanocytes are not pigmented, the reticular lines are created like in nonmelanocytic lesions (only by melanin in keratinocytes). When melanocytes are pigmented, reticular lines can be formed by nests of melanocytes in rete ridges with or without pigmentation of keratinocytes [4]. Among nonmelanocytic lesions that can present with reticular lines are solar lentigo, seborrheic keratosis, and dermatofibroma. Figure 3 shows the pigment network in melanocytic (nevi, lentigo simplex) and nonmelanocytic lesions (dermatofibroma).

Figure 2 shows dermatoscopy and histopathology of lentigo simplex (A, B) and the melanocytic nevus with melanin deposits in stratum corneum (C, D).

Many nonmelanocytic lesions have pigmented variants and may mimic melanocytic lesions. Among them are benign and malignant epidermal and appendageal tumors [such as basal cell carcinoma (BCC), actinic keratosis (AK), squamous cell carcinoma (SCC), melanoacanthoma, poroma, lichen planus-like keratosis (LPLK)], cutaneous metastases of malignancy, exogenous pigmentation. In these lesions, pigmented structures such as lines, globules, dots, structureless areas, and circles can be found. The topic is extensive, and the discussion of the dermatoscopy pathology correlations in each pigmented lesion goes beyond the scope of the article.

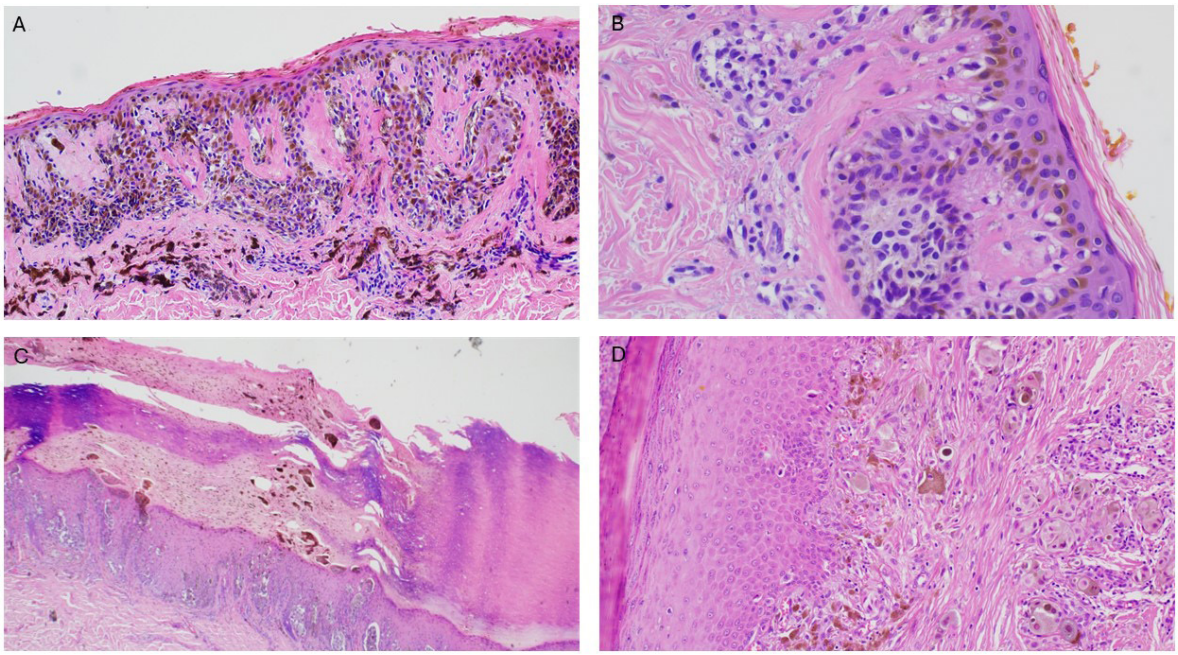

Figure 1. Irregular melanin deposits on different levels of the epidermis and the dermis; **A.** Lentiginous nevus; **B.** Junctional nevus; **C, D.** Superficial spreading melanoma

