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Contents

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Editorial

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Dear Readers,

I am pleased to inform you that *Nowotwory. Journal of Oncology*, the official journal of **the Maria Sklodowska-Curie National Research Institute of Oncology** and of the Polish Society of Oncology and also the journal of the Polish Society of Surgical Oncology, **received the score of 100 points** in the current list of journals of the Ministry of Education and Science.

This marks another step in the gradual development of our Journal. Last year we changed the method of submitting manuscripts and introduced changes in the presentation scope of tables and graphs, restoring the *invited editorials*. This year, we have introduced a new cover, which is more transparent and which reflects current trends observed in medical journals. Moreover, our Journal is indexed in many biomedical databases and the number of submitted manuscripts, also from abroad, is continually increasing.

What is more, we have **concluded the first edition of the *Best Original Paper Award***. The award is given to the best original paper published in the preceding year in *Nowotwory. Journal of Oncology*. The members of the competition jury are: Professor Jan Walewski – the Director of the **National Research Institute of Oncology**, Professor Adam Maciejczyk – the President of the Polish Society of Oncology, Professor Dawid Murawa – the President of Polish Society of Surgical Oncology and the editor in chief of *Nowotwory. Journal of Oncology*, signed below. **This year, the jury selected the paper authored by Joanna Kufel-Grabowska et al., titled *Breast-conserving surgeries in HER-positive breast cancer patients are performed too rarely in Poland* (*Nowotwory. Journal of Oncology* 2020; 70(6): 225–229).**

Another edition of the competition will be held this year, that is why I strongly encourage the authors to submit the original scientific papers, which can be uploaded via our website: nowotwory.edu.pl.

Wojciech M. Wysocki
Editor in Chief

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Original article

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The impact of neck lymph node volumetric status on local control of the primary tumour (LTC) in radiotherapy for oral cavity and oropharyngeal cancer

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The study analyses the impact of volumetric nodal involvement (total nodal volume – TNV) on local control of the primary tumour (LTC) in radiotherapy for oral cavity and oropharyngeal cancer. The results show a significant decrease of the LTC (within a constant GTV) by about 10–20%, when the TNV increases from 10 to 40 cm^3. It suggests delivering an extra boost dose of 3–4 extra fractions of 2.0 Gy fractions to the primary tumour in the case of nodal involvement (initial total nodal volume).

Key words: total nodal volume, local tumour control, extra boost dose

Introduction

Standard radiotherapy protocols for head and neck cancers define techniques and dose fractionation regimens for primary tumours and for regional neck lymph nodes when they are involved or not. Both depend on tumour (T) or neck nodes (N) stages defined by the TNM staging system. It sounds illogical to use the TNM staging to design technique and dose fractionation, because the direct target for radiation is tumour or nodal volumes (which reflect the initial number of stem cells which have to be eradicated), but not the T and/or N stage. This argument is supported by increasing number of published studies [1–8].

There is no doubt that malignant tumours are highly heterogeneous as regarding their biological characteristics and response to radiotherapy. The ability of a cancer to metastasize to regional lymph nodes is one of its universal characteristics. This does not mean, however, that cancer cells which escape to regional lymph nodes are the same as those which remain in the primary tumour. It is probable that the biology and sensitivity of primary cancer stem cells which remain in the tumour do not necessarily stay unchanged. Therefore, it is interesting to answer to the question whether there is any impact of the involved neck lymph nodes on radiation response (local tumour control – LTC) of the primary tumours compared with those with N0 status.

Material and methods

The retrospective study consists of consecutive 103 patients with oropharyngeal or oral cavity cancer (OPC) treated with radiotherapy alone (3D-IMRT) in a single institution. Based on frequent, serial CT/MRI scans, volumes of primary tumours and neck lymph nodes were estimated using the formula:

$$V = 4/3\pi r^3 = 4.186 \times r^3 \text{ (radias)} \quad [1]$$

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Volumes of individual lymph nodes were added giving total nodal volume (TNV):

$$TNV = \Sigma_i VN_i \quad [2]$$

The distribution of TNM tumour stages, primary tumour volumes (GTV) and nodal volumes (TNV) is presented in table I. Involved neck nodes (N+) occurred in 62 patients (60%) and this group was used to analyze the impact of the TNV on 3-year local control of the primary tumour (LTC). The remaining group of 41 cases withstatus was used as a *control group*.

Three different N0 dose fractionation regimens were used including conventional treatment with 66–71 Gy in 42–46 days, accelerated CAIR with 70–72 Gy in 35–40 days and hyperfractionated split-course (CHA–CHA) with 64 Gy in 28 days. Since total doses (TD), doses per fraction (di) and overall treatment times (OTT) differed, to analyze and compare their clinical efficacy, the biologically equivalent dose (BED) was estimated using the following linear-quadratic formula [9]:

$$BED_{2.0/45} = [TD\ (di + \alpha/\beta) / (2.0 + \alpha/\beta)] + [-\ (OTT - 45\ days) \cdot 0.7\ Gy/d] \quad [3]$$

which, is a biologically equivalent total dose if given in 2.0 Gy fractions in the OTT of 45 days ($BED_{2.0/45}$) using $\alpha/\beta = 10$ Gy. Parameter 0.7 Gy/d represents an average daily dose, the biological effect of which is neutralized by accelerated repopulation of cancer cells [10, 11]. The OTT of 45 days represents an average time factor. If the OTT was shorter/longer than 45 days, then the respective factor of the repopulated dose was added to or deducted from the estimated $BED_{2.0/45}$ [3]. Physical parameters and respective $BED_{2.0/45}$ of the three fractionation regimens are presented in the table II.

All cases had at least a 3 years follow-up, and therefore the LTC curves estimated using the Kaplan-Meier method are raw, not actuarial. The statistical significance of the LTC differences was estimated using a t-Student test modified by Yates and $p = 0.049$ was accepted as a limit of significance.

Table I. Characteristics of 103 OPC patients in relation to the TNM and volumetric staging

Stage		No. cases	%
TNM stage			
T1–2N0		27	26%
T1–2N+		13	13%
T3–4N0		14	14%
T3–4N+		49	47%
volumetric diameter primary tumour (PTV)			
≤5 cm^3	≤2 cm	10	10%
5.1–14 cm^3	2–3 cm	28	27%
14.1–27 cm^3	3.1–3.7 cm	32	31%
27.1–33 cm^3	3.8–4 cm	7	7%
33.1–47 cm^3	4.1–4.5 cm	16	15%
>47 cm^3	>4.5 cm	10	10%
neck lymph nodes (TNV)			
N0	0 cm	41	40%
≤5 cm^3	≤2 cm	31	30%
5.1–14 cm^3	2–3 cm	17	16%
14.1–17 cm^3	3–3.3 cm	8	8%
17.1–35 cm^3	3.3–>4 cm	6	6%

Results

For 103 analyzed patients, overall 3-year Local Tumour Control (LTC) was 78% and 67% of Locoregional Control (LCR). The LTC-TNM stage relationships (tab. II a) have shown no significant impact of N stage on the LTC for T1–2, whereas for T3–4 tumours, neck node involvement (N+) resulted in lower LTC, compared with N_0 data sets, however a significant difference ($p < 0.01$) was noted only between T1–2N0 and T3–4N+.

For primary tumour GTV volumes, an increase of their sizes resulted in significant ($p < 0.01$) decrease of the LTC. However, changes in the GTV do not linearly correlate with changes in the total nodal volume (TNV) and any analysis of relationships between four variables, which are: LTC, NTD izoGy$_{2.0/45}$, GTV and TNV, and the impact of the TNV on the LTC is not simple and

Table II. 3-year local control of primary tumour (LTC) depending (a) TNM status, (b) volumetric status

Stage		NTD in izoGy $_{2.0/45}$			Overall
		60–65	66–70	≥75	
TNM	**(a)**				
T1–2	N0	80%	90%	95%	85%
T1–2	N+	75%		90%	85%
T3–4	N0	50%	70%	80%	79%
T3–4	N+	45%	50%	60%	59%
volumetric	**(b)**		70 ± 3 izoGy$_{2.0}$		
GTV cm^3	**TNV cm^3**				
≤5	<10		5/5–100%		
10	10		7/8–88%		
20	<10		5/7–71%		
30–50	20–40		8/16–50%		
40–60	40–60		2/6–33%		
60–90	50–70		1/6–17%		
			$p < 0.0005$		

precise; it is likely to be a source of uncertain interpretation. For that reason, to enhance the reliability of the achieved results *claster* (which simply means a bunch of grapes) analysis is based on grouping the data into fairly homogenous sets (at least in one or two parameters e.g. GTV and TNV). The aim of such analysis is to find the interrelationship among the analyzed variables and to determine whether some variables can be grouped together based on their similarities. Therefore LTC-TNV-$NTD_{2.0/45}$ – relationships were analyzed in the marked out small subsets of data being fairly homogeneous regarding at least one or two parameters. Four *clasters* include all together 62 cases irradiated with $NTD_{2.0/45}$ in the range 65–75 $izoGy_{2.0/45}$.

Figure 1 shows that primary tumour control (LTC) in relation to primary GTV and TNV cannot be represented by a single LTC curve, but there are series of LTC curves that depend on the relations between the tumour and nodal volumes. In *claster* A overall arrange LTC equals 86% but for GTV (<5 cm^3), TNV in the range 5–10 cm^3 has no impact on the LTC, but for a bit larger GTV (5–10 cm^3), TNV of >10 cm^3 causes a decrease of LTC by about 25%, although this tendency is not significant. For larger GTV (>20 cm^3) significant ($p < 0.005$) impact of the increasing TNV to more than 50 cm^3 results in significant ($p < 0.005$), decreasing LTC from 65% (*claster* B) to 33% (*claster* D). In *claster* D local recurrences of primary tumours predominate. This negative impact of the TNV on primary LTC is shown in table II b, which includes only cases irradiated with the $NTD_{2.0/45}$ within the narrow range of 70 ± 3 $izoGy_{2.0/45}$. Increasing TNV from <10 cm^3 to 50–70 cm^3 for larger GTV (from 5 cm^3 to 90 cm^3) significantly ($p < 0.005$) lowers 3-year primary LTC. In the group of N0 cases (tab. II a), the LTC only depends on the $NTD_{2.0/45}$ value.

Figure 2 shows that the LTC curve for N0 cases (solid lines) depends on primary GTV compared with the lower LTC curve which represents the impact of involved neck lymph nodes (dotted lines for TNV > 10 cm^3). The relationship between three variables LTC, GTV and TNV shown in figure 2 convincingly

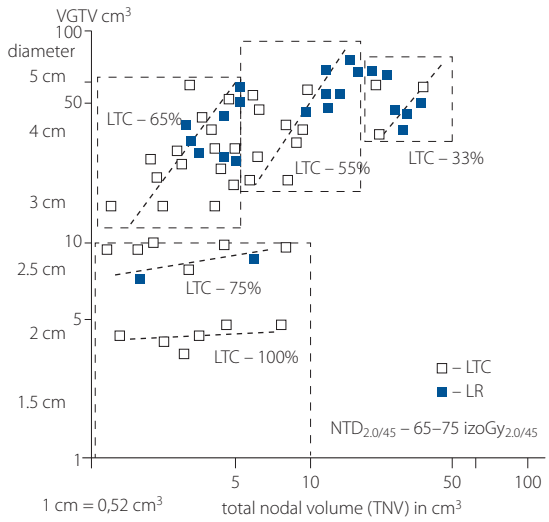

Figure 1. Four data clasters of primary tumour control (□) or recurrence (■) depending on tumour (GTV) and nodal (TNV) volumes

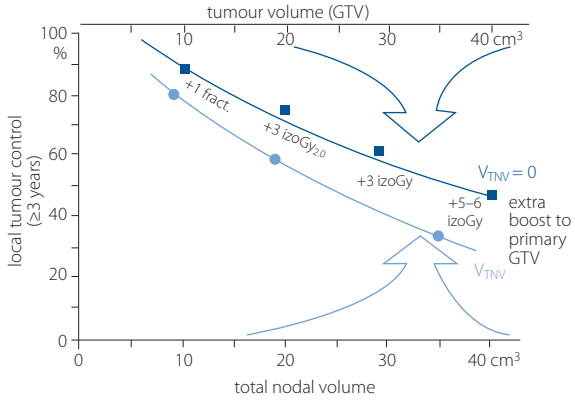

Figure 2. Local tumour control curves for non-involved (■) and metastatic (●) neck lymph nodes depending on their total nodal volume (NTV)

confirms the significant negative impact of the total volume of positive neck nodes (TNV) on the lowered LTC, than in the case of the GTVs with no evidence of regional nodal disease; and suggests that in the case of positive TNV, a boost dose of 3–6 $izoGy_{2.0}$ to the primary tumour should be considered to increase the LTC to the level expected for N0 status.

Discussion

For a number of years, growing interest has been focused on the impact of tumour heterogeneities on their response to radiotherapy. A lot of efforts have been focused to identify various types of heterogeneities which may limit tumour radiocurability. Differences in the intrinsic radiosensitivity of tumour cells and environmental factors affecting tumour responses to radiation. Tumour stage and dose fractionation have been considered important parameters to design radiotherapy strategy, including that for head and neck cancers. Primary tumour control (LTC) and neck lymph node curability (RNC) are traditionally considered separately, since techniques and delivered dose fractionation also differ. It is obvious that local control (3- or 5-years) lowers when T and N stage increases (tab. II a).

In the 1980s, some authors [12, 13] noted the adverse effect of lymph node involvement on local tumour control, however, for the first time, Wall and Peters et al. [14] demonstrated the direct impact of neck lymph node disease on local control of the primary tumour of the supraglottic larynx (fig. 3). Although authors convincingly documented the negative impact of regional nodal involvement on 5-year local control of the primary laryngeal tumour, this fact was ignored for the next 3–4 decades, until the present study was undertaken. The authors widened N in TNM staging from 0–3 to 0–9 N scores for the group of 248 patients with supraglottic cancer (149 patients with N0 status). Treatment to the neck varied – only 59 patients (24%) received whole neck indication, and 38 patients (15%) had a neck dissection prior to radiotherapy. Moreover, the average total dose (Gy) delivered to the primary tumour was not modified by N stage, and did not differ much, being in the

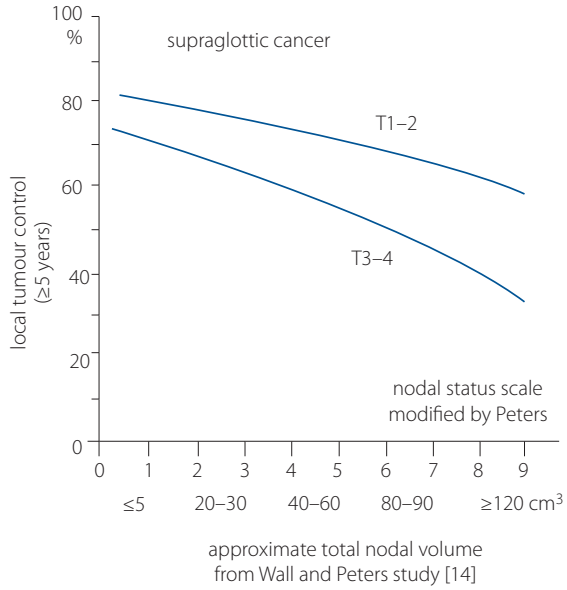

Figure 3. Wall and Peters [14] local control of T1–2 and T3–4 supraglottic cancer depending on neck lymph node scale (0–9) of metastatic involvement

range of 65 ± 10 Gy. Despite of that, Wall and Peters clearly showed a significant ($p < 0.03$) decrease of 5-year TCP of T1–2 and T3–4 with increasing N scores from 1–9 compared with N0 status (fig. 3). The results of these authors are very similar to those found in the present study (fig. 2). As opposed to their study, in the present one, T and N scores are replaced by more precise parameters as GTV and TNV volumes. Despite the different tumour types, both studies show the same adverse impact of neck node disease on the TCP of the head and neck primary tumour.

According to Wall and Peters, a plausible explanation for such adverse impact of nodal involvement on the primary tumour TCP could be that both primary tumour radioresistance and nodal metastatic potential might result from a higher proportion of clonogenic cancers cells. More *jaunly*, well oxygenated clonogens escaping into the lymphatics are able to establish metastatic lesions in the regional lymph nodes. The cells which remain to stay in the primary tumour may likely be characterized by slower cell turnover. It is hard to dismiss the possibility that they are synchronized in the most resistant phase of the cell cycle, being even more resistant than hypoxic cells in the more sensitive phase. This does not exclude the other option that the greater the number of clonogenic cells in the tumour and involved population of nodes, the lower the probability that they will be sterilized by a given dose of radiation. Such a concept was defined by Peters et al. [15] as "probabilistic radioresistance". On the other hand, cellular genetic factors may determine primary radioresistance and metastatic potential. Increasing cellular aneuploidy could likely be considered as one such factor. High ploidy H&N tumours has been recognized as more resistant [16]. Finally Wall and Peters et al. [14] suggest that primary tumour radioresistance was due to inherent cellular characteristics, reflected by nodal metastases. Wall and Peters [15] used a very similar range of delivered doses independent of early or advanced T and N stages. Similarly to the present study, the $NTD_{2.0/45}$ for various clasters of the GTV and TNV did not differ very much. Both studies clearly show that a given T stage or GTV volume is not represented by a single dose and the same TCP values, but its differ depending on N status (N0–9) or in our study, by the TNV volume (0–> 40 cm^3).