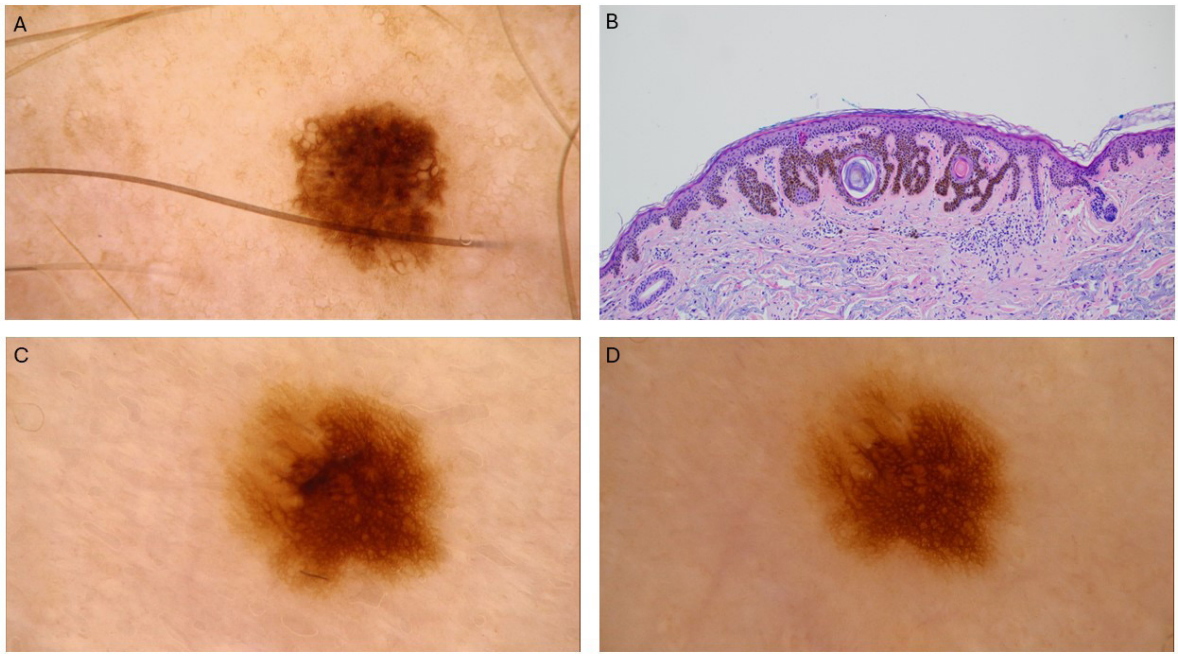

Figure 2. A. Lentigo simplex with irregular pigmentation. The lesion was misdiagnosed as atypical nevus and excised; **B.** Histopathology of lentigo simplex. Hyperpigmentation of basal layer of keratinocytes with proliferation of melanocytes; **C, D.** Melanin deposits in stratum corneum. The melanocytic nevus **A.** before and **B**. after removing the horny layer of the epidermis

Melanoma vs. nevus

In dermatoscopy, we cannot see where melanin is deposited (melanocytes, keratinocytes, melanophages, extracellularly) but we can see colors. Colors (black, dark brown, light brown, gray, blue) correspond to the layer in the epidermis or dermis of pigment (melanin) deposition (Tab. I) [4].

According to the chaos and clues method introduced by Rosendahl et al., there are nine clues to malignancy: 1) eccentric structureless area, 2) peripheral black dots or clods, 3) thick reticular lines, 4) grey or blue structures, 5) segmental radial lines or pseudopods, 6) white lines, 7) polymorphous vessels, 8) angulated lines, 9) parallel lines on the ridges (acral) [5, 10]. The algorithm helps a clinician select lesions that should be excised or biopsied. We do not discuss parallel lines on the ridges as we focus on non-facial non-acral lesions.