Conclusions

Whatever the mechanism of such an effect is, both studies suggest that primary tumours in patients with nodal involvement should likely be treated more aggressively than those with the same T (or GTV), but without nodal involvement. According to the present results, in the N+ patients, primary tumours should receive an extra boost dose depending on initial GTV and TNV. For the GTV and TNV of about 10 cm^3 (early stage), one extra fraction of 2 Gy is recommended which should increase to 2–3 fractions (each of 2 $izoGy_{2.0/45}$) with increases in GTV and TNV above 40 cm^3.

Conflict of interest: none declared

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Neoadjuvant therapy for breast cancer patients and its impact on surgical treatment and radiotherapy (part 2.)

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Neoadjuvant therapy (NAT) is increasingly applied in patients with initially inoperable breast cancers and, frequently, in those with tumours that are initially operable, too. In most cases, the response to the applied NAT affects the scope of surgical treatment and radiotherapy, and in some situations also the complementary systemic postoperative treatment. The available studies indicate importance of response to NAT within the breast and regional lymph nodes. Assessment of response to treatment allows personalization of treatment and in some cases a change of therapy, which improves long-term outcomes.

This article summarizes the current rules of conduct in patients with early breast cancer qualified for neoadjuvant therapy, paying attention to the practical aspects and possibilities of national health insurance-covered therapies in Poland. It discusses in detail the applied regimens of systemic therapy, surgical techniques, eligibility rules and complementary radiotherapy. Systems for assessing response to neoadjuvant treatment are also presented.

Key words: breast cancer, surgery, systemic therapy, neoadjuvant therapy, adjuvant therapy

Surgical treatment

The canon of surgical treatment outlined by W. Halsted in 1894 consists in treatment of the mammary gland and axillary lymphatic drainage. Despite numerous modifications, the standard of surgical treatment of cancer patients is as follows:

- in the breast area:
  - sparing treatment (various methods) or
  - mastectomy (various methods with / without simultaneous reconstruction),
- in the axillary area:
  - sentinel lymph node biopsy (SLNB), or
  - axillary lymph node dissection (ALND) [1].

Mammary gland surgery

There are five forms of response of the breast tumour to systemic neoadjuvant therapy:

1. complete disappearance of neoplastic changes,
2. reduced size,

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3. multifocal atrophy of neoplastic tissue without a change of the tumour contour (tumour fragmentation, the tumour resembles a honeycomb),
4. no response to treatment,
5. progression during treatment [2].

There are different definitions of pathological complete response (pCR) to NAT, therefore the post-operative histopathology report should always describe presence or absence of a residual component of the DCIS (ductal carcinoma *in situ*). Progression during NAT in the case of inoperable lesions (cT4N2/3, inflammatory breast cancer) is observed in about 3% of cases. Patients with symptoms of disease progression during NAT have a poor prognosis regardless of whether a surgery can be performed [2].

Size of the tumour, along with the biological subtype is one of the eligibility criteria for NAT. The Livingstone-Rosanoff study analysed 38,864 cases of patients who had had neoadjuvant therapy. Pathological complete response was recorded in 19% of the patients, including 15% of those with tumours above 5 cm (cT3) and 20–21% of those with tumours up to 5 cm (cT1–2). The effect of the biological subtype on response to the treatment was much higher. The highest rates of clinical response were observed with HER2+ and TNBC cancers [3].

Microcalcifications are found in some patients after NAT with or without a tumour visible on imaging studies. In 38.5% of patients, the extent of microcalcifications assessed by mammography after NAT does not correlate with the extent of the remaining tumour. Patients who initially had steroid receptors present (HR+) have more malignant microcalcifications after NAT as compared to patients with no such receptors in the tumour (HR–) (48.9% *vs.* 13.5%, $p = 0.019$) [4]. Within microcalcifications, only 24–50% of pathological complete responses to NAT are found. Further, microcalcifications often indicate the presence of a residual DCIS component. Therefore, considering lack of efficient imaging methods (digital mammography and magnetic resonance mammography) in assessing response (pCR) to NAT, surgery should involve complete removal of microcalcifications [5].

For various reasons, not all patients undergo surgical treatment of the primary lesion after NAT. In an assessment of 350 patients who had not undergone surgery after NAT (they had only had external beam irradiation [XRT] applied) in comparison to a group of patients who had been operated on (breast conserving treatment [BCT]) no statistical differences were found with respect to OS (95.7% *vs.* 86.9%, $p = 0.26$) [6]. It may be a very tempting option for patients to forego a surgery, in the case of clinical and radiological response to NAT, confirmed as pCR by a vacuum-assisted biopsy (VAB). At the San Antonio Breast Cancer Symposium 2019, results were presented of 4 trials assessing effectiveness and accuracy of VAB in the case of clinical and imaging complete response in breast MRI after NAT. False-negative rate (FNR) ranged between 17.8 and 39%, while negative predictive value (NPV) was between 75 and 84%. No residual neoplastic disease was identified in 2/3 of patients. Thus, there is no scientific evidence to justify foregoing resection of the primary breast cancer focus after NAT, even in the case of clinical and imaging complete response [7–10]. However, it should be stressed that sensitivity of VAB in identification of the residual disease after NAT depends on thickness of the applied needle and number of samples – the best results can be obtained with 7–8 G needles and large number of samples.

There is a discussion about the problem of potential local recurrence after NAT in patients who had a breast-conserving surgery. A meta-analysis by Early Breast Cancer Trialists Collaborative Group, based on data from a follow-up of patients treated in 1983–2002, revealed higher rates of local recurrences after pre-operative chemotherapy as compared to post-operative chemotherapy: 21.4% *vs.* 15.9% ($p = 0.0001$) [11]. A more recent study by the German Breast Group brought opposite results. This organisation's meta-analysis covered more than 10,000 patients with NAT, who had participated in 9 clinical trials applying systemic neoadjuvant therapy between 199 and 2013. It proved that the 5-year rate of locoregional recurrence (LRR) was 7.8% for breast-sparing treatment, 11.3% for mastectomy, 4.1% in the case of pathological complete response (pCR), and 9.5% in the case of pathological partial response (pPR) (HR – 3.33, $p < 0.001$). Depending on the biological subtype, LRR was: for LA / LB – 6.9%, HER2-LB – 7.6%, Her2-NL – 10.5% and 14.4% for TNBC. The multivariate analysis showed that it was the patients' young age, clinically changed lymph nodes, G3 grade, and not the type of surgery, that influenced the partial response to treatment (pPR) [12].

The period of neoadjuvant systemic therapy allows for further diagnostics, enabling identification of patients with hereditary predisposition to breast cancer. If such changes are found and upon consultation with the patient, the planned scope of the surgery can be changed, e.g. to plan a bilateral mastectomy with reconstruction instead of a breast-sparing surgery.

In breast surgery, the dominating approach can be described as breast-contour-preserving procedure (BCPP). After a surgery, the patient's silhouette should be preserved, including breast prominence. In the Netherlands, the percentage of BCPP is steadily increasing. In 2015, BCPP made 71% of surgeries, mostly due to the increasing number of breast-conserving surgeries (BCS) – a significant part of them after NAT – with immediate breast reconstruction (IBR) after mastectomy. BCS is dominant in the 50-60 age group (57-63% of surgeries), BCS after NAT among patients under 50 years of age (12–14% of surgeries), and IBR mastectomies among patients under 40 years of age (26-44% of all surgeries in this age group). Depending on the hospital, BCPP procedures are performed in 47–88% of operated patients in the Netherlands [13]. In women with operable breast cancer, a decreasing trend is observed in performance of BCS, while the percentage of

mastectomy is growing (mostly nipple sparing mastectomy [NSM]) with immediate breast reconstruction – direct to implant (IBR-DTI) [14].

Kołacińska analysed surgeries at 8 centres in Poland. At 7 wards, BCS was performed in 50–70% of patients and only at 1, it made 24% of surgeries. IBR mastectomy was performed in 6–42% of patients, including 5 oncology centres performing surgeries after systemic neoadjuvant therapy [15].

A very important criterion for selecting the type of surgery is patient satisfaction. The BREST-Q questionnaire (a tool measuring patients' satisfaction after surgical treatment) enables estimation that satisfaction with the physical effect of the surgery decreases with time elapsing after its performance, while satisfaction in psycho-social aspect and sexual satisfaction increases. However, patients after BCT display higher satisfaction in all aspects as compared to patients after SSM / NSM ($p < 0.001$). Probably it also matters for satisfaction that BCS, in contrast to NSM, allows for retaining sensation in the nipple, areola and skin and for natural "aging" of the spared breast, similar to the natural process. Radiotherapy leads to lower BREST-Q results throughout the observation period and in all analysed aspects ($p < 0.05$) [16].

Breast-sparing treatment

Breast-sparing treatment remains a standard in surgical therapy, also after the systemic neoadjuvant therapy [17]. The surgical resection margin must be free of any tumour infiltration, i.e. it should be assessed as R0 (no-ink-on-tumour) in the post-operative histopathology test. That's why after NAT, a surgeon removes the mammary gland tissue in the "new range", removing also the residual fragment of the tumour or only the site marked before the surgery (if the tumour is not identified clinically or in pre-operative imaging). The resection does not involve the mammary gland covering the area originally affected by the tumour, i.e. within the "prior" boundaries before NAT [18–21]. It is used only in the case of pPR and numerous diffuse changes reaching the borders of surgical cuts within the entire bed (the tumour resembles a honeycomb). Resection of the tumour bed can be considered then [22].

Depending on the centre's practices, re-surgeries performed in the case of non-radical resection of the tumour at the first surgery concern 10–50% of cases, and BCS after NAT – 6–36% [23]14/40 (35%). Resection of mammary gland tissue with oncoplastic breast-conserving surgery (OBCS) allows for oncological safety and aesthetic acceptability surgery, especially in the case of more locally advanced breast tumours. Due to the non-radical nature of the OBCS, re-surgery was required in 6% of cases after NAT and 4.3% after primary surgery. Complications were found in 23% of patients after NAT and 27% of those without neoadjuvant therapy [17]. OBCS is a safe and aesthetically acceptable option for a breast-conserving treatment after NAT.

In a three-year follow-up of patients after NAT and breast-sparing surgery for unifocal, multifocal and multicentric breast cancers, locoregional failure risk (LRFR) survival rate after a radical surgery (R0 margin) were: 92.9%, 95.1% and 90.4% respectively ($p = 0.002$) [24]. No difference was found in 10-year LRR after NAT between the BCT group and the mastectomy group (9.2% *vs.* 10.7%, $p = 0.8$). The OS was 63% *vs.* 60%, respectively ($p = 0.8$). In this group, all patients underwent postoperative radiotherapy [21].

Mastectomy

Non-reconstructive mastectomy is still the standard option in patients with inflammatory breast cancer (IBC) and cT4 staging [18, 19, 25]. In the case of complete remission after NAT, some expert recommendations allow conservative surgery or NSM + IBR [24, 26]. For women after mastectomy, simultaneous reconstruction allows for psychological benefits: it improves self-esteem and appearance, and reduces anxiety and depression associated with cancer treatment [27]. Skin-sparing mastectomy (SSM) described by Toth and Lappert (1991) and mastectomy sparing the skin and nipple-areola complex (NSM) originally performed by Freeman (1962) have become the standard surgical treatment of invasive breast cancer [28]. The European Society of Breast Cancer Specialists recommends a simultaneous reconstruction in a minimum of 40% of patients who underwent mastectomy [27]. In an analysis held in France in 2012, 27.4% of primary mastectomies were associated with reconstructions. These operations were more often performed in women under 65 (42.1%) than in older women (7.7%, $p < 0.001$). Reconstructions were performed more often at university hospitals and oncology centres than at public hospitals [29]. According to a report by the American Society of Plastic Surgeons (ASPS), the most common form of simultaneous post-mastectomy reconstruction is implant reconstruction. In 2017, over 80% of patients had 1-stage (direct-to-implant – DTI) or 2-stage (initially expander, then final breast prosthesis) reconstructions [30]. NAT had no effect on postoperative complications after IBR, regardless of the method of reconstruction (1- or 2-stage) [31].

Even if BCT treatment after NAT is possible, more and more young women choose mastectomy with simultaneous reconstruction [14]. In an analysis by the European Institute of Oncology in Milan, among 1,711 patients who underwent NSM, as many as 48.4% patients had cancers up to 2 cm (pT1) [32]. In Europe and Asia, in the case of TNBC cancers without BRCA mutation, a breast-sparing surgery is chosen by 55% of patients, and by 80% in the USA [33]. It should be highlighted, however, that there is no evidence of improved oncological results after application of broader procedures (uni- or bilateral mastectomy) instead of breast-sparing surgery in patients who are not diagnosed as carriers of mutations associated with increased risk of breast cancer. Further, most evidence suggests that the sparing therapy is associated with better

prognosis and better quality of life; therefore in cases where breast-sparing surgery is possible, mastectomy is not recommended or considered as an optimal option in management [34–41]. Moreover, many studies reveal worse outcomes in terms of local recurrence in patients with selected subtypes of breast cancer after mastectomy as compared to breast-sparing surgeries [42]. Therefore, a mastectomy should not be proposed or performed, if less radical treatment is feasible [43].

According to the analysis of National Cancer Database data (for 2010–2014) concerning almost 0.25 million women with T1–3N0–3 stage cancers who had had combined treatment (surgery and chemotherapy), NAT was provided to 25.3% of the patients. Pathological complete response (pCR) increased from 33.3% to 46.3% (p = 0.22). Lower frequency of unilateral mastectomies was observed (43.3% *vs.* 34.7%), while the rate of bilateral mastectomies without reconstruction remained on the same level (11.7% *vs*. 11.%, p = 0.82), with an increase in BCS (37.0% *vs.* 40.8%, p = 0.02) and bilateral mastectomies with IBR (8.0% *vs.* 13.1%, p = 0.02) [33].

In Poland simultaneous reconstructions were analysed by Kołacińska et al. Depending on the centre, IBR was performed in 6–42% breast cancer surgeries, including 70% with NAT at certified oncology centres [15]. Local recurrence rate is similar for SSM and NSM after NAT as in the case of mastectomy. LRR depends on the original tumour stage and is not correlated with the type of surgery [44].

NSM is the type of mastectomy preferred by women. Despite the fact that in a vast majority of cases the range of superficial sensation within the skin of the breast, and especially the nipple, is disturbed, this method enables a very good aesthetic, but also oncological effect, if patients are correctly qualified for surgery [32]. The NSM reconstruction success after one-year follow-up was 96.7% [45]. The major problem in performance of NSM involves ensuring a cancer-free surgical margin on the nipple side. In one study, neoplastic infiltration of the nipple-areola complex (NAC) was found in 13.3% of NSM surgeries without NAT and in 9.8% with NAT. Tumour infiltration of NAC was associated with the size and multifocality of the tumour [44]. Postoperative nipple necrosis was found in 3.3% of patients after a surgery [32, 46]. Complications after NSM / SSM and IBR occurred in 7.5–47.3% of treated patients [51, 68–70], while local recurrence was found in 3.2–5.3% of cases [32, 46]. Postoperative complications were not associated with NAT but with body mass index (BMI), smoking, adjuvant radiotherapy, and concurrent ALND [28, 45–47].

Currently, prepectoral breast reconstructions, popular in the 1960s, are regaining importance with improved production technology of implants and meshes applied in breast reconstruction – biological ones (acellular dermal matrix – ADM) or synthetic ones, fully or partially absorbable. This type of reconstruction is frequently applied by surgeons who reconstruct defects after mastectomy and it's popular among patients, too. Maintaining unchanged anatomy of the chest wall (muscles), acceptable rate of complications and very good aesthetic effect are the factors contributing to its popularity. In an analysis of 6 prospective clinical studies, "capsular contracture" in the case of ADM in prepectoral reconstruction was found in only 1.2% of patients [48, 49]. Another study assessed frequency of all complications of prepectoral ADM reconstructions at 28.6%. Skin necrosis occurred in 5.2% of operated patients and infection in 3.2%. According to the univariate analysis, serious complications were related to the body mass index (BMI), ALND performed, weight of the operated breast and size of the implants used [50]. Complications were found in 25% of overweight women and in 10% of women of normal weight. In patients with BMI of 30–35, complications rate was at the level of 18%, and those with BMI> 35 – at 41% [51].

Recommendations by the international team of surgeons led by Vidya which concern prepectoral reconstructions describe the following counterindications against NSM: BMI > 40, diabetes which is difficult to control, smoking, chronic immunotherapy, previous radiotherapy of the chest wall, tumour infiltration of the skin and the chest wall. The authors of these recommendations state that the 1-step technique (DTI) is more frequent in Europe and the 2-step technique in the United States. In the second stage of treatment, expander is exchanged for a permanent prosthesis, and frequently fat cells are additionally transplanted. The authors of the recommendations approve various techniques of covering the implant with a mesh: complete, only partial from the side of the skin pocket, and combined technique: mesh with a stripped skin flap from the bottom. They indicate also that it is possible to perform NSM with a prepectoral mesh technique if the patient is eligible for postoperative radiotherapy [48], but they stress that in addition to the mentioned contraindications, the patient's skin flaps must be sufficiently thick [34]. Finally, they highlight that previous observations are based on short-term follow-up (as compared to follow-up of patients with submuscular reconstructions), and there are no randomised trials to compare oncological outcomes and distant cosmetic results of pre- and retropectoral techniques.

Before applying prepectoral techniques, especially in patients who will undergo radiation therapy, it is important to bear in mind these conditions and the fact that previous observations concern selected groups of women, most often with very favourable parameters determining good quality of the skin flaps. So far, there have been no randomised trials considering surgery technique, scope of the surgery, radiotherapy design (changing in recent years), disease stage, subcutaneous tissue thickness and other factors which affect the rate of lost implants and the risk of formation of a fibrous pouch around the implant. The authors stress that qualification for surgery should be careful and balanced and the patient should be informed that the prepectoral technique is quite new and there are no long-term observations on its outcomes. Undoubtedly, frequency of prosthesis rippling at the neckline should be

mentioned, as it requires procedures of filling the defects with fat transfer. The cost of ADM meshes is important, too, and in Poland the procedure of filling defects with free fat transfer is not reimbursed by the state insurance.

Prepectoral location of the implant and adjuvant radiation therapy are new methods that are observed very closely. Initial results of simultaneous prepectoral reconstructions are very promising and they suggest favourable surgical and cosmetic outcomes. In Sigalow's study (52 patients), during 25 months' follow-up complications occurred in 5.9% of patients with post-operative radiation therapy, and the implant had to be removed in 2.9% of the patients. No case of "capsular contracture" was recorded [30, 52].

Sinnott et al. assessed the incidence of complications after prepectoral and retropectoral reconstructions in patients after radiotherapy. Prepectoral reconstructions were performed using Wise technique, i.e. the "pocket" for the prosthesis was the lower, deepithelialized lobe of the mammary gland with an ADM mesh sewn from above. "Capsular contracture" occurred in the non-radiotherapy group in 3.5% of the patients and after radiotherapy in 16.1% of the cases ($p = 0.0008$). In patients after radiotherapy, complications were three times more frequent after retropectoral reconstruction (52.2% *vs.* 16.1%, $p = 0.0018$) and they were more intensive ("capsular contracture", 3–4 grade in Baker scale: 83.3% *vs.* 22.2%, $p = 0.0092$) as compared to patients with prepectoral reconstruction. However, the authors stressed the short follow-up time and the increased incidence of prosthesis rippling [53].

With the increasing use of NSM technology, both in surgeries in patients with diagnosed invasive cancers, and in cases of mastectomy in women with indications for surgery to reduce the risk of breast cancer (prophylactic mastectomy), increasing attention has been paid to radicality of the surgery and possibility to leave residual breast tissue (RBT) on the skin "envelope" (NSM and SSM surgeries). In a survey, 550 doctors (radiotherapists and surgeons) were asked about frequency of RBT after SSM/NSM. The answer "never" or "rarely" was chosen by 69.4% radiotherapists and 75.8% of surgeons. Meanwhile the question whether 10 mm of RBT was acceptable in terms of oncological safety, was answered affirmatively by 39.2% of radiation therapists and 59.9% of surgeons [54].

In the SKINI-Trial (10 to 14 envelope skin points were studied after NSM/SSM), RBT was identified in 51.3% of mastectomies. In the case of SSM, RBT was found in 40.4% of the operated patients and for NSM – In 68.9% ($p < 0.001$). Residue varied depending on the surgeon from 26.2% to 100%. Flap necrosis was found in 28% of NSM surgeries and 15% of SSM surgeries ($p = 0.051$). It was emphasized that the heterogeneous anatomical structure of the gland surface could affect radicality of the removal of glandular tissue. When performing subcutaneous excision of the mammary gland and generating even very thin skin flaps for the "skin envelope", the surgeon may leave intact vascular system, allowing for radical and uncomplicated mastectomy [55, 56]. In their study, Gianotti et al. found RBT in 29.9% of mastectomies performed. RBT was found at 2.8% of the studied points after a radical mastectomy, 13.2% after SSM and 73.8% after NSM. The presence of RBT correlated with flap thickness ($p < 0.001$), patient weight ($p < 0.001$), mastectomy type ($p < 0.012$ for SSM, $p < 0.001$ for NSM/MRM) and breast reconstruction with a flap ($p < 0.019$). In 9 out of 11 measurement points, the thickness of the flap exceeded 5.5 mm [57]. The clinical significance of residual breast tissue (RBT) after NSM/SSM is unknown, so further patient follow-up and prospective studies are necessary [56].

In some patients after mastectomy with reconstruction and radiation therapy, autologous transplant of fat tissue to the surgery site is necessary for aesthetical reasons. This method is widely applied by oncologic surgeons and plastic surgeons and it is safe in the oncological aspect [58].

Lymph node surgery

Historically, after systemic neoadjuvant therapy, axillary lymph node resection was performed, regardless of the condition of the nodes. Introduction of the sentinel lymph node biopsy (SLNB) has changed the standard procedures in diagnosis and management of patients with breast cancer. SLNB is the only verified and reliable method of diagnosing regional lymph drainage. Patients with clinically unchanged lymph nodes (cN0) are eligible for SLNB. If systemic neoadjuvant therapy is applied, cN0 is diagnosed in two situations:

1. initially cN0,
2. initially cN1 with conversion to cN0 after NAT (ycN0).

Both national and international guidelines recommend SLNB after NAT. This allows the following benefits:

- performance of only one surgery within the lymph node drainage system (in cases of ypN0), i.e. breast cancer surgery with SLNB,
- evaluation of the response to the applied systemic treatment, both within the breast tumour, and regional lymph nodes,
- achieving successful pCR within the axillary lymph node (conversion from pN1 to ypN0) in order to avoid ALND [18,19, 59, 60].

Pilewski et al. found that personalisation of the therapeutic sequence is a way to reduce the number of ALND procedures performed. The decision whether to start the treatment with a surgery or NAT should depend not only on the biological subtype of the cancer, but also on the scope of surgery within the breast (BCS *vs.* MT). These authors strongly recommend primary systemic treatment (NAT) for: HER2-positive cancers and TNBC, as such a treatment strategy reduces the proportion of performed ALNDs [61]. Depending on the biological subtype of the breast cancer, response of nodal metastases to NAT varies. Complete response to neoadjuvant therapy was achieved in lymph nodes in approximately 20% of patients with LA/LB biological subtype of cancer, and in 48–70% of

patients with HER2-LB, 60–97% of patients with HER2-NL and in 47% of cases with TNBC [62, 63].

The study by Samiei et al. compared the response to preoperative chemotherapy in breast tumours metastasising to regional lymph nodes. For initially cN0 cancers (with pCR within the breast itself), 97.7% had ypN0 stage, while in cases with pPR within the breast, only 71.6% were ypN0 stage. For initially cN1 cancers, if pCR occurred in the breast, 45% of patients had ypN0 stage, while with pPR in breasts only 9.4% had ypN0 stage [64, 65]. Experience of multiple centres which perform sentinel lymph node biopsies after the systemic treatment shows that NAC changes SLNB outcomes by reducing identification of sentinel lymph nodes and increasing FNR [66]. Based on an analysis of NSABP B-18 and B-27 studies, Mamaunas et al. concluded that the most important predictor for LRR after NAT involves the residual lymph node metastasis (ypN+) [67].

When qualifying a patient for SLNB after NAT, the therapeutic team should determine accuracy of the method used (SLNB) and its oncological safety [66].

Initially cN0 lymph nodes

Multiple studies and meta-analyses show that SLNB performed according to the given centre's standard (usually this a radioisotope +/− stain) is equally effective in patients assessed at cN0 before the systemic treatment as for those without the primary systemic therapy. SLN identification is assessed at >90%, and FNR at <10% (method reference values). No differences were observed in loco-regional recurrence, DFS and OS in patients with cN0 cancer (pN0) who underwent only SLNB as compared to those qualified for ALND. The rate of regional recurrences was at 1% [66, 68]. Therefore, for cN0 patients, SLNB is recommended after NAT [18, 19, 60, 69, 70]. Genea2 study showed that about 25% of clinically suspicious lymph nodes contain metastases after NAT (cN0 ypN1). The initial size of the tumour at T2–3, G3 feature and luminal subtype of breast cancer correlate with frequency of identified metastases to sentinel lymph nodes after NAT (tab. I) [71].

The standard SLNB procedure in patients with cN0 tumour who begin oncological treatment with systemic therapy should include:

Table I. Metastases to SLN after NAT, depending on the stage of breast cancer and its biological subtype [71]

Stage	Biological subtype	Drainage of SLN containing metastases (%)
cT1–3N0	LA/LB (ER+HER–)	23.8–41.7%
	HER2-LB (ER+HER+)	7.2–11.5%
	HER2-NL (ER–HER+)	0–6.3%
cT1–2N0	TNBC	2.9–6.2%
cT3–N0	TNBC	30.4%

- SLNB performed after NAC,
- application of SLNB technique which is standard at the given centre, as in the case of primary surgical treatment ("isotope", "dual technique", or another one, e.g. SentiMag),
- identification of the number of sentinel lymph nodes (SLN) according to the surgery technique (although some institutions recommend sampling 2 SLN).

Patients should be referred for ALND if:

- SLN are not identified,
- there are metastases to SLN (including ITC).

Initially cN1 lymph nodes

The increased rate of referrals for systemic neoadjuvant therapy affects surgical management of some patients with primary metastases to axillary lymph nodes – cN1/pN1. After NAT, frequency of ALND performed decreases, while there are more SLNB procedures. At Mayo Clinic in 2009–2017, a decrease of 60% was observed in the case of ALND after NAT, and an increase of 60% in the case of SLNB, while an Italian centre recorded an increase of SLNB procedures from 9.1% in 2011 to 46.5% in 2017 [72, 73]. A prospective study by Mamtani et al. showed that after NAT, it is possible to perform SLNB in approximately 70% of patients with initial cN+ cancer and in 48% it is possible to forego ALND [64].

Currently, international and national guidelines recommend:

- SLNB in patients with ycN0 cancer after systemic treatment,
- ALND in any case of ycN1 or ypN+ cancers [18, 19, 59, 60, 70].

So far, there have been organised four multi-centre prospective clinical trials to assess possibility of performing SLNB after a conversion from cN+ to cN0 after the systemic oncological treatment (tab. II).

As shown in table IV, SLNB performed in such a group of patients carries relatively low identification index below 90% and quite high FNR – above 10%. These values are inacceptable, if the method should be recommended as a reference.

To improve SLNB outcomes in patients with initial cN1/pN1 cancer and conversion to ycN0 stage after NAT, two variants of the surgery have been developed.

Option 1. Classical biopsy of sentinel nodes. In these patients, it is required to apply the "dual method" (staining and isotope) for identification of SLN and sampling of at least 3 lymph nodes corresponding to SLN criteria.

It was noted that SLNB after NAT performed analogically to the group without NAT (single biopsy with a radioisotope and identification of 1–2 sentinel lymph nodes), bears an unacceptably high FNR rate. In GENEA2 study, FNR was 19.3%, when only 1 SLN was identified, and in ACOSOG Z1071 it was 21%, when at least 2 SLN were identified. Meanwhile, the SENTINA study (C arm) revealed FNR of 24.3% for a single SLN and 18.5% for 2 SLN. In four meta-analyses which assessed SLNB in 9,266 patients, FNR ranged from 13–17% (14.8% on average) and

Table II. Prospective clinical trials concerning SLNB performed after NAT in the case of conversion from cN1/pN1 to ycN0 [74, 75]

Trial		SENTINA	ACOSOG Z1071	SN FAC	Genea 2
number of patients		592	689	153	307
stage		N1–2	T0–4 N1–2	T0–4 N1–2	
identification of SLNs (%)		80.1	92.3	87.6	80.0
FNR (%)		14.2	12.6	13.4	11.9
number of SLNs (average)		2	2	2.7	1.9
SLN FNR (%)	1 SLN	24.3	31.5	18.2	19.3
	2 SLN	18.5	21	4.9*	7.8*
	≥3 SLN	7.3	9.1	NR	NR
	sngle technique	16	20.3	16	
	dual technique	8.6	10.8	5.2	
	FNR with IHC in pathology	NA	8.7	8.4	
definition of a metastasis		ITC	>2 mm	ITC	

* reported ≥2 SLN; NR – no data

fell to 10.4% with application of isotope and staining in biopsy and sampling of 2 SLN.

Analysis of study results presented in table II allowed a conclusion that application of the dual method in SLNB and identification of at least three lymph nodes corresponding to SLN criteria allow for reduction of FNR below 10% and improve SLN identification within drainage of the biopsied nodes. Therefore, in order to reduce FNR (below 10%), and thus to increase a chance of identification of the residual disease in the regional lymph nodes, international and national organisations recommend application of the dual method in patients with ycN0 disease and identification of at least three SLN (some organisations suggest even four SLN) [18, 19, 74, 75, 59, 70]. Meanwhile, guidelines by the American Society of Breast Surgeons provide for necessary identification of at least two SLN, or preferably three of them. The guidelines are based on expertise of American surgeons who participated in the I-SPY study, in which SLN biopsy techniques after NAT were developed [63, 70].

Histopathology testing with immunohistochemistry (IHC) staining is not a routinely recommended method of histopathology diagnostics of sentinel lymph nodes in breast cancer, although it has been applied in some prospective studies with randomised patient selection. Application of IHC allows for identification of isolated tumour cells (ITC) and reduces FNR to 8.4–8.7% [62]. Identification of ITCs and micro-metastases in SLN after NAT may result from partial response of the micro-metastasis to the applied treatment or else they may be a pool of tumour clones refractory to systemic treatment [76]. If a metastasis to SLN (of any size) is found in the post-operative histopathology test, probability of metastases to other axillary lymph nodes increases by 17–69%. This is why any size of metastasis to SLN after NAT is an indication to ALND [77–79]. It seems that an intra-operational test of sampled SLNs would be interesting. Unfortunately, this is not a way to find ITCs or micro-metastases, but it allows good identification of macro-metastases. Intraoperative tests have FNR above 10%: 30% of the false negative results concern ITCs, and 46% – micro-metastases [80, 81]. A. Barrio argues that identification of 88% of drainage ≥3 SLN after NAT allows for resignation of labelling of the lymph node that was metastatically changed before NAT, this is why the Memorial Sloan Kettering Cancer Centre prefers SLNB with dual marking and sampling of ≥3 SLN (four SLN on average). This centre does not apply TAD technique in SLN biopsy after NAT [64, 82]. Other centres' experience shows that in about 2/3 of patients with ypN0 cancer after NAT (conversion from pN+), ≥3 lymph nodes can be identified [83].

Option 2. TAD biopsy of sentinel lymph nodes. It involves sampling within SLNB of a lymph node labelled before NAT, where a metastasis was found before the systemic therapy. The following methods of labelling nodes are used:

- attaching a marker to the metastatic lymph node,
- performing a tattoo of the metastatic node with carbon particles,
- application of a marker with radioactive isotope ^{125}I to the metastatic node,
- application of an electromagnetic marker to the node, analogically to the SentiMag biopsy method.

Each of the above methods improves effectiveness of SLNB. However, depending on the centre, its technical and financial capabilities, different node marking techniques are used [84]. Attaching the marker to the metastatic lymph node before the start of NAT, analogically to the breast tumour, allows precise labelling of the lymph node containing metastasis. The problem is its identification during SLNB.

One of the identification techniques is the intraoperative ultrasound of the axillar cavity and identification of the SLN containing the marker. After NAT, the marker was identified in an ultrasound study in 72–83% of patients [85, 86]. Another

method to facilitate identification of a labelled lymph node is to establish an "anchor" on the day of surgery, similar to the location of the cancer in the mammary gland. This technique is applied by the team of the Department of Breast Cancer & Reconstructive Surgery of the National Research Institute of Oncology in Warsaw. Meanwhile, some centres before the surgery apply the ^{125}I isotope marker to the lymph node.

A single-centre study of MD Anderson in the United States concerned biopsies of sentinel lymph nodes with subsequent ALND. For SLNB using staining and isotope, FNR was 10.1%. Sampling of stained SLN/SLN collecting the isotope and necessary sampling of the node labelled before NAT with the ^{125}I isotope marker allowed reduction of FNR down to 2.0, and in the case of the labelled node itself – to 4.2%. Meanwhile, with intraoperative sampling of lymph nodes which corresponded to the sentinel lymph node criteria (isotope uptake and staining), and no identification of the node with a marker among them, FNR was 23% [2].

Multiple studies confirm the value of TAD technique in SLNB [17, 24]. The problem of identifying the right lymph node may arise from marker migration outside the labelled node due to its involution caused by chemotherapy. However, these inconveniencies do not affect benefits perceived by multiple oncological associations which recommend this technique of SLNB [18, 19, 59, 75].

Tattooing of the metastatically changed lymph node with carbon particles or injecting the node with an electromagnetic marker, analogically as in the SentiMag breast biopsy method, is another type of TAD biopsy. However, tattooing the node with carbon particles may be inaccurate, as there have been reports of migration of the staining to other nodes in the region. During SLNB procedure, in 45% of cases of drainage, more tattooed SLN were found than were actually tattooed before NAT [87]. Thus, tattooing is a less accurate alternative method to application of a marker [18, 19, 59, 74, 75]. Injection of an electromagnetic marker, analogically as in the case of SentiMag breast biopsy method, is performed by very few institutions, experienced in SLNB with application of this carriers. In the Netherlands, it is recommended to apply a marker containing a radioactive ^{125}I isotope (MARI clinical trial), allowing for reduction of FNR down to 7%. However, this is not a typical SLNB method, because a colloid containing ^{99}Tc or stain is not administered preoperatively. Meanwhile, in the ACOSOC 1071 trial and one-centre MD Anderson study, sentinel lymph node biopsy with ^{125}I isotope marking enabled reduction of FNR below 2% [2].