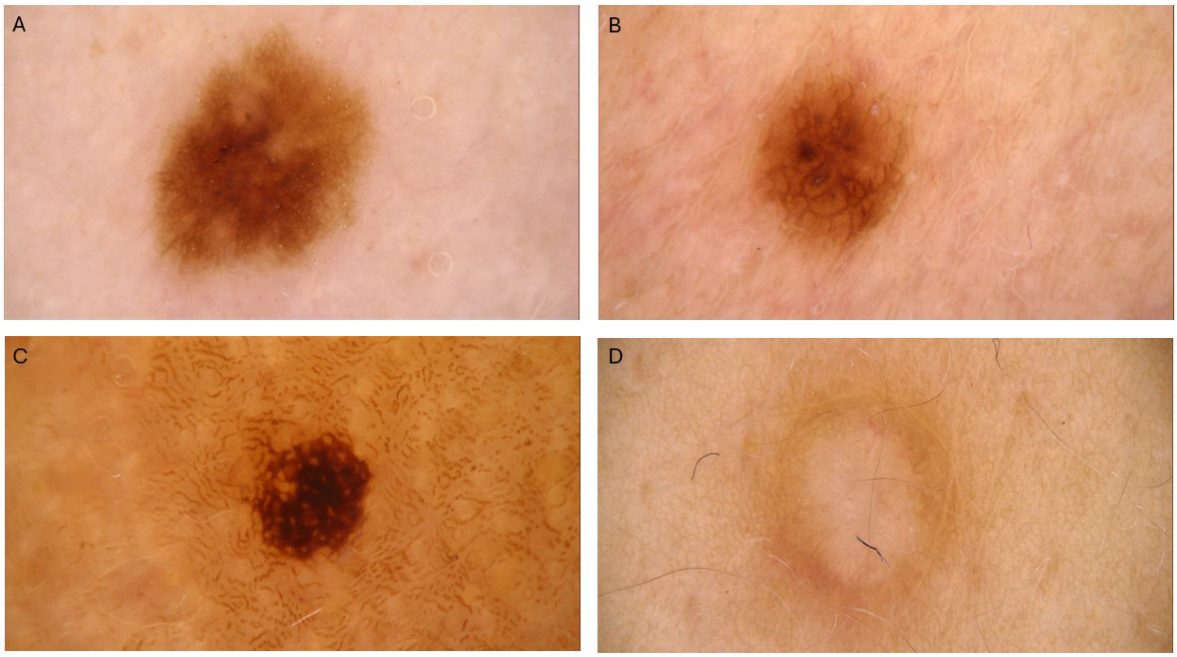

Figure 3. Pigment network; **A, B.** Melanocytic nevi; **C.** Lentigo simplex; **D.** Dermatofibroma

Table 1. Colors in dermoscopy correspond to melanin deposits at different levels of the epidermis and dermis. Adapted from Kittler et al. [4]

Color in dermoscopy	Melanin deposits
Black	Horny layer
Dark brown	Epidermis, big deposits
Light brown	Epidermis, small deposits
Grey	Papillary dermis
Blue	Reticular dermis

Eccentric structureless area

The meaning of an eccentric structureless area is defined by its color. When it's black, dark brown, light brown, grey, or blue, it represents melanin deposits on different levels in the epidermis and dermis. Irregular deposits of melanin may correlate with the proliferation of malignant melanocytes. Moreover, grey and white colors may represent areas of regression when lymphocytes attack neoplastic melanocytes and induce fibrosis. Red areas may correspond to increased blood flow in the lesion. Lallas found that irregular areas (blotches) were present in 41% of invasive melanomas, 18% of melanoma in situ (MIS), as well as in 14% of excised nevi, and 5% of non-excised nevi [11].

Peripheral black dots or clods

Peripheral clods are clues to the growth of the lesion, which is a frequent event in adolescence, but suggests malignancy in adult patients.

One of the vital histopathologic criteria of melanoma is pagetoid spread of atypical melanocytes. That means that atypical melanocytes go up to superficial layers of the epidermis. Figure 4 shows melanocytes in A) melanoma, B) normal skin, and C) blue nevus. If melanocytes contain melanin deposits, we can see dark brown or black globules and clods. However, similar structures (dark brown or black) could be observed in irritated nevi, when melanin deposits lie free in the horny layer. Lallas et al. [11] found irregular dots or globules in 69% of invasive melanomas, 50% of MIS, 54% of excised nevi, and 54% of non-excised nevi. They also found that not only peripheral dots and clods but also irregular small black or dark brown areas in the central parts of a lesion (irregular hyperpigmented areas and blotches) were indicators of MIS [11].

Thick reticular lines

As mentioned above, reticular lines in nevi are formed by pigmented nests of melanocytes in rete ridges or by pigmented keratinocytes. In such cases, reticular lines are thin, and lines are narrower than holes. On the opposite in thick reticular lines, holes are small, and lines are broader. This pattern is developed when pigmented nests of melanocytes are in a horizontal position and go beyond the rete ridges. In melanoma, this may correspond to the confluence of intraepidermal nests or confluent proliferation of neoplastic melanocytes along the basal layer of the epidermis. In nevi, a large amount of melanin deposited in the upper layers of the epidermis creates thick lines. In metaphoric language thick reticular lines are part of an atypical network. In the study by Lallas et al. [11], an atypical network was present

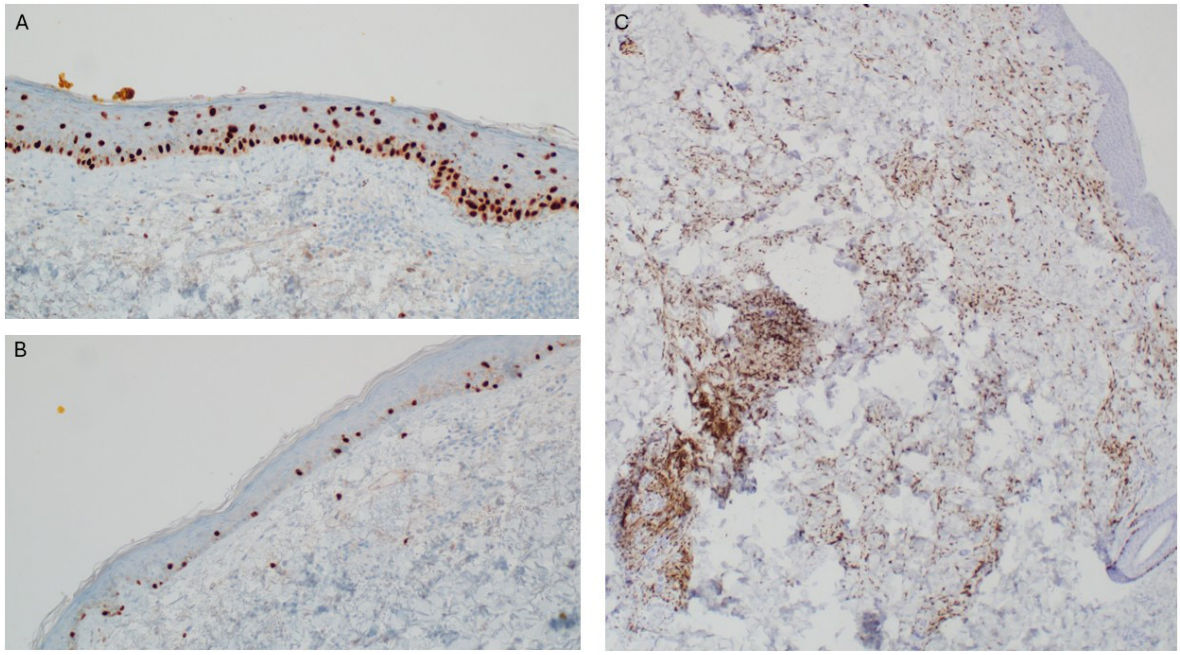

Figure 4. SOX-10 nuclear staining highlighting melanocytes; **A.** Melanoma with pagetoid spread of atypical melanocytes; **B.** Normal skin adjacent to melanoma with melanocytes only in the basal layer of epidermis; **C.** Blue nevus with melanocytes in the reticular dermis