According to a 2017 survey of members of the American Society of Breast Surgeons – ASBrS, 67% of surgeons use markers for lymph nodes. The most common markers used intraoperatively in SLN were "anchors" (52%) and isotopic markers (9%). After a biopsy, 82% of surgeons performed an intraoperative mammography of the preparation to confirm presence of the marker in SLNB. According to this survey, still, 21.9% of surgeons routinely performed ALND after NAT without attempting to perform SLNB [80, 88]. It appears that "extended SLNB" (endoscopic sentinel lymph node biopsy – ESLNB), i.e.:

- biopsy using staining and isotope,
- removal of at least 3 SLN (including nodes with a metastasis diagnosed before NAT and a marker attached), and
- ALND, if no pCR in sampled SLN (including even ITC),

is an oncologically safe method and allows avoiding ALND in patients with initially cN1 cancer and conversion to ycN0 after NAT [72, 62].

Axillary lymphadenectomy without attempting to perform SLND after NAT is recommended in patients:

- with clinically altered axillary nodes at presentation – cN2/3 (or >2 suspicious lymph nodes in ultrasound),
- with any histopathologically confirmed metastasis to SLN after preoperative therapy (ypN+ – including ICT and micro-metastases),
- if there are fewer than three SLN identified (in some institutions the threshold is two SLN) in the case of application of the "dual" technique in SLNB,
- if the lymph nodes with a marker affixed are not identified in the TAD method [18, 19, 59, 70].

In the case of patients with cN2-3 disease after NAT, the effect of ALND on improved survival in this groups has not been determined. The trial by Park et al. suggests a positive effect of lymphadenectomy in this group of patients (HR – 0.68, $p < 0.0010$) [73]. The authors listed multiple limitations of the study, including inability to assess the patients' overall condition, inability to assess LFR and DFR, inability to unequivocally identify patients who underwent SLNB and ALND beside the arbitrarily assumed number of removed lymph nodes. It should be stressed that most flagship studies, including NSABP B-04, indicate no benefit from ALND as compared to SLNB in patients with N2–N3 at presentation [89]. Bonneau et al. found no differences in survival between patients with 3 or more metastatic lymph nodes, whether or not these patients had SLNB or ALND [90].

Pathomorphological assessment of response to systemic treatment in breast cancer

Evaluation of postoperative material after systemic treatment is an important issue in pathomorphological diagnostics, considering the lack of a single, broadly accepted method of its reporting. The following terms are used the most frequently in pathomorphological analysis of the response to treatment:

- the system associated with the TNM classification (tumour-node-metastasis) by the American Joint Committee on Cancer (AJCC),
- system for describing residual cancer burden (RCB),
- Pinder system.

Post-treatment surgical procedures – a tumorectomy or mastectomy with sentinel nodes sampling or lymphadenec-

tomy – are primarily of therapeutic nature, but they also allow determination how the cancer responded to the applied systemic treatment. Thus, the likely future development of the disease can be forecasted, too.

The pathomorphological assessment of cancer after systemic treatment has been standardised in recent years. Sampling is key for getting comparable results. It is recommended to harvest samples containing the entire cross-section through the tumour bed. Tumour bed is the area within the breast that was originally occupied by cancer. In the case of little response to treatment, there is no difficulty in finding, measuring and sampling this area. In cases of complete or near-complete response, sampling must be correlated with the tumour's radiological description (its location, size, potential multifocality) and involves finding the marker placed in the tumour during the diagnostic biopsy. However, in cases of significant pathomorphological response, finding the metastatically changed lymph nodes is sometimes difficult in the process of harvesting diagnostically reliable samples.

For many years, pathomorphology reports described the degree of damage to tumour cells after the treatment (significant, insignificant, none) and occurrence of necrosis (percentage of necrotic tissue). However, it is difficult to define the degree of damage. This type of assessment is subjective and difficult to use clinically. The assessment methods described below use more measurable response parameters and their results are more objective and comparable. Their value is documented by clinical studies. In the proposed systems, it is important to refer to changes both within the primary tumour and in metastases to lymph nodes. The system proposed by the VIII edition of AJCC (TNM) is better adapted to non-pathomorphological diagnostic techniques, but it should be included in the pathomorphology report, too. It suffices to determine T and N parameters and compare them to respective results before the treatment (tab. III).

Table III. Classification of breast cancer after neoadjuvant therapy according to AJCC (VIII edition of 2018)

Category of response to treatment	Definition	Sample entry
CR complete response	no tumour infiltration or metastases	ypTisypN0cM0 pCR
PR partial response	reduced T and/or N parameter and no increase in T or N parameter	ypT1ypN0cM0 pPR
NR no response	unchanged T and/or N parameter or increase in T and/or N parameter	ypT2ypN1cM0 pNR

The system to describe the residual cancer burden (RCB) (tab. IV) applies easily defined parameters which can be assessed in microscopic evaluation of H-E staining. The mathematical formula of RCB is complicated, but it can be calculated within several seconds with an online calculator (RCB calculator) (tab. V), available at: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

If there is no internet connection, only its components required for its calculation can be defined:

- 2 dimensions of the initial tumour,
- tumour cellularity,
- *in situ* tumour tissue,
- number of metastases to lymph nodes,
- size of the largest metastasis to a lymph node.

Due to inclusion of more parameters and the numerical, easily compared form of the result, RCB seems more valuable for an oncologist analysing a post-operative pathomorphology report. From the point of view of people and organisations involved in analysing efficiency of breast cancer treatment, this system with no additional financial expanses allows for objective and reproducible assessment of response to cancer treatment.

Table IV. Calculating the residual cancer burden (RCB)

Components required for assessment of the residual cancer burden (RCB)			
tumour	1.	size of the original tumour (2 dimensions) – the largest tumour in the case of multinodular breast cancer (mm)	$d_{prim} = d_1 d_2$
	2.	tumour cellularity after treatment – percentage of the area covered by neoplastic cells (%)	$f_{inv} = (1 - (\%\ CIS/100) \times (\%\ CA/100)$
	3.	percentage of ***in situ*** tumour tissue after treatment (%)	% CIS
lymph nodes	4.	number of metastatic lymph nodes	LN
	5.	diameter (largest dimension) of the largest metastasis (mm)	d_{met}
Method of calculation of the RCB Index and definition of RCB categories [91]			
RCB index		$RCB = 1.4\ (f_{inv}\ d_{prim})^{0.17} + [4(1-0.75^{LN})\ d_{met}]^{0.17}$	
RCB groups		RCB 0 = RCB 0 index or pCR	complete remission (pCR)
		RCB I = index above 0 to 1.36	minimal residual disease
		RCB II = index above 1.36 to 3.28	moderate residual disease
		RCB III = index above 3.28	massive residual disease

RCB evaluation with online calculator (RCB calculator) http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Table V. Describing residual cancer burden (RCB) [91]

www.mdanderson.org/breast-cancer_RCB	
RCB 0 (pCR)	no cancer in the breast or lymph nodes (pCR)
RCB 1	partial response, minimal residual cancer
RCB 2	partial response, moderate residual cancer
RCB 3	chemoresistance, massive residual cancer

A report in the case of tumorectomy or mastectomy after systemic treatment includes the same elements as a routine pathomorphology report. Additional elements to be specified:

- cellularity,
- presence of changes in the breast resulting from the treatment applied,
- presence of changes in lymph nodes resulting from the treatment applied,

The Pinder scale (tab. VI) is recommended in the European Union's guidelines as a method of presenting response to treatment, although it is not referred to in literature as frequently as the RCB system.

Application of neoadjuvant therapy in breast cancers affects also other parameters, including predictive factors. The status of the steroid receptors, estrogen ER and progesterone PgR, as well as HER2, may be altered. It concerns from a few to over ten percent of cases, depending on the parameter. There may also be a change in the mitotic index of cancer, determined by immunohistochemical expression of the Ki-67 protein, which most often decreases compared to before treatment. Therefore, if a complete pathomorphological response has not been achieved, it is advisable to repeat the assessment of predictors in the section containing the residual infiltrating cancer tissue. A pathomorphological report of these parameters after systemic treatment is analogous to that of an untreated tumour.

Radiotherapy after systemic neoadjuvant treatment

Table VI. Assessment of response to systemic treatment in breast cancer according to the Pinder scale [92]

Breast
1. pCR: (1) no residual cancer or (2) no residual infiltrative cancer but cancer *in situ* present
2. partial response (1) minimal residual disease (<10% of the residual tumour) or (2) evidence of response with 10-50% persistent cancer, or (3) >50% of persistent cancer with evidence of post-treatment damage
3. no evidence of response to treatment.
Lymph nodes
1. no metastases and no evidence of response to treatment
2. no metastases, but evidence of treatment response present
3. metastases present but with evidence of response to treatment
4. metastases present and no evidence of response to treatment

Changed rules of proceeding in clinical oncology and breast cancer surgery, introduced in recent years, have led to changes in radiotherapy. Currently, in consideration of referral for adjuvant therapy, the following should be taken into account:

1. initial clinical stage of the disease,
2. application of the systemic neoadjuvant therapy and degree of response to treatment,
3. type of breast surgery performed (breast-conserving surgery vs. mastectomy),
4. type of axillary surgery (sentinel node biopsy *vs.* axillary lymphadenectomy),
5. final result of postoperative histopathological examination.

Currently, two groups of patients undergo preoperative systemic treatment: those with initially operable breast cancer, mainly (TNBC or HER2-positive) of cT1–2N0–1 clinical stage, and those with locally advanced, initially inoperable breast cancer, regardless of biological type.

Irradiation of patients with initially operable cT1–2N0–1 HER2-positive or TNBC breast cancer after systemic neoadjuvant treatment and after surgery

Breast irradiation

In all cases of invasive breast cancer, the remaining mammary gland is irradiated after the conserving surgery, but the extent of irradiation within the breast depends on the risk of local and regional recurrence.

In patients at high risk of recurrence – i.e. under 50 years of age, with a biological type of triple-negative or HER2-positive cancer, histological G3 grade, with invasion of lymphatic and blood vessels by cancer cells or with a narrow / questionable margin of healthy tissue around the excised tumour – the entire remaining mammary gland is irradiated and the dose to the bed after the excised cancer has to be increased (boosted).

In patients at average risk of recurrence – that is, at the age of 60 and more, with biological type of luminal cancer, histological grade of G1, G2 – irradiation to the tumour bed can be foregone after irradiation of the entire breast, provided that the patients receive hormone therapy.

The technique of choice in treatment of patients after a breast-sparing surgery is 3D conformal radiotherapy (3D CRT) with application of a computer-aided treatment planning system. A modification of this technique involves 3D irradiation with simultaneous integrated boost (SIB) in the tumour bed [93]. In exceptional cases, when the 3D CRT treatment plan is unacceptable due to the unsatisfactory distribution of the radiation dose in the treated breast or too high radiation dose to critical organs (heart, lung, other breast), the patient after a breast-sparing surgery is irradiated with a technique using modulation of beam intensity (intensity modulated radiation therapy – IMRT) from static fields or using dynamic

techniques (e.g. arc technique [volumetric intensity modulated arc therapy – V-MAT]). By using a multileaf collimator (MLC), a three-dimensional dose distribution is obtained, adapted to the shape and size of the irradiated area [94]. In order to reduce the exposure of the heart to radiation, in patients who have undergone surgery on the left breast, the technique of irradiation in deep breath hold (deep inspiration breath hold – DIBH, 4D radiotherapy) is used. Thus, the average dose to the heart and coronary vessels can be reduced [95] .

Based on the Ontario Trial, START A and START B studies, in which fractional doses (hypofractionation) higher than 2 Gy were tested, irradiation in 15–16 fractions of 2.5–2.67 Gy is a standard in breast-sparing treatment and after mastectomy, irrespective of the patient's age and applied neoadjuvant chemotherapy [32, 96–98]. Basing on its own results [99, 100], the National Research Institute of Oncology in Warsaw applies mild hypofractionation in a fractional dose to the whole breast of 2.25 Gy up to a total dose of 45 Gy and a fractional dose per tumour bed: 2.7–2.8 Gy up to a total dose of 54–56 Gy.

Nodal area irradiation

Indications for nodal irradiation are a much bigger problem in patients with initially operable breast cancer after systemic neoadjuvant treatment. In this group of patients, the principles of radiotherapy for patients after the primary surgery do not apply, because the radiotherapist has no information on the number of axillary lymph nodes initially involved by metastases. Before starting systemic neoadjuvant treatment, only a biopsy of the breast tumour and axillary lymph nodes is performed, obtaining information only about the presence or absence of neoplastic cells in the lymph nodes, without precise determination of the number of nodes affected by metastases (1–3 *vs.* 4 and more).

In patients with clinical features of cN0 stage (no palpable lymph nodes) at presentation, if the sentinel lymph node procedure after neoadjuvant chemotherapy confirms the absence of pN(sn)0 lymph node metastases, there is no indication for radiotherapy in the nodal area.

In patients with the initial clinical features of cN0 stage, if the sentinel node procedure after neoadjuvant chemotherapy confirms the presence of axillary lymph node metastases (pN1), then axillary lymphadenectomy should be performed, followed by irradiation of all nodal regions, especially if there are additional risk factors for recurrence (TNBC cancer, age <40 years, G3, poor response to systemic therapy) [75, 101].

In patients with the initial clinical features of cN1 stage (palpable metastases to axillary lymph nodes, confirmed in fine-needle biopsy), if the sentinel node procedure performed after neoadjuvant chemotherapy still confirms the presence of lymph node metastases (pN1), then after axillary lymphadenectomy all nodal areas should be irradiated [101].

In patients with the initial clinical features of cN1 stage (palpable metastases to axillary lymph nodes, confirmed in fine-needle biopsy), if the sentinel node procedure performed after neoadjuvant chemotherapy reveals no lymph node metastases (pN0) and axillary lymphadenectomy has not been performed, then nodal areas should be irradiated.

In patients with initial clinical features of cN1 stage (palpable metastases to axillary lymph nodes, confirmed in fine-needle biopsy), if no metastases to lymph nodes are found after neoadjuvant chemotherapy and axillary lymphadenectomy, then additional recurrence risk factors should be assessed (especially the patient's age, G stage, Ki-67, response to the therapy within the breast) and the team should decide on irradiation of all nodal areas [32, 98, 101]. A pending clinical trial NSABP B51 assessed the role of radiotherapy in patients with cN1–>pN0 features after the systemic neoadjuvant therapy of an initially operable breast cancer [75, 101].

Irradiation of patients with locally advanced, inoperable breast cancer after systemic neoadjuvant treatment and mastectomy

Patients with locally advanced breast cancer (in clinical stage III, with T4 and/ or N2/ N3 features), after systemic neoadjuvant treatment and mastectomy with lymphadenectomy, always have indications for postoperative radiotherapy of the chest wall and regional lymph nodes, regardless of the achieved clinical and pathological response after systemic treatment. This applies even to patients with complete pathological regression of lesions (pCR), in whom the risk of local and locoregional recurrence without radiotherapy is 33%. The decision about radiotherapy in this group of patients is influenced by the initial stage of the cancer [102].

Irradiation after mastectomy covers the area of the chest wall after the removed breast and the area of supraclavicular nodes, three levels of the axillary and parasternal nodes. Controversies concerning advisability of irradiation of parasternal nodes concern low risk of recurrence in this nodal group, associated with high risk involved in relatively high-dose irradiation of main coronary arteries which supply both the left and right heart ventricle. According to current recommendations, post-operative irradiation of parasternal lymph nodes is applied in patients with cancer located in medial chest quadrants, with multiple metastases to axillary lymph nodes, upon confirmation that the heart will not be irradiated with too high a dose [101].

In irradiation of the chest wall and regional lymph nodes, 3D photon techniques, IMRT photon techniques (static or V-MAT) are applied, and so are photon-electron techniques, but less frequently. Usually a total dose of 50 Gy is administered in 25 fractions. Hypofractionation is also allowed at a fractional dose of 2.67 Gy, although the scientific evidence of safety of such treatment in patients after mastectomy is lesser than in the case of patients after breast-sparing treatment [75, 96]. In Poland, most radiotherapy centres irradiate patients after mastectomy with a fractional dose of 2.25 Gy and a total dose

of 45 Gy – according to the results of a clinical trial carried out at the Oncology Centre in Warsaw [99].

In patients with features of T3N1 after neoadjuvant chemotherapy with significant regression within the breast, a sparing surgery may be considered, however, in all cases, postoperative irradiation of the breast and regional lymph nodes is necessary.

Supplementary irradiation of patients with pT3N0 stage was a subject of controversy due to the lack of randomized clinical trials on this issue. However, the analysis of 4,291 patients with pT3N0 breast cancer showed a clinical benefit from irradiation of the chest wall and regional lymph nodes - reducing the risk of recurrence and prolonging survival of patients, especially <75 years of age [103, 104].

Benefits of the systemic neoadjuvant treatment in patients treated for breast cancer

Neoadjuvant systemic therapy in patients treated for breast cancer:

- facilitates surgery in cases of inoperable breast cancer,
- facilitates performance of a breast-sparing surgery instead of radical mastectomy,
- enables obtaining information on the individual response to the applied systemic treatment,
- allows modification of adjuvant treatment in the case of partial pathological response (pPR) after systemic treatment,
- provides the necessary time to perform genetic testing and a possible change in the scope of the operation,
- enables development of a reconstructive surgery plan - in patients who choose to undergo mastectomy [19].

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Has fractionation in head and neck cancer radiotherapy reached a summit or is there still room for novel therapeutic strategies?