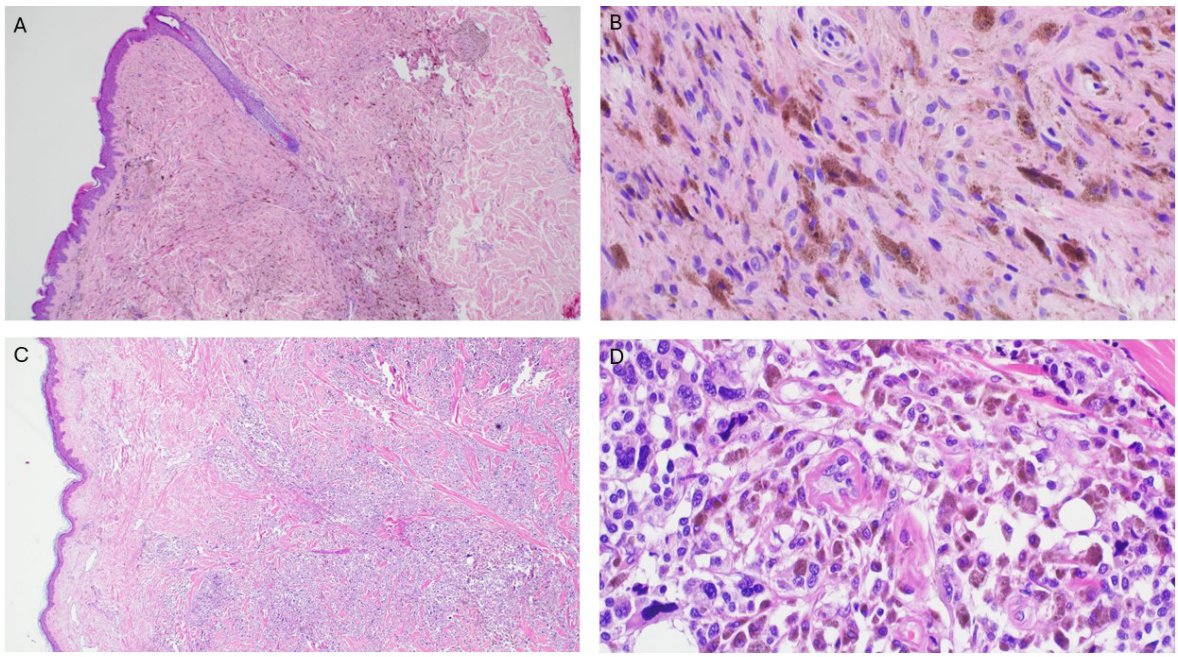

Figure 5. Melanin deposits in the reticular dermis. The pigment is in melanocytes or macrophages; **A, B.** Blue nevus; **C, D.** Melanoma metastasis. Compare the morphology of melanocytes in blue nevus (regular spindle cells with regular nuclei) and melanoma metastasis (atypical cells of various sizes with hyperchromatic nuclei)

in 66% of invasive melanomas, 85% of MIS, 83% of excised nevi, and 55% of non-excised nevi.

Grey and blue structures

Grey and blue structures are observed in melanomas, pigmented basal and squamous cell carcinomas, as well as in common and blue nevi. Grey and blue structures include lines, clods, dots, circles, and structureless areas. A grey color corresponds to melanin deposition in the papillary dermis, whereas a blue color correlates with melanin in the reticular dermis (deep dermis). In histopathological examination, pigment is in melanocytes, macrophages, or both. Figure 5 shows melanin deposits in the reticular dermis. Grey circles correspond to melanin around the hair infundibula, and are more common

in the face, but can be found in any part of the body. Lallas et al. [12] found blue structures in benign (blue nevi, angiomas, seborrheic keratoses) and malignant tumors (melanomas, BCC). It was shown that blue clods or irregular structures, combination of blue color and gray or linear vessels are clues to malignancy. Braun et al. [12] found multiple blue-grey dots (granularity) in 26,5% of benign lesions and in 93,5% of melanomas. In the prospective part of the study, 3773 lesions were examined. They found 41 (1%) lesions with blue-grey granularity (11 melanomas, 12 high-grade dysplastic nevi, eight congenital nevi, four low-grade dysplastic nevi, and three lichen planus-like keratosis) [12].

In metaphoric language, blue and white structureless areas are called a blue-white veil. In a study by Lallas et al. [11], a blue-white veil was present in 24% of invasive melanomas, 10% of MIS, 16% of excised nevi, and 4% of non-excised nevi. Blue-grey regression was present in 66% of invasive melanomas, 80% of MIS, 80% of excised nevi, and 49% of non-excised nevi [11].

Recently, peripheral hyperpigmented microcircles were proposed as a novel dermatoscopic clue to non-facial non--acral melanoma [13].

Segmental radial lines or pseudopods

Irregular radial lines or pseudopods in melanoma correspond to the extension of the intraepidermal nests beyond the dermal component, and are signs of radial growth of the lesion. Symmetrical radial lines or pseudopods are also observed in Spitz nevi: benign neoplasms with specific genetic alterations and a distinctive histological presentation. Moreover, radial lines are found in pBCC and pSCC. Lallas et al. [11] showed irregular lines (streaks) in 26% of invasive melanomas, 28% of MIS, 28% of excised nevi, and 7% of non-excised nevi.

White lines

White lines are whiter than normal skin and correlate to increased collagen and stromal alteration. Some white lines can only be seen in polarised light, they are shiny and oriented perpendicularly. They are detected in both malignant and benign lesions, such as melanomas, basal cell carcinomas, nevi, seborrhoeic keratoses, dermatofibromas, and others. It was shown that the presence of white lines increases the risk of malignancy and risk of invasive melanomas *vs.* in situ melanomas by a factor of 10 [14].

Polymorphous vessels

In polymorphous vessels (also called atypical vessels), more than one pattern is seen (including lines, dots, and clods). In histopathology, they reflect increased vessel formation/dilatation due to uncontrolled tumor growth. Polymorphous vessels, especially with dotted type, suggest melanoma diagnosis. Lallas et al. [11] showed that atypical vessels were present in 35% of invasive melanomas, and 30% of MIS, but also in 34% of excised nevi and 10% of non- excised nevi. Polymorphous vessels can be found also in BCC (1.8–8.6%) [15, 16] and SCC (8.9%) [17] .

Angulated lines

Angulated lines are lines that connect at different angles forming polygons. Histopathology of extrafacial lentigo maligna can show lines of atypical melanocytes with melanophages below neoplastic cells, with no relation to hair follicles (in contrast to facial lentigo maligna) [18]. Jaimes et al. [19] found angulated lines in 44% of melanomas. They are more common on chronic sun-damaged skin. Lallas et al. found angulated lines in 20% of invasive melanomas, 11% of melanomas in situ, 5% of excised nevi, and 2% of non-excised nevi [11, 12].

As presented above, the clues for malignancy can be seen not only in melanoma or skin cancers but also in nevi and non-melanocytic tumors. However, regardless of which diagnostic algorithm you choose to diagnose skin lesions, the diagnostic value is comparable. Carrera et al. [3] analyzed the diagnostic accuracy of six simplified algorithms (the 7-point checklist, CASH, Menzies method, the ABCD rule, the 3-point checklist, and chaos and clues). Their sensitivity varied between 69 and 95%, and their specificity was 25 to 59%. The diagnostic accuracy was estimated as modest variable agreement between doctors was demonstrated for various dermatoscopic criteria [3].