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The aim of this paper is to answer to the question whether various dose fractionation regimens are highly effective up to the summit of normal tissue tolerance. Data from 45 trials on altered fractionation, radio-response of the HPV(+) oropharyngeal cancer (OPC) and concurrent chemoradiation (11 533 data) have been selected from the published papers and re-analysed. Altered fractionation regimens showed an average therapeutic gain (TG) of local tumour control (LTC) of about 2.7% per each 1 izoGy$_{2.0}$ above 65 Gy. For HPV(+) OPC, TG increased by 3–3.5%/1izoGy$_{2.0}$. Concurrent chemoradiation for locally advanced H&N cancer produced about 60% LTC using 65 Gy (about 20% more than altered RT). Despite randomization, data sets in the trials remain clinically and biologically heterogeneous. It is not possible to separate the TG rate as the result of change in dose per fraction from that caused by changing the overall treatment time. This is major weakness of the trials. Moreover, the results are presented as an average value of the LTC or survival. The overstepped tolerance summit is very rarely precisely presented. It likely seems that the tolerance summit is not a single value and is only partly related to dose fractionation intensity, it mainly depends on radiosensitivity and the irradiation volume of normal tissue(s) and their potential repair capacity, and an activation of immunological defense. Finally, it is difficult to accept average trial' results as evidence based guidelines for personalized radiotherapy for individual patients; what is more the individual tolerance summit is not universal and well quantified.

Key words: radiotherapy and chemoradiation regimens, weaknesses and benefits, tolerance summits

Introduction

In the 1930s, Coutard proposed to divide a total dose into small daily doses (fractions) instead of a single-dose or a few large fractions. This would spare normal tissues surrounding the tumour, and therefore decrease the risk of severe acute and late complications. This method was called "simple fractionation", i.e. the delivery of small fraction sizes at relatively high dose-rates. Coutard's regimen gained wide interest across many centers, and it was brought to the US by Gilbert Fletcher and established as a curative standard radiotherapy using 60 Gy in 30 fractions, in 42 days, up to 70 Gy in 35 fractions, in 49 days. It was eventually defined as "conventional fractionation" and has been continuously applied through consecutive decades in almost all radiotherapy centers. The only exception was 51 Gy in 17 fractions in 22 days used by Paterson in Manchester during World War II; this was curative therapy for early stage head and neck cancer, and it is still used in Manchester.

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Until the late 1970s conventional radiotherapy was commonly applied, and serious efforts were done to determine which conventional schedule could maximize the therapeutic gain [1, 2]. However, over the past ten decades, the terms "tolerance dose and patient's tolerance" have not been precisely defined and counted. Does tolerance concern patient's specific organ, tissue, or its part, still remains unclear, and it is unlikely to design a dose reaching the summit of undefined target. Nevertheless, after many years of clinical experience, conventional fractionation has met with growing disappointment, since it resulted in average 30–40% locoregional control, mainly because the majority of patients had locally advanced stages of cancer. However, a new, and promising wind was blowing from radiobiology.

Many experimental and clinical studies have shown that the time factor – OTT (the shorter the better) and the size of dose per fraction (di) have a major impact on radiotherapy treatment outcomes.

A new term "altered fractionation" has appeared on the market. Many different "new" fractionation regimens were designed and tested clinically. In principle, they represent one of the three following categories: accelerated (with shortened OTT), hyperfractionated (dose per fraction lower than 2.0 Gy, usually given twice or trice-a-day) and hybrid-accelerated hyperfractionated with both a low fraction size and short OTT [3, 4]. Between the 1990s and 2015 more than 50 clinical studies (mainly trials) were carried out that recruited more than 50 000 patients. However, two meta-analyses [5, 6] selected only 15 trials (30%) and have shown rather disappointing results with an average 4–6% local control benefit (TG). Glatstein [7–9] convincingly questioned the reliability of statistics and results of meta-analyses, emphasizing their doubts and uncertainties. He pointed out that the statistical significance in clinical trials does not necessarily mean clinical importance. The same uncertainties apply to the meta-analyses of combined chemoradiation [10–15].

Among others, doubts and low confidence are caused by the fact, that oropharyngeal cancers were the most frequent tumour site of the recruited cases. Radiosensitivity and local tumour control (LTC) of the HPV(+) oropharyngeal cancers (OPC) are higher than for other sites of H&N tumours and have been well documented [16, 17]. Therefore they could likely affect the final results of clinical trials and meta-analyses as well, but they were not quantified at the time the trials were carried out.

Both clinical trials and meta-analyses data are highly heterogeneous regarding clinical (location, staging), biological (sensitivity) and dose fractionation parameters. It likely makes the accuracy and reliability of the results highly uncertain; the real benefit of altered radiotherapy and combined chemoradiation remains partially negligent. For that reason, reanalyses of the available data sets of these two radiotherapy issues is the aim of the present study.

Material and methods

The present study includes only those trial' data sets which precisely document clinical factors (localization and staging), fractionation parameters (total dose – TD, dose per fraction – di, overall treatment time – OTT), and the rates of at least 3 year locoregional control, that are:

- 22 studies (trials) on altered fractionation (6027 head and neck cancer patients),
- 8 studies (trials) evaluating the impact of the HPV status of the OPC on the RT outcome (2195 patients),
- 15 studies (trials) on concurrent chemoradiation (3311 patients).

Together this gives 11 533 data. In the majority of cases they are locally advanced head and neck cancer cases in stage III–IV, with a pronounced number of OPC tumours. The rate of T1–2N0–1 tumours was usually very small. Different regimens of accelerated (A), hyperfractionated (H), a hybrid (H–A) dose fractionation were used. The analysed data sets characterize wide differences in clinical factors (i.e. tumour localization, staging). Similar variety concerns fractionation parameters of RT (TD, di, OTT). Therefore, in the present study they are unified by the following normalized total dose (NTD) formula:

$$NTD = TD\ [(di + \alpha/\beta) / (2.0 + \alpha/\beta) - 0.6\ Gy/d \cdot (OTT - 42\ days)]$$

in which $\alpha/\beta = 10$ Gy is used, and NTD represent an izoeffective biological total dose ($izoGy_{2.0}$), if given in 2.0 Gy fractions, in the OTT of 42 days.

The range of 60 Gy in 42 days (TD = 60 $izoGy_{2.0}$) to 70 Gy in 50 days (NTD = 65.2 $izoGy_{2.0}$) is arbitrarily chosen as a standard conventional RT, which usually resulted in 30–40% of 3-year locoregional control (LRC).

At least 3-year therapeutic gain achieved by altered fractionation (A, H, H–A) was counted for each of the selected studies as follows:

$$TG_{LRC} = \%\ LRC_{altered} - \%\ LRC_{control}$$

Results

Altered fractionation

The therapeutic gain (TG) achieved in the altered fractionation trials is presented in table I in details. In 10 of 22 studies (45%), the local tumour control (LTC) rate of conventional fractionation (control arm) was within the arbitrarily accepted rate of 30–40%, however in 7 studies (32%) the LTC was higher than 40%, whereas in three trials (14%) it was below 30%. It already reflects a huge clinical and biological heterogeneity of the recruited patients. Only in 5 trials (23%), the TG of altered regimens higher than 10%. An unexpectedly high TG of 42% was noted in the CAIR, which included fairly homogenous tumours T1–4N0–1. However, this result was criticized by some authors, who suggested careful conclusion, since the relatively small number of patients recruited to the prematurely closed trial

Table I. Characteristics and local tumour control. Therapeutic gain of selected studies (trials) on altered fractionated irradiation

Fractionation		No. patients	Schedule			NTD $izoGy_{2.0}$	Therapeutic gain (LTC%) 3 years	Author(s), trial
			TD in Gy	di in Gy	OTT in days			
standard conventional			60 70	2.0 2.0	42 49	60 65.8	average: 35–45%	
1.	H–A	918	54	1.5 (tid)	14	68.6	+5% (49% *vs.* 42%) 0 % after 10 yrs.	CHART, Saunders [3, 4]
2.	H–A	70	46	1.4 (tid)	14	60.5	+5% (54% *vs.* 49%)	Awward [3, 4]
3.	H–A	429	54.4	1.6 (bid)	24	63.4	no diff.	RTOG 9104 [3, 4]
4.	H–A	161	54	2.0 (tid)	12	72.0	+9% (44% *vs.* 35%)	Olmi [3, 4]
5.	H–A	336	58	1.45 (bid)	28	63.7	+8% (45% *vs.* 37%)	PMH, Cummings [3, 4]
6.	H–A	350	59.4	1.8 (bid)	25	68.6	+5% (48% *vs.* 43%)	Poulsen [3, 4]
7.	A	791	66	2.0 (sid)	36	69.6	+9% (66% *vs.* 57%)	DAHANCA, Overgaard [3, 4]
8.	A	82	66	2.0 (bid)	25	70.2	+4% (62% *vs.* 58%)	Jackson [3, 4]
9.	A	268	63	2.0 (bid)	24	73.8	+12% (46% *vs.* 34%)	Bourhis [3, 4]
10.	A	100	70	2.0 (7d/wk)	35	74.2	+42% (75% *vs.* 33%)	CAIR (CLE) Składowski [3, 4]
11.	H–A	500	72	1.6 (tid)	35	73.8	+7% (59% *vs.* 46%)	EORTC 22851, Horiot [3, 4]
12.	H	178	72	0.9 x 8/d	42	72	no gain (40%)	Nguyen [3, 4]
13.	H	165	60–75	1.2 (bid)	35–45	61–67.9	no gain (40%)	Moez [3, 4]
14.	H	447	67.2 72.0 76.8 81.6	1.2 (bid) 1.2 (bid) 1.2 (bid) 1.2 (bid)	38 42 51 54	65 67.2 69.8 69.9	+ 19% (44% *vs.* 25%) no gain (45% *vs.* 43%)	TRTOG 8313, 9003 Cox, Fu [3, 4]
15.	H	356	80.5	1.15 (bid)	49	70.5	+18% (56% *vs.* 58%)	EORTC 22791 Horiot [3, 4]
16.	H–A	79	72	1.8 (bid) (boost last 2 wks)	42	70.8	+13% (79% *vs.* 66%)	RTOG 85-88, Ang [3, 4]
17.	A	350	59.4	1.8 (bid)	24	69.2	+3% (54% *vs.* 51%)	TROG 910, Denham [3, 4]
18.	H–A	145	66	1.1 (bid)	45	62.9	+10% (74% *vs.* 69%)	Pinto [3, 4]
19.	A	94	60	2.0 (bid)	35	64.2	+1% (30% *vs.* 29%)	Marcial [3, 4]
20.	H–A	105	58.5	1.5 (tid)	18	70.5	+10% (44% *vs.* 34%)	Belau [3, 4]
21.	H–A	91	79.2	1.2 (bid)	45	72.1	+15% (43% *vs.* 28%)	Datta [3, 4]
22.	H–A	12	76	1.2–1.6 (bid)	35	77	no gain (CLE!)	HARDE, Harari [3, 4]

RT: A – accelerated; H – hyperfractionated; H-A – accelerated hyperfractionation; sid – once-a-day; bid – twice-a-day; tid – thrice-a-day; TG – % gain in LTC compared with standard arm; NTD – normalized total dose if given in 2.0 Gy fractions = TDi (di = 10 Gy) / (2.0 Gy + 10 Gy) for a/b = 10 Gy; CLE – consequential late effects, severe acute reactions

raises well-grounded uncertainties. In the other 5 trials (23%) zero TG benefit of altered regimens was noted. For example, in the CHART the average 5-year TG of 5% dropped down to zero after 10-years follow-up [10].

An altered fractionation TG of 10% or higher was found in the trials which in the tested arm used a dose per fraction much lower than 2.0 Gy, given twice- or trice-a-day (pure hyperfractionation or accelerated hyperfractionation). Bourhis et al. [5] and Lucas et al. [6] reported an average 6.4% benefit of LTC (at 5-years; $p < 0.0001$) in favour of altered regimens. Such average value does not reflect the real benefit of some individual studies. Figure 1 shows that LTC at the level of 40% raises by about 20% with increasing NTD by 7.5 $izoGy_{2.0}$ (from 66.5 $izoGy_{2.0}$ to 73 $izoGy_{2.0}$), which gives an average increase in the TG of 2.7% by each 1 $izoGy_{2.0}$ above 66.5 $izoGy_{2.0}$. It has to be pointed out that this single value represents highly heterogeneous sets of patients recruited to the trials (from T2N0 to T4N3), and therefore it is likely to be biased. For carefully

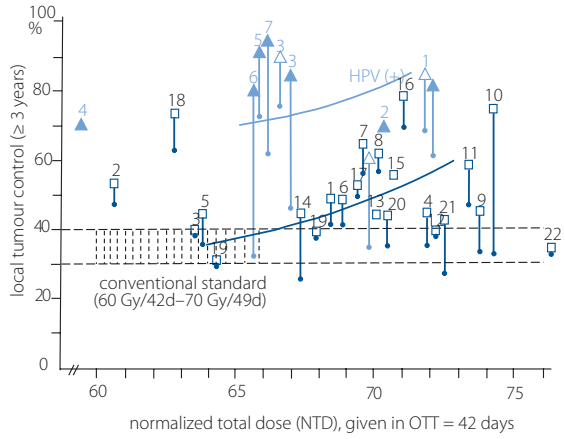

Figure 1. Local tumour control – NTD relationship for altered fractionation series compared with HPV(+) oropharyngeal cancer (Δ – LTC – OC)

selected data sets with a single tumour site and homogeneous stage, the LTC benefit in favour and of an altered regimen might be even higher than 2.7%/1 izoGy$_{2.0}$ (at least for intermediate local stages of disease).

HPV(+) status of oropharyngeal cancer (OPC)

Intensive interest has focused on oropharyngeal cancer (OPC), because of the beneficial impact of HPV(+) status on radiotherapy outcomes. Patients with HPV(+) OPC have much better prognosis, higher locoregional control and overall survival than those with HPV(–) or other head and neck tumours. Nowadays, HPV(+) OPCs are widely recognized as a distinct head and neck cancer entity.

Although numerous studies have been focused on that topic, except the strengths, some results are uncertain. For that reason, the present study includes only detailed and pertinent data to analyse the importance of the HPV status of the OPCs relevant to clinical practice. The results of 8 studies (trials) with almost 3000 patients are presented in details in table II. The range of the NTDs is similar to that used in the "altered" series, which should not surprise since some of them were also a part of the "altered" trials. Moreover, with the exception of the RTOG 0129 trial (tab. II, No. 1), the RT was combined with chemotherapy (inductions, adjuvant or concurrent). Usually, the major end-point was overall survival (OS), but in 4 studies, the LTC was also reported. At the first glance, the LTC therapeutic gain for the HPV(+) OPCs was much higher than that achieved in the "altered" studies, which was also accompanied by significant increase of the OS. Figure 1 illustrates this tendency within the NTD of 66.5–73 izoGy$_{2.0}$ (the same as for "altered" data).

The LTC rates were on average 20–30% higher than those representing the "altered" data sets, which gives an average increase of the TG of about 3–3.5% by each 1 izoGy$_{2.0}$, above 66.5 izoGy$_{2.0}$. Even though this value is not far away from the "altered" TG/1 izoGy$_{2.0,}$ but the HPV(+) LTC curve is on a higher level than that representing the "altered" results. It likely suggests higher sensitivity and radioresponsivenes of the HPV(+) OPCs (25–30% higher LTC) than that for other H&N tumours. The ECOG 1308 trial (tab. II, No. 4) showed that induction chemotherapy with paclitaxel and carboplatin for HPV(+) OPCs combined with a total dose lowered to 54 Gy in 37 days gave very high LRC (83%) and OS (95%). Therefore, for low risk HPV(+) OPC patients it may likely advocate for de-escalation of radiotherapy dose if combined with chemotherapy [12–14].

Chemoradiation

For the last 2 decades, chemotherapy combined with radiotherapy (mainly concurrent chemoradiation) with locally advanced H&N cancers has been an object of extensive cli-

Table II. Radiotherapy alone or chemotherapy for PV(+)/HPV(–) oropharyngeal cancer

L. p.	Therapy regimen	No. patients	Schedule		NTD in izoGy$_{2.0}$	Therapeutic gain		Author(s)
			TD in Gy	OTT in days		in LRC HPV+/HPV–	in OS HPV+/HPV–	
1.	RTOG 0129	720	72	42	72	+21% (86% *vs.* 65%)	+25% (82% *vs.* 57%)	Ang [11, 12, 13]
2.	DAHANCA 6–7 with nimorazole (Nm)	331	68	40	~70 Nm (+)	+26% (61% *vs.* 35%)	+30% (70% *vs.* 40%) +21% (63% *vs.* 42%)	Lassen [11, 12, 13]
3.	PMH (2011–2013) ± cispl (concur.)	449	70	49	66.4 + cispl no cispl	+17% (93% *vs.* 76%) +14% (90% *vs.* 76%)	+45% (89% *vs.* 44%) +26% (70% *vs.* 44%)	O'Sullivan [11, 12, 13]
4.	ECOG 1308 induc palitaxel + carboplatin.	90	54	37	57 <10 pck.+ >10 pck.+	not reported	95% 76%	Marur [11, 12, 13]
5.	TROG 02.02. tirapazamin/cispl	185	70	49	65.8	not reported	+17% (91% *vs.* 74%)	Risch [11, 12, 13]
6.	TAX 324 include. CHT docetaxel, cispl, 5-Fu	264	70	49	65.8	not reported	+49% (80% *vs.* 35%)	Posner [11, 12, 13]
7.	ECOG 2399 carbopl, paclitax + adj. paclitaxel.	111	70	49	65.8	not reported	+33% (95% *vs.* 62%)	Fakhry [11, 12, 13]

NTD calculated as in app. 1; di – in all studies was 2.0 Gy

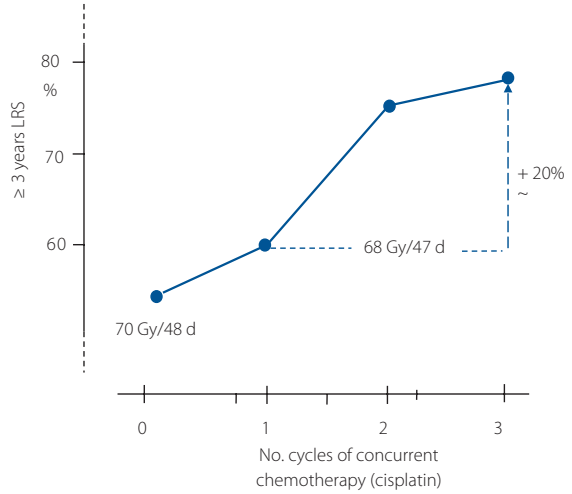

Figure 2. Local tumour control – NTD relationship for differed radiotherapy versus chemoradiation (TX – taxans)

nical studies (more than 70 trials). Some of them, including meta-analyses [15–17] have reported the therapeutic benefit of combined chemoradiation, whereas others [18, 19] have concluded that such benefit remains as yet uncertain.