Hemoglobin and keratin

In certain situations, hemoglobin and keratin may mimic melanin deposits and suggest a diagnosis of a melanocytic lesion. On dermatoscopy, hemoglobin is usually red or purple, but thrombosed blood produces a dark red or black color. The best example is subungal hematoma imitating acral melanoma. Keratin comes from the stratum corneum and is white or yellow, but when mixed with melanin, it turns orange or light brown. For this reason, many seborrheic keratoses are misdiagnosed as nevi or melanomas [4].

Micromelanomas and featureless melanomas

"Micro-melanoma", "small diameter melanoma", and "mini-melanoma" are names for melanoma with a diameter less than 5 or 3 mm [20–22]. Some small melanomas cannot be diagnosed by dermoscopy during the first examination [20–26]. However, as Słowińska et al. [22] showed, the 7-point checklist and TADA dermoscopic algorithms can help in the majority of cases. Spitzoid patterns were the most common in this group of MM, followed by multicomponent asymmetric patterns [22]. In addition, Ferrara et al. [27] underlined that the diagnostic value of dermoscopy over clinical examination is higher in small lesions. The difficulty with micro-melanomas is that although they are small in diameter, they can already be invasive. In one study, only 44 of the 103 mini-melanomas (≤ 5 mm) were melanomas in situ [21]. In another study, 206 suspicious pigmented

skin lesions with a diameter ≤ 3 mm were evaluated. Among them, 23 cases were diagnosed as melanomas: 4 MIS and 19 invasive melanomas with Breslow thickness of 0.2 to 1.08 mm [20]. The small diameter of a lesion does not exclude the possibility of melanoma diagnosis. In light of these data, it is hard to agree with Welch et al. [28] that lesions with a diameter below 6 mm should not be examined and excised.

"Featureless melanoma" is melanoma that cannot be diagnosed on first examination, and only digital dermatoscopy monitoring (DDM) and side-by-side comparison of dermatoscopic pictures allow correct diagnosis [29, 23]. Słowińska et al. [22] showed that among 50 micro-melanomas (< 5 mm) staged pTis and pT1a, 40% did not present with specific melanoma criteria. Babino et al. [29] compared melanomas (diagnosed on first examination or with digital dermoscopy monitoring) and benign lesions. They showed that approximately 60% of melanomas detected on DDM did not present with specific melanoma criteria, and were found only based on a comparison of dermatoscopic images taken at specific time intervals. On follow-up visits, when melanomas showed melanoma-specific criteria, irregular hyperpigmentation was the most frequent one [29].

Kittler et al. [23] evaluated 499 lesions that were qualified for digital dermatoscopy monitoring and then excised on follow-up visits (after 1.5 to over 8-month intervals). Among these lesions, 91 (18%) were melanomas and 408 melanocytic nevi. The study confirmed that the evaluation of changes during monitoring can improve melanoma detection. On the other hand, 408 melanocytic nevi presented with changes in DDM were removed as well. Kittler et al. [23] found no significant differences between melanoma and nevi in terms of dermatoscopic changes with short-term follow-up (1.5–4.5 months). With longer follow-up (over 8 months), 62% of melanomas showed asymmetrical enlargement in comparison to 20% of nevi ($p < 0.001$). Among the independent predictors of malignancy after a follow-up longer than 4.5 months were broadening of pigment network, focal increase in pigmentation, and increase in black dots. Kittler et al. [23] also suggested excising the lesion (when the lesion grows irregularly or presents with regression elements, or changes in color (new color), pigmentation, and structure.

Another vital issue is that histopathologic diagnoses of a melanocytic lesion are not always definitive. The study by Hosler et al. [30] showed that 24% of melanocytic lesions received equivocal diagnoses after independent, blinded evaluation by dermatopathologists. In terms of dermatoscopy pathology correlation, it was shown that difficult lesions with regression structures in dermatoscopy were also difficult in histopathological examination.