Table III presents 15 carefully selected studies on chemotherapy combines with radiotherapy (mainly hyperfractionation). The three-year LTC therapeutic gain ranged from 8% to more than 20%, and generally is higher than that achieved by "altered" regimens. However, contrary to "altered" results, 20% TG was achieved by CH-RT using $NTD_{2.0}$ lowered from 70 $izoGy_{2.0}$ to 65 $izoGy_{2.0}$. Thus, about 60% 3-year LTC of locally advanced H&N cancers can be expected using hyperfractionation combined with concurrent chemotherapy. An interesting study was carried out by Składowski using concurrent CH-RT (cisplatin) for cancer of the oro-hypopharynx and larynx (T2-4N0-1). He has noted about 20% higher LTC when 2 cycles of concurrent CHT was used instead of one cycle. The use of 3 cycles instead of 2 although producing further increases in the LTC, was not particularly substantial (fig. 3).

Discussion

Altered radiotherapy vs. concurrent chemoradiation

A major question in radiotherapy, which still waits to be answered, is what does the word summit actually mean? Is it

Table III. Dose fractionation and LTC therapeutic gain of selected chemoradiation studies (trials)

L. p.	Therapy regimen	No. patients	TD in Gy	di in Gy	OTT in days	NTD $izoGy_{2.0}$	Therapeutic gain (LTC%) 3 years		Author(s), trial
1.	V-CHART with mitomycin on day 5	239	55.3	1.65 (bid)	17	68.6	+17%	(48% *vs.* 31%)	Dobrovsky [3, 4]
2.	German trial with carbopl + 5-Fu	240	69.9	1.8+1.5 (bid)	38	71.7	+6%	(51% *vs.* 45%)	Staar [3, 4]
3.	MGH trial with cispl + 5-Fu	416	76	di x 6/wk	42	76	+11%	(27% *vs.* 16%)	Wang [3, 4]
4.	H + cispl daily (low dose)	218	77	1.1 (bid)	48	68.7	+14%	(50% *vs.* 36%)	Jeremic [3, 4]
5.	H + cispl + 5-Fu for 5 d	136	75	CB (bid)	42	73	+5%	(332% *vs.* 27%)	Corvo [3, 4]
6.	H + cispl + 5-Fu, wk. 1, 6	122	70	1.25 (bid)	46	66.6	+26%	(70% *vs.* 44%)	Denham [3, 4]
7.	H + cispl + 5-Fu + leucovorin	270	70.2	1.8 (bid)	42	69	+19%	(36% *vs.* 17%)	Byhardt [3, 4]
8.	H + cispl daily	130	77	1.1 (bid)	48	68.7	+14%	(50% *vs.* 36%)	Denham [3, 4]
9.	H + 5-Fu + mitomycin	384	70.6	2.0 + 1.4	42	69.2	+13%	(50% *vs.* 35%)	Budach [3, 4]
10.	std. + carbopl. + 5-Fu French trial 94–01	226	70	2.0	48	66.4	+23%	(48% *vs.* 25%)	Denis [3, 4]
11.	stand + cispl + 5-Fu	100	70	2.0	48	66.4	+ 20%	(55% *vs.* 35%)	Adelstein [3, 4]
12.	stand + MMC	195	68	2.0	46	65.6	+22%	(76% *vs.* 54%)	Haffty [3, 4]
13.	stand + A. induction 5-Fu + cispl B. concurrent cispl C. RT alone	547	70 70 70	2.0 2.0 2.0	48	66.4 66.4 66.4	+5% +22%	(61% *vs.* 56%) (78% *vs.* 56%) 56%	R91-11 Forestier [3, 4]
14.	H–A + paclitaxel 5-Fu + hydroxyurea	55	75	1.5 (bid)	35	76	+20%	(40% *vs.* 20%)	phase II, Vokes [3, 4]
15.	H–A + paclitaxel + carbopl	33	66.6	1.8 (bid)	35	69.7	60%		phase II, Chongule [3, 4] Składowski [personal, 28]
16.	stand + concurrent cispl 2 cycles 3 cycles	114	68	2.0	47	68	+20% +25%	(75% *vs.* 55%) (~80% *vs.* 75%)	

NTD calculated as in app. 1

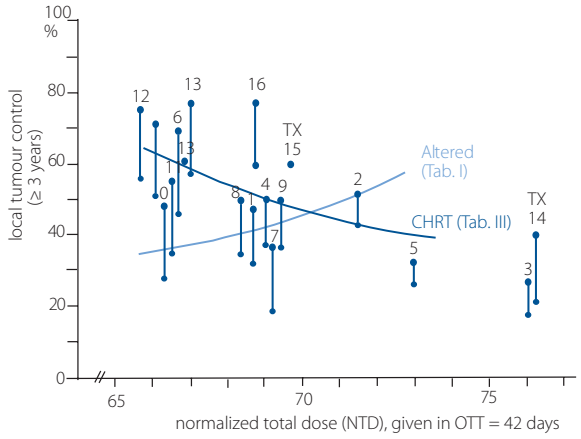

Figure 3. Improvement of 3-yr. LTC depending on the number of concurrent CH used during the course of RT

a real or merely theoretical term? What is the optimal limit for dose escalation? Theoretically, an escalation of the fractionated dose might be unlimited to achieve permanent patient' cure. However, the tolerance (repairable injury) of normal tissues surrounding the tumour was recognized relatively early as a summit for fractionated dosing.

In the head and neck region, the severity and area of early mucosal reactions are the major factors which define the limit which a dose can be escalated to, but it differs on an individual basis. The sensitivity of acute reactions can be quantified during the course of therapy, whereas the risk of late effect (complication) can only be predicted [20].

Therapeutic gain considered as an increase in the LTC is a function of the steepness of the dose-response curves for the tumour and acute or late injury specific normal tissues [2]. The highest TG can be expected if the reference (control) TCP is defined by the central or steeper part of the dose-response curve (i.e. about 40–50%) which usually refers to the response of locally advanced H&N cancers. It likely suggests that conventional dose fractionation seems to be not powerful enough to produce high TCP, and "altered" fractionation could be a promising alternative. For over 20 years, the results of about 50 "altered" trials and meta-analyses [5, 6] gave a disappointing average TG of 6.4%, much lower than initially expected [5]. Present results (tab. I) show that such average disappointment is not necessarily well-grounded because in some trials (tab. I, No. 9, 14, 15, 21) the TG was higher than 10%.

Glatstein [7, 8] convincingly criticized the statistics of the trials' and meta-analyses results and indicated the various biases and pitfalls involved. Interpreting the 3–5-year LTC and OS curves he used the term "the tyranny of the median value". In general, there is the tempting tendency to limit the LTC or OS curves to a single value (3- or 5-year), which is a means value and the remaining part of the LTC or OS curves (the noise of individual data points prior, around, or after the mean value--point on the curve) is usually ignored.

Apart from these doubts, there are two major weaknesses and faults of "altered" trials and meta-analyses. Although the obligatory rules of randomization and stratification were strictly complied, only 19 of the 50 trials were selected for meta-analyses, because of various violations in the remaining studies (70%!). Moreover, patients in both arms of the selected trials still represent high heterogeneity regarding clinical and biological factors (various tumour sites and wide range of stages from T2N0 to T4N3). Although an enormous amount of clinical data was gathered, it is still impossible to separate the clinical effect of changes in dose per fraction from that being the result of change in the OTT.

In the present study, use of the Normalized Total Dose (NTD) allows to express different values of the TD, di and OTT as a single parameter. Figure 1 shows that increase NTD above 65 izoGy$_{2.0}$ resulted in an increase of the TG by 2.7%, by each extra 1 izoGy$_{2.0}$. It gives the TG higher than the mean value of 6.4% reported by Bourhis et al. [5]. Nowadays, the preliminary hypothesis that clinical testing an efficacy of various fractionation regimens could miraculously provide a single "altered Holy Grail regimen" for all various advanced head and neck cancers, seems somewhat naive. On the other hand, for some carefully selected and homogeneous subgroups of tumours, the TG could be higher than the estimated average mean value. This suggestion is confirmed by the DAHANCA trial. For selected well differentiated squamous cell cancers, the TG increased from 9% to about 20%.

Finally, it seems that altered fractionation regimens did not reach a summit, although in a few studies it even over stepped. Nguyen et al. [3, 4] designed an interesting regimen using 8 very small fractions of 0.9 Gy per day, but with only 2-hours interfraction intervals. Despite the rather high LTC in more than 50% patients early severe and extensive necrosis occurred (consequential late effect – CLE) which led to a patient' death. A similar overstepped summit was observed in the early period of the CAIR (tab. I, No. 10) and HARDE (tab. I, No. 22) trials, it was a consequence of a too high accumulated dose per week in these purely accelerated regimens. Finally, despite a lot of effort being put into testing various altered fractionation regimens, the hyperfractionated concomitant boost regimen remains that which is used in clinical practice.

The majority of patients recruited to "altered" trials had oropharyngeal cancer (OPC). It was well documented that HPV(+) OPCs are more radiosensitive with their LTC and OS being much higher than those for HPV(–) tumours. Hyperfractionated RT combined with chemotherapy resulted in significantly higher TG for the HPV(+) tumours compared with HPV(–) (tab. II), ranged from 14% to over 25% (the LTC was in the range of 61–93%). Similarly, the OS gain was also higher (24–45%), when compared with HPV(–) cases. LTC benefit of the HPV(+) OPC patients was significantly higher (70–80%) then that achieved by altered fractionation (40–60%). Therefore, it has been suggested that the high LTC benefit of the

HPV(+) OPC patients can likely be achieved by using a total dose de-escalated by 10–15% (tab. II, No. 4), which is illustrated in figure 1. Since the OPC patient quite often participated in "altered" trials, it can likely be assumed that at least 25% of them were HPV(+). Figure 1 shows the HPV(+) LTC higher by about 20% compared with that representing the overall "altered" series. Therefore the real TG rate of altered RT for H&N tumour sites other than OPC (HPV status was not counted during "altered" trials) might be even a quarter lower (about 1.5–2%) than that estimated in the meta-analyses by Bourhis et al. [5].

During the last 20 years combined chemoradiation has become an attractive option of therapy offered to patients with locally advanced H&N cancer. Results of many trials (15–20, 22) have approved the promising efficacy of this modality (tab. III), with 3-year LTC therapeutic gain in the range of 6 –> 20% compared with RT alone. The highest TG has been reported when concurrent CH-RT used three agents including taxane. A comparison of CH-RT with "altered RT" (fig. 2) shows that similar or even higher 3-year LTC of the advanced H&N cancers after CH-RT was achieved using NTD doses lower than those applied in the "altered RT". Składowski [28] noted that for fairly homogeneous group of orohypopharyngeal and laryngeal cancer (T2-4N0-1) 2 cycles of CHT during RT produced much higher TG than one cycle, and the use of 3 cycles of CHT also improved the TG but not as substantially as 2 cycles.

Other therapeutic options

Progress in advanced RT technology has resulted in the development of precise static or dynamic 3D-IMRT, IGRT, V-MAT, proton therapy and stereotactic radiosurgery (which in fact is 4D, – the fourth dimension is time). All these techniques and strategies are an important step forward in radiotherapy. The aim of radiotherapy has always been a major challenge: to deliver a higher dose to the tumour to improve LTC, in addition to a much lower dose beyond its margins to reduce treatment volume and to spare normal tissue (organs). Despite the many advantages, a risk of "dose cold spots" within the GTV cannot be ignored. If the planned total dose predicting high TCP is referred to D_{95} within the GTV, but some GTV subvolume receives a slightly lower dose (cold spot) than real TCP lowers than predicted. Therefore Fowler et al. [24, 25] strongly advocated to use D_{100} covering whole GTV in 3-, 4-D-RT plannings instead of D_{95}, as recommended by the UICC [26].

The point which should be emphasized is that although all these high-tech 3,4-D-RT modalities are promising, not a single word has been presented concerning the lack of long-term results. According to Glatstein [8], trials objectively evaluating the IMRT have not yet been undertaken.

Protons therapy has been advised as an attractive challenger to photons, due to the higher RBE and specific dose distribution [26]. It is an extremely precise and combined method, but capital and realization costs are prohibitively high. Proton therapy planning faces many physical and biological traps. Except for the base of the skull, and some types of brain and child specific tumours, no substantial advantage of protons over photons has been proved as yet. Therefore, important questions arise, such as, to what extent very high capital and operational costs justify clinically relevant therapeutic benefit of proton therapy? Despite many studies, including trials, there is still a "lack of evidence" in favour of protons over photon therapy, except for some specific tumour sites and types, mentioned earlier.

During the last decade stereotactic hyperfractionated radiosurgery (SHRS) has become an important and effective challenger to conventional and altered radiotherapy [27]. However, as usual in practice, there are some *pros* and *cons* of the SHRS. The *pros* are technological innovations of linear accelerators (CyberKnife) which generate a great number (even more than 100) of pencil beams focused on the tumour GTV boundary with a drop-down dose gradient beyond. SHRS can be termed like a "back to the future", which means, the use a single or a few large fraction doses (1 x 20–25 Gy, 3–4,5 x 5–10 Gy), that were used in the early years of radiotherapy but pretty quickly abandoned because of the severe, often lethal consequential late reactions in the normal tissues. After many decades, new technological developments have nowadays allowed us to return to this method using new tools. The SHRS is comfortable for patients since it lasts one or only a few days, and therefore, the negative part dose neutralized effect of tumour cell repopulation does not play a role. Furthermore, large doses modulate the immunological response, which effectively supports (radiation) cytotoxic effects. The SHRS produces high 80–95% 2–3 year LTC with acceptable tolerance. However, the *cons* are that the use SHRS in practice is limited to very small (primary or metastatic) tumours.

The SHRS produces radical, curative but only local effect but not necessarily leading to permanent patient' cure. Thus, the number of candidates to the SHRS is limited. SHRS results in local control (at least 3-years) of small brain and extracranial lesions and is also highly effective in eradicating small, single or multiple metastatic lesions. Until now, SHRS has been used for head and neck cancers, to treat local recurrence after conventional RT producing about 60% of local control.

Last minute!

Nano-radioimmunotherapy (RIT) is advised as a promising new therapeutic strategy, and it has been tested in a few pilot clinical studies. Radiolabeled (^{90}Y, ^{131}I) monoclonal antibodies and radioimmunoliposomes loaded with a cytotoxic agent (i.e. ^{99}Tc-anti-Iter2 Doxil) are delivered directly to tumour cell surface antigens where its radiolabeled and cytotoxic components are released into the tumour cells. The RIT pilot clinical efficacy is mainly tested for lymphomas and some solid tumours i.e. lung, colon, breast, prostate, kidney and ovary cancers.

Another new and promising field of interest is so-called FLASH radiation therapy which uses a very high pulsed dose

rate of about 150–170 Gy/second. This method is in its experimental phase of animal and cell culture studies. It has already been established that FLASH increases radioresistance of various normal tissues by about 2-fold or more. Tumour effect (TCP) has not been established, yet. However, both concepts seem interesting and promising.

Conclusions

Reviewing the efficacy of various fractionated modalities used in daily practice leads to the conclusions that there is no a single privileged fractionation modality which produces highly beneficial results, at least 3-year LTC and OS, and therefore a single tolerance summit level also does not exist. It seems that the tolerance summit is only partly related to fractionation intensity, and in fact the summit for dose level depends on individual biological characteristics, radiosensitivity and irradiated volume of normal tissue(s) and the potential for repair capacity and immunological defense. Figure 4 summarizes the therapeutic gain of various dose fractionation regimens, and this shows that each regimen has its own summit. It raises upwards HPV(+) oropharyngeal cancer and SHRS therapy. On the other hand, Figure 3 shows that the rate of the TG strongly depends on so-called dose intensity – DI (TD/OTT), which expresses variations of four parameters, i.e. total dose, di, time intervals between daily fractions and the OTT. The larger the DI values the higher the TG benefit. Considering the various summits for different fractionation modalities, results are presented of many studies including trials that suggest that hyperfractionated radiotherapy combined with concurrent chemotherapy (with 3 agents including taxanes) is the most often used in daily practice to treat locally advanced head and neck cancer. The recent pilot study on erlotinib (anti EGFR) and bevacizumab (anty VEGFR) integrated with CH-RT (cispl) for locally advanced H&N cancer resulted in 82% LTC. We should probably continue to follow this path.

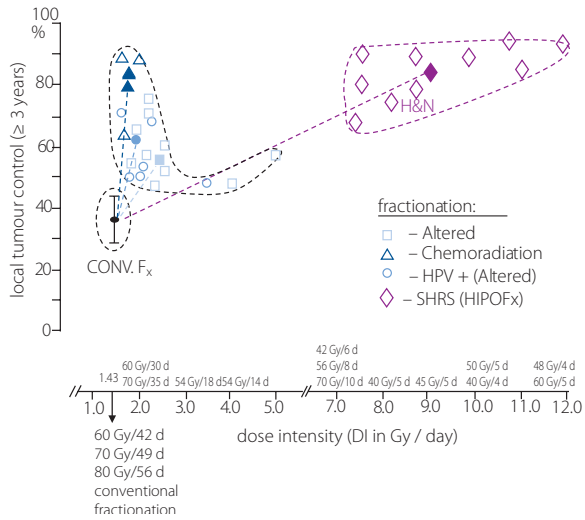

Figure 4. Local tumour control – dose intensity (DI) relationship for various dose fractionation regimens

Finally, should the average results of clinical trials often defined as "evidence based" be used as precise predictors for personalized radiotherapy for individual patients remain an open question? After all, the tolerance summit is not a single, universal dose level, but it is a variable characteristic for each individual patient.

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The role of dermoscopy in dermato-oncological diagnostics – new trends and perspectives

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Medical history and clinical examination are the most basic elements of medical diagnostics. Clinical examination in the context of dermatology should be combined with the taking and archiving of clinical, dermoscopic and/or video dermoscopic photographs. Dermoscopy is a non-invasive examination and is the recommended method of examining skin lesions. It requires many years of experience and extensive training, and subsequently can be very helpful in the diagnostic process since it allows for a more thorough examination than the unarmed eye. The diagnosis of malignant skin tumours has been significantly improved by noninvasive real-time diagnostic devices. Based on the data from the literature available, we discussed the most commonly used algorithms in the diagnostic process. It should be emphasized that a dermoscopic evaluation may facilitate the diagnosis and early treatment of micromelanoma and basal cell carcinoma. Finally, the role of dermoscopy in the follow-up procedure of oncologic patients should not be forgotten.

Key words: dermoscopy, dermato-oncology, skin cancer, cutaneous melanoma, skin malignancies

Introduction

Medical history and clinical examination are the most basic elements of medical diagnostics. It should be emphasized that a clinical examination in the context of dermatology should be combined with taking and archiving of clinical, dermoscopic and/or videodermoscopic photographs [1, 2]. Dermoscopy is a non-invasive examination and it is the recommended method of examining skin lesions since it allows for a more thorough examination than the unarmed eye. This diagnostic tool has several uses. The first one is self training, when a specific diagnosis is straightforward. In this case, this method provides us with an enormous amount of data. We are able to correlate our macroscopic thinking with the dermoscopic image, which consequently broadens our knowledge. In the second situation, a diagnosis is very likely and we use a dermoscope to confirm our assumptions and this ensures we can refrain from performing a biopsy. In the next case, a dermoscopy reverses the diagnosis and corrects mistakes. In the latter case, a dermoscopy can lead to a diagnosis by visualizing the feature, resulting in a list of differential diagnoses.

Diagnosis of malignant skin tumours

The diagnosis of malignant skin tumours has been significantly improved by noninvasive real-time diagnostic devices. It is obvious that such a diagnosis must be confirmed by histopathological diagnosis [3]. Dermoscopy requires several years of experience and extensive training, and subsequently can be very helpful in the diagnostic process leading to the final confirmation in the form of a histopathological examination [4]. Consequently, it is worth mentioning and characterizing the

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classic patterns of the most common skin cancer, i.e. basal cell carcinoma (BCC) in dermoscopy. Undoubtedly, the presence of arborizing vessels, large blue-grey ovoid nests, ulceration, leaf-like areas and spoke wheel-like structures and numerous blue-grey globules indicate the basal cell carcinoma (fig. 1A, B) [5].

The second diagnosis we should look at is melanoma. We observe an increasing number of algorithms that help in the early diagnosis of melanoma which are listed and described below. We have dealt with the differences between patients with a solitary lesion, of which a surgical excision is the best procedure. On the other hand, there are patients with numerous lesions which cannot all be cut out; in this case, a dermoscopy with computerized photo archiving is very useful. In addition to tumour diagnosis, the morphological features of the tumour may be important in designing a treatment strategy. It is suggested that the presence of multiple minor erosions or ulceration is a crucial predictor of basal cell carcinomas' response to imiquimod and the presence of pigmentation is a negative predictor of a worse response of this cancer to photodynamic therapy [6, 7].

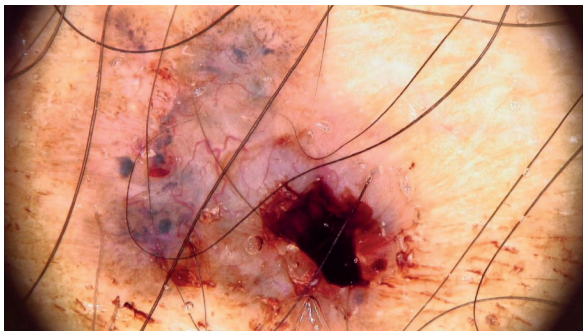

Figure 1A. Dermoscopic features in a non-polarized dermoscopy (NPD) of basal cell carcinoma include the presence of arborizing vessels (bright red, thick diameter vessels (0.2 mm or more) from which emanate branching vessels with progressively thinner diameters), large blue-grey ovoid nests (confluent, well-circumscribed, pigmented ovoid areas), multiple blue-grey dots (pinpoint blue-grey structures) and globules (well-defined round or oval structures), ulceration (shallow erosions that may be covered with congealed blood). Dermoscopic definitions based on dermoscopedia.org [49]

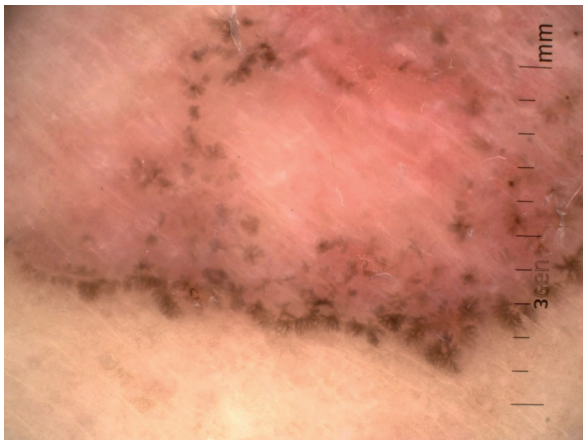

Figure 1B. Dermoscopy in a polarized dermoscopy (PD) of basal cell carcinoma indicates the presence of leaf-like structures (linear to bulbous extensions connected at an off-center base area) and spoke wheel-like structures (radial projections that surround a central darker point). Moreover, in the centre of the lesion shiny white strands (parallel and linear white areas that do not usually intersect) are noticed. Dermoscopic definitions based on dermoscopedia.org [49]

Algorithms for melanocytic lesions

A dermoscopic examination performed by experienced doctors is more accurate than the clinical examination itself. In the study of the observed features visible in a dermoscopy, many algorithms have been established that allow an approximation of an accurate diagnosis. The most commonly used algorithms are discussed below. Kamińska-Winciorek et al. in their review present in detail the older algorithms widely previously used and described in literature [8].

Three-Point Checklist

The Three-Point Checklist algorithm takes into account three criteria to which it belongs:

1. asymmetry in dermoscopic structures' distribution,
2. an atypical pigmented network and
3. blue-white structures.

This Three-Point Checklist can be used by clinicians in diagnostics not only for melanoma (fig. 2A) but also basal cell carcinoma [9]. Soyer et al. showed that the presence of either of these two criteria indicates a high probability of melanoma [9].

Seven-Point Checklist

The Seven-Point Checklist algorithm includes seven characteristics, including: atypical pigment network, gray-blue areas, atypical vascular pattern, radial streaming (streaks), irregular diffuse pigmentation (blotches), irregular dots and globules, regression pattern (a presence of white scar-like depigmentation or peppering known as multiple scattered blue-grey granules) (fig. 2B). Historically, a minimum score of three for adding individual features of the above-mentioned seven is required for the diagnosis of melanoma [10]. Previously, at least

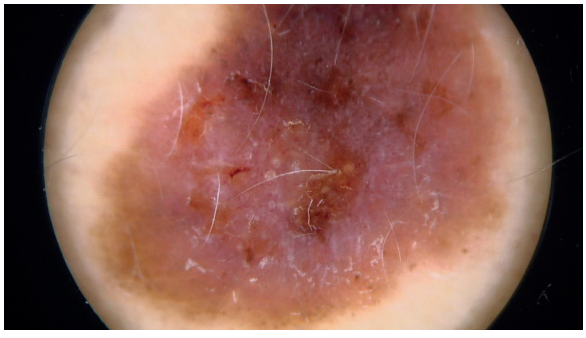

Figure 2A. Dermoscopic assessment of a superficial spreading melanoma (SSM) according to the Three-Point Checklist reveals the presence of asymmetry in dermoscopic structures' distribution (according to two axes), an atypical pigmented network and blue-white structures. Moreover, white structures which are seen in the presented case of SSM in polarized light, so-called shiny white streaks (former synonyms: chrysalis – chrysalids – crystalline) in definition as lines, white, perpendicular shiny white streaks usually correspond with invasive type of melanomas. Dermoscopic definitions based on dermoscopedia.org [49]

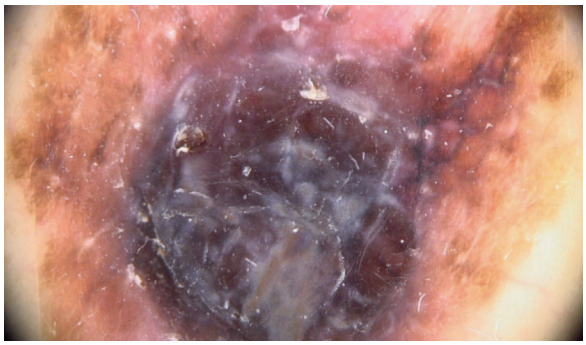

Figure 2B. Dermoscopy of a nodular melanoma in polarized light. The Seven-Point Checklist algorithm indicates the presence of 7 characteristic features, including: atypical pigment network, grey-blue areas, atypical vascular pattern, radial streaming (streaks), irregular diffuse pigmentation (blotches), irregular dots and globules, regression pattern. Moreover, multiple shiny white streaks and strands corresponding with deep dermal fibrosis are visible

two dermoscopic criteria (one major and one minor) must be present for a suspicious diagnosis (a score of three or more). In 2011, Argenziano et al. revised Seven-Point Checklist. They showed in their study that in order to increase the sensitivity of the assessment in the Seven-Point Checklist, the excision threshold of the lesion should be adjusted compared to the original [11]. In the revised Seven-Point Checklist, each criterion receives 1 point, the notch threshold is 1 point, not 3 points like in the earlier version [11].

Two Step Algorithm

In the previous traditional two-step algorithm, assessment is divided into two steps including the differentiation between melanocytic and non-melanocytic changes. When the lesion is classified as melanocytic, the observer then proceeds to the second stage consisting in qualifying the change as mild or malignant. During this second step a decision must be made whether the melanocytic lesion is benign, suspect, or malignant. For this purpose, the mentioned algorithms can be useful, including pattern analysis, ABCD rule, Menzies method and the Seven-Point Checklist which was discussed above [12, 13].

Pattern analysis is a method that involves assessing all the dermoscopic features that a lesion shows. In general terms, malignant – suspected lesions have several colors that are disordered in structure and are asymmetrical in dermoscopic distribution. The ABCD rule of dermoscopy is based on the following criteria: asymmetry (A), border (B), colour (C) and differential structures (D) [14].

The Menzies method aims to distinguish between benign lesions and melanomas. This method includes negative features (symmetrical pattern, single color) indicating benign changes and positive features indicating melanoma. The positive features include blue-white veil, multiple brown dots, pseudopods, radial streaming, scar-like depigmentation, multiple (5–6) colors, multiple blue/grey dots, broadened network [15]. Exceptions to the two-step algorithms have been observed over the years. Moreover *hybrid* dermoscopes allow the user to toggle between polarized and non-polarized light and consequently a diagnosis becomes more likely. Some dermoscopic structures are more prominent in non-polarized dermoscopy (NPD) and others in polarized (PD) [16]. In 2010, an update of this 2-step algorithm was proposed, which consists in adding 2 decision levels to help doctors correctly classify some of the so-called featureless neoplasms as melanocytic or non-melanocytic tumours. In the revised two-step algorithms, the main queries of conducted analysis is to establish a specific diagnosis (step 1) and to rule out melanoma (step 2). This algorithm impedes the use of unpolarized dermoscopy [17].

Triage Amalgamated Dermoscopic Algorithm (TADA)

It is worth noting that the algorithms mentioned so far have been used to detect specific subsets of pigmented skin neoplasms – mainly pigmented melanoma. This is a limitation of these algorithms because many melanomas, basal cell carcinomas and squamous cell carcinomas do not have this pigment. Thus, compared to the above algorithms, the TADA algorithm allows the identification of pigmented and non-pigmented skin malignancies. At the very beginning, this algorithm requires the exclusion of three common and clearly benign lesions, i.e. cherry haemangioma (fig. 3A), dermatofibroma (fig. 3B) or seborrheic keratosis (fig. 3C. In the next step, dermoscopic patterns are taken into account, i.e. the distribution of colours and structures within the lesion. If there is an architectural disorder/disorganized pattern, a biopsy should be performed. If we have organized lesions with a starburst pattern (fig. 3D) or with any of the following features: blue-black/grey colour, shiny white structures, negative network, ulcer/erosion, vessels (fig. 3E, F) a biopsy should be performed [18, 19].

Metaphoric and descriptive terminology

According to Blum et al., the more metaphorical assessment called *blink* and more descriptive one colloquially called *think* complement each other and are used all over the world [20]. However, in a clinical and scientific context, clear and universal language should be the basis. In 2016, Kittler et al. published a consensus aimed at standardizing the dermoscopic description [21].

Early detection of micro-melanoma and basal cell carcinoma

We should pay attention to the change of the type of micro-melanoma, which, due to its size, i.e. 5 mm, does not meet the criterion D of the ABCD assessment and is often overlooked. In this case, a dermoscopic evaluation may facilitate diagnosis and early treatment. So far, there are very few published studies evaluating micro-melanomas. Megaris et al. in their retrospective study suggest features that increase the probability

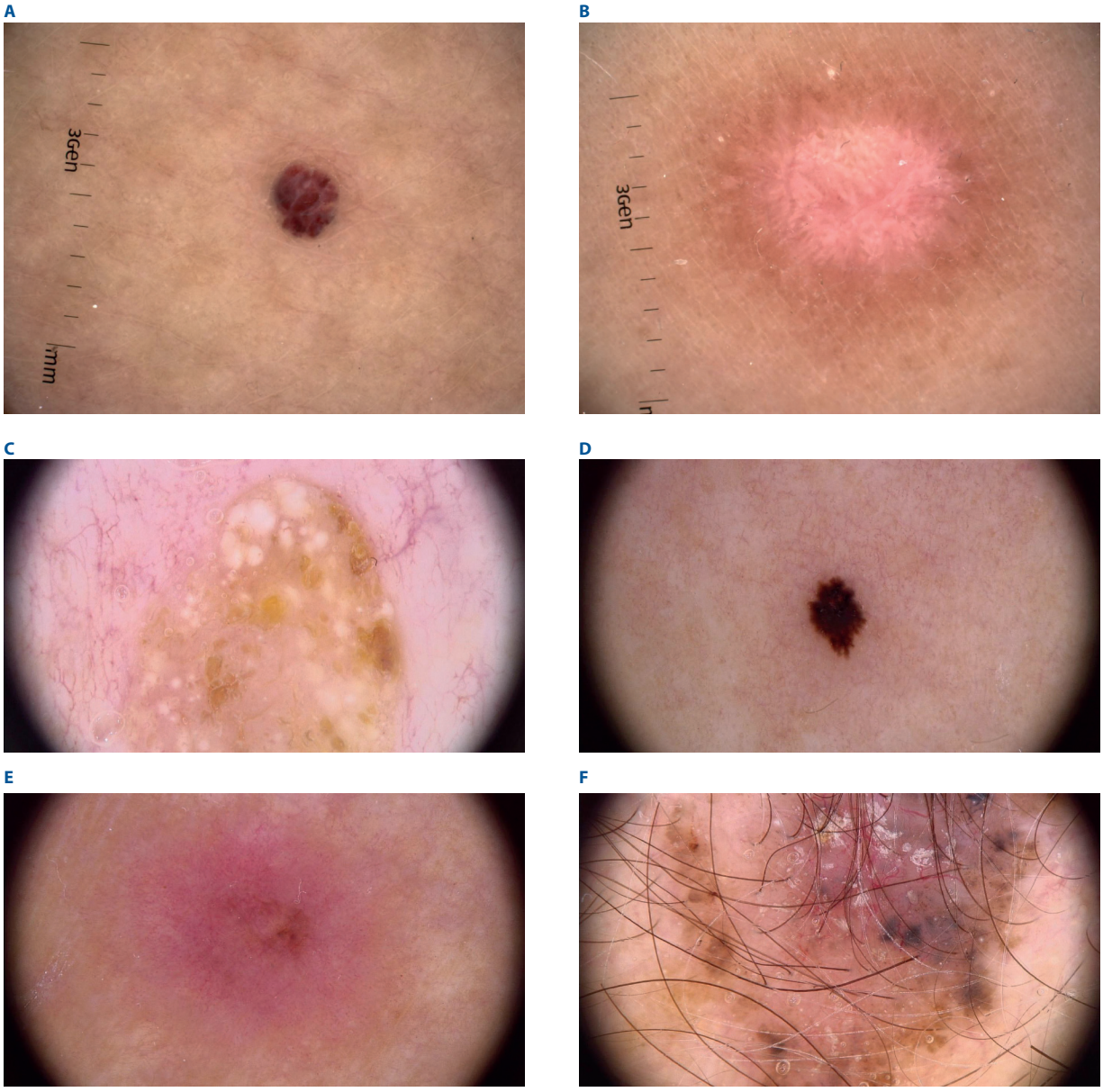

Figure 3. At the very beginning, theTriage Amalgamated Dermoscopic Algorithm (TADA) requires the exclusion of three common and clearly benign lesions; **A** - cherry haemangioma (with the presence of lacunae defined as round to oval red, reddish-brown or reddish-blue areas that commonly vary in size and colour - PD); **B** - dermatofibroma (the peripheral network with a central white scar-like area with a pink hue and shiny white lines in polarized light) or **C** - seborrheic keratosis (with multiple dots or clods white disseminated in NPD). In the TADA algorithm, if we have organized lesions with **D** - a starburst pattern (typified by streaks, pseudopods, or finger-like projections regularly distributed on the periphery; Reed nevus in NPD) or any of the following features: **E** - vessels (multiple dotted and linear irregular vessels in SSM in NPD); **F** - blue-black/grey colour (BCC in NPD), negative network, shiny white structures, ulcer/erosion, a biopsy should be performed

of malignancy in lesions up to 5 mm. Such features include irregular hyperpigmented areas, atypical dots/globules, and an atypical network, within a reticular or unstructured global pattern (fig. 4A) [22].