Conclusions

The reasons for the discrepancies between dermatoscopy and histopathology of PSL are complex. First of all, we evaluate different structures in dermatoscopy (pigment distribution) and histopathology (architecture and morphology of melanocytes). Next, dermatoscopic algorithms have limited accuracy with varied interobserver agreements. Every single dermoscopic structure can be seen both in benign and malignant lesions [11, 12, 19]. Nevi may present with melanoma-specific clues and change over time to suggest malignancy. On the other hand, we must be aware of the lack of specific dermoscopic criteria in a selected group of melanomas, including featureless and micro-melanomas. Finally, there is discordance among pathologists in terms of final diagnoses in a group of melanocytic lesions. Difficult dermoscopic lesions may be confusing for pathologists as well.

Knowing discrepancies in dermatoscopy pathology correlation is crucial for understanding the method and its limitations. We must be aware that there is a group of pigmented lesions we cannot name in dermatoscopy, or even say whether the lesion is benign or malignant. Despite its limitations, dermatoscopy has significantly increased melanoma detection, especially in the early stages.

Article information and declarations

Authors contributions

Magdalena Misiak-Gałązka — conceptualization, investigation, supervision, visualization, writing — original draft preparation, writing — review & editing.
Małgorzata Lenarcik — writing — review & editing.
Adam Gałązka — visualization, writing — review & editing.

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Conflicts of interest

The author declare no conflict of interest.

Supplementary material

None.

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Effectiveness of imiquimod in the treatment of recurrent basal cell carcinoma on the face

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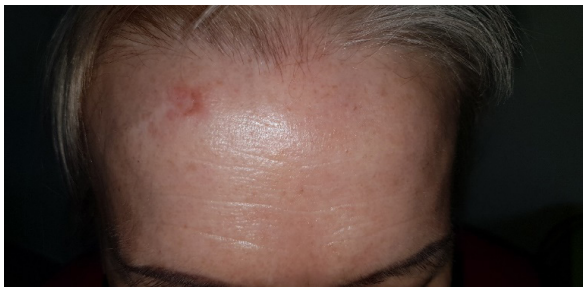

Figure 1. Clinical presentation of recurrent basal cell carcinoma (BCC) on the forehead

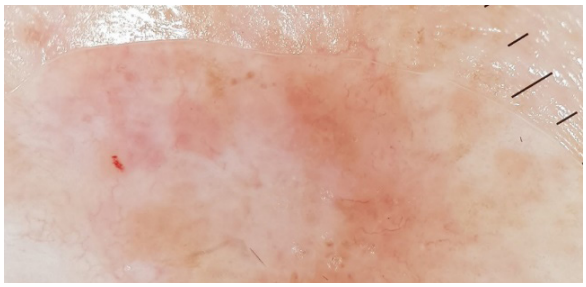

Figure 2. Dermoscopic image of recurrent basal cell carcinoma (BCC) on the forehead — linear vessels in the peripheral area and pink and white area in the middle of the lesion

Basal cell carcinoma (BCC) is a malignant skin cancer. The risk of recurrence of BCC within 5 years after surgical excision was estimated as 1–8%. [1] Treatment of facial malignant lesions is challenging due to the need for complete removal and good aesthetic effect. [2]

A 67-year-old female patient presented erythematous lesion and erosion within the right side of the forehead. The lesion was surgically removed. Histopathological examination confirmed diagnosis of superficial BCC (sBCC) but single cancerous cells were found in the lateral margins. Due to lack of dermoscopic signs of BCC within the scar and the patient's preferences, the lesion stayed under further observation. The clinical and dermoscopic findings after 6 months of observation indicated recurrence of BCC (Fig. 1, 2). Due to the patient's preference for good aesthetic effect, treatment with 5% imiquimod was initiated with cream application for 6 weeks, once daily 5 times a week. During the 3 year follow up, the clinical and dermoscopic findings did not reveal any signs of recurrence of BCC. Good aesthetic outcome was obtained.

The presented case underlines the importance of careful observation in patients with a history of BCC, and shows the efficacy of the imiquimod in the treatment of recurrent BCC. Thus in some cases, non-surgical methods could be considered as an alternative for surgical ones.

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