The routine use of dermoscopy allows the detection of melanomas of which patients are unaware [23]. Moreover, the digital follow-up enables recognition of early melanoma when specific structures or criteria for malignancy may not be present [24]. The combined use of total-body photography and sequential digital dermoscopy enables the detection of incipient melanomas that might have been overlooked if assessed solely by the naked eye [23, 24]. Moreover most melanomas are diagnosed with digital dermoscopy monitoring by side-by-side image comparison [25].

Dermoscopy can also aid early diagnosis of small basal cell carcinomas less than 5 mm in diameter, especially characterized newly arised lesions located on the skin of the head and neck [26]. They are characterized by the presence of multiple blue grey dots and large blue-grey ovoid nests [26] especially in its pigmented variants of very small BCC (3 mm-sized) (fig. 4B) [27]. Moreover the presence of arborizing vessels with the existence of shiny white blotches and strands may also help

can the BCC recognition although 1/3 of small lesions did not exhibit the typical dermoscopic criteria of BCC [28]. It is evident that in small size BCC classic dermoscopic criteria (the presence of arborizing vessels and ulceration) are often substituted by non-classical criteria [29]. Only blue-whitish veil and blue in--focus dots dermoscopic features among non-classic criteria which represent the neoplasm's early phase indicated a good agreement among low experience observers [29].

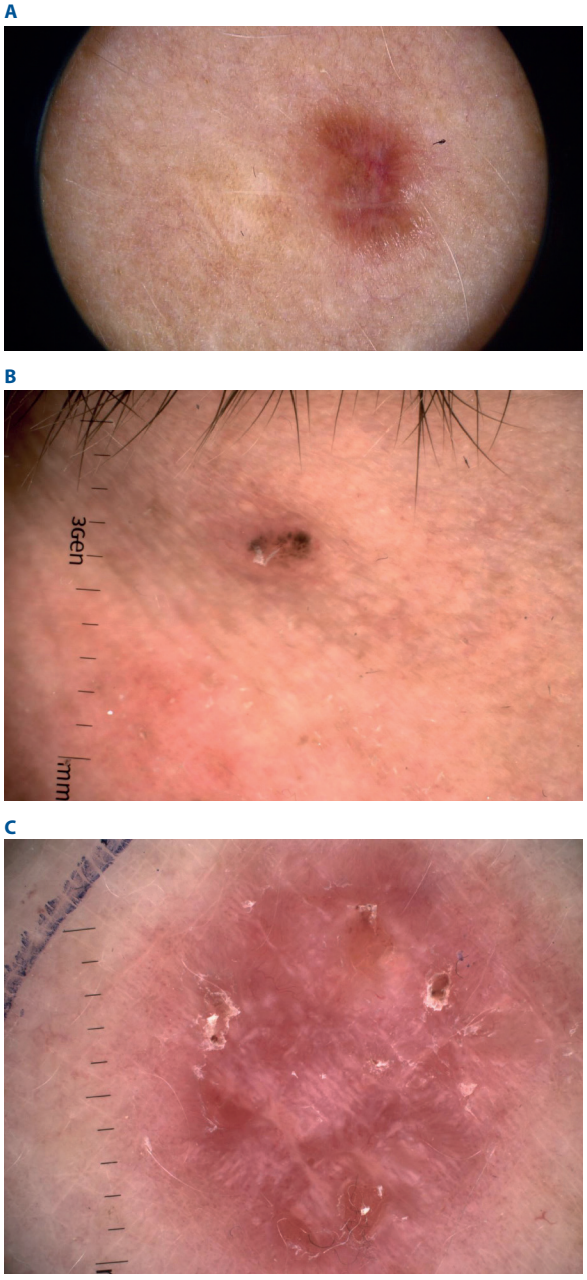

Figure 4. A - a micro-melanoma measuring 3 mm proved histopathologically as SSM located on the décolletage. Dermoscopy in polarized light exhibits the presence of short shiny white streaks and an atypical network, within an unstructured global pattern; **B** - small basal cell carcinoma sized less than 2 mm in diameter located on the skin of the face, characterized by the presence of multiple blue grey dots and globules; **C** - non-classic BCC criteria include inter alia: pink-white areas with: white strands (bright-white less well defined lines, oriented parallel or distributed haphazardly) and shiny white blotches (as white structures in the form of large areas, clods or circles), micro-erosions (covered by crusts and blood) and short fine telangiectasias seen in polarized dermoscopy. Dermoscopic definitions based on dermoscopedia.org [49]

Dermoscopic follow-up in dermato-oncology

Dermoscopic assessment of the surgical margins before excision

Preoperative digital dermoscopy is a better method for detecting tumoral margins than clinical evaluation, and is an effective, simple, non-invasive method for the pre-surgical evaluation of margins [30]. Preoperative dermoscopy is a better method to determine the margins of neoplasms than clinical evaluation alone [31]. Moreover, the preoperative dermoscopic assessment using non-classic BCC criteria including pink-white areas and short telangiectasias in the area between clinically and dermoscopically detected margins, helps define the neoplasm's margins and to achieve a really radical excision (fig. 4C) [32].

Dermoscopic follow-up after surgical procedures

Dermoscopy, as a non-invasive method, works well in secondary prevention, i.e., early detection of neoplasms with the use of dermoscopic assessment of the entire skin, covering areas that are difficult to access during the examination. We should emphasize the importance of this method in the follow-up stages of patients after cancer treatment. These are high-risk patients at risk of relapse and should be regularly monitored using the above method along with image archiving. Dermoscopic follow-up is used in the control of post-excision malignant tumour scars enabling the diagnosis and assessment of tumour (eg. lentigo maligna melanoma – LMM) persistence after surgery (fig. 5A) [33], rapid recognition of the features of tumour recurrence among others, melanoma within the scar (fig. 5B) [34] with an assessment of its healing or leaving sutures (fig. 5C). In addition, a dermoscopic observation of the whole body of patients with diagnosed malignant neoplasms enables early detection of metastases the nature of satellitosis, *in-transit* (fig. 5D) or distant localized within the skin and subcutaneous tissue [35, 36] as well as allowing for additional monitoring dermoscopic effects of the therapies used in patients with, inter alia, metastatic melanoma (blood vessel morphology and distribution, degree of vascularization, ulceration, background). Dermoscopy is also used in patients diagnosed with cutaneous malignancies for the early detection of synchronous melanoma [37, 38] and basal or squamous cell carcinoma (SCC) with dermoscopic assessment of the selected therapies of skin cancers.

Dermoscopic assessment of the selected therapies of skin cancers

Moreover, patients' response to treatment can be easily monitored with this noninvasive medical device, thus allowing further modulation of the therapy [4]. It is worth mentioning

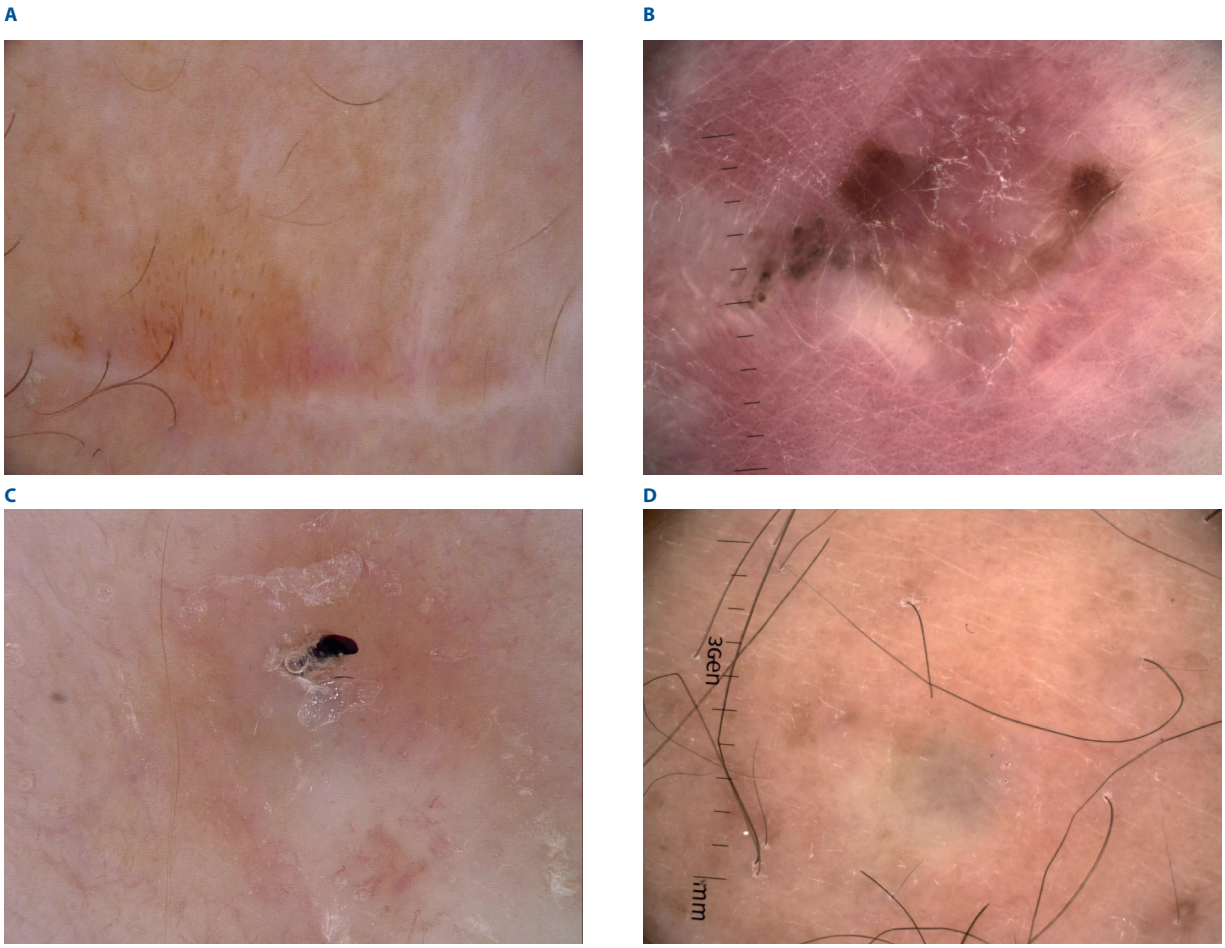

Figure 5. Dermoscopic follow-up in the control of post-excision scars of malignant tumours enabling diagnosis and the assessment of tumour persistence after surgery; **A** - lentigo maligna in NPD (with a pattern of hyperpigmented follicular openings as fine circles and semicircles), rapid recognition of the features of tumour recurrence; **B** - thick melanoma within the scar (the presence of an atypical pigmented network and irregular grey and brown clods, PD); **C** - assessment of leaving sutures (black-blue solitary clod corresponding with a non-absorbable suture within the scar, NPD); **D** - according to melanoma metastasis, dermoscopic classification [35] distinguish four dermoscopic patterns based on metastases' colour: blue, pink, brown and mixed pattern. The blue pattern of in-transit melanoma metastasis revealed the presence of structureless bluish areas in polarized dermoscopy

the treatment with the use of appropriate methods that can be considered and applied in the case of BCC and SCC, characterized by low risk of recurrence or in patients with contraindications to the use of basic methods such as surgery. Imiquimod (5%) is used in the treatment of actinic keratosis, *in situ* SCC/Bowen's disease, and non-invasive forms of superficial spreading BCC [39]. Based on the Husein-ElAhmed study, dermoscopic evaluation improves the accuracy of the assessment of clinical response to imiquimod in pigmented BCC [40].

Dermoscopic follow-up was useful in monitoring the therapeutic response to selected topical therapies including ingenol mebutate in BCC [41], Bowen's disease [42] and imiquimod in LMM [33] as well as systemic therapy with vismodegib in BCC [43]. Dermoscopy was also used in monitoring BCC's treatment effects using high dose ionizing radiation therapy [44], changes in the course of LMM radiotherapy [45], or dermoscopic margin delineation in radiotherapy planning for superficial or nodular basal cell carcinoma [46]. In addition, the dermoscope can be used to assess skin toxicity or lesions occurring in existing and newly formed melanocytic changes during the treatment of melanoma, including with the use of BRAF inhibitors [47, 48].

Conclusions

Modern perspectives regarding dermoscopy emphasize its multidisciplinary scope and nature concerning not only the preoperative diagnosis of skin cancers but also the post-operative and post-therapeutic stages – including topical and systemic implemented therapies.

The high-resolution illustrations are available in the electronic version of this article in the *Supplemetary materials* section on the website nowotwory.edu.pl.

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Case report

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Oligosymptomatic neuroendocrine neoplasm of the small intestine with metastases spread to the heart, bones, muscles and intraperitoneally after a few years in remission – diagnostic and therapeutic challenges

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A fifty-one-year-old male patient with a history of recurring abdominal pains and signs of subileus, without carcinoid syndrome signs, underwent a laparatomy with a resection of the small intestine segment. Histopathology revealed a well-differentiated neuroendocrine neoplasm of the small intestine. Due to the lack of hormonal activity and low malignancy potential the patient was not qualified for adjuvant therapy. The yearly computed tomography did not indicate a recurrence of the neoplasm. The patient did not report any "red flag" symptoms. After a few years in remission [^{68}Ga]-DOTATATE PET/CT revealed a dynamic development of the illness. The patient was qualified for palliative treatment with long-acting somatostatin analogue. Due to the treatment's ineffectiveness and further progression of the disease, the patient received Peptide Receptor Radionuclide Therapy (PRRT). In spite of the therapy his condition did not improve and progression was observed. The patient died because of a malfunction of the cardiac conduction system caused by metastases in the heart.

Key words: neuroendocrine neoplasm, carcinoid syndrome, somatostatin analogue, radioisotope therapy

Introduction

Gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) form a diverse group of neoplasms arising from the cells of the diffused endocrine system in the gastrointestinal tract. Although they are usually benign and develop slowly, they can present a whole spectrum of malignancy and become resistant to therapy. They make up to 70% of the neuroendocrine neoplasm (NENs) group and are most often found in the small intestine, rectum, appendix and large intestine [1, 2]. The prevalence rate is about 35 cases per 100 000 and they can occur at any age, but peak incidence is usually in the sixth decade of life [1]. Clinical classification is based on the tumours' ability to secrete hormones. Non-secreting ones cause a variety of nonspecific symptoms, usually associated with mass effect. Active ones are able to secrete various substances, depending on which cells they arise from. The mentioned substances are responsible for characteristic symptoms. In the case of the small intestine NENs, the most often secreted substance is serotonin, which can cause carcinoid syndrome. This syndrome occurs in approximately 40% of patients with small intestine NENs and is associated with rapid flushing of the face and the

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upper torso, diarrhoea, abdominal pain, teleangiectasia and bronchoconstriction [3]. In 50% of cases the syndrome is accompanied by damaged heart valves induced by increased exposure to to serotonin (Hedinger syndrome), which may result in right-sided heart failure – the most common death cause among people suffering from carcinoid syndrome [4].

Case report

A fifty-one-year-old male patient with a history of recurring abdominal pains was admitted to the surgery department on February 2011 due to the suspicion of subileus. An ultrasound examination (US) showed partial dilatation (up to 40 mm) of the small intestine, with a colonoscopy revealing polyps and multiple diverticula in the descending colon. An X-ray of the digestive tract suggested advanced subileus. The patient was qualified to laparotomy and during surgery a part of the narrowed ileum with tumour was resected. Histopathology revealed well-differentiated NEN in submucosal localisation, invading the muscular layer of the intestinal wall, without lymph node involvement (NEN G1 pT2N0). The patient was referred to the M. Sklodowska-Curie National Research Institute of Oncology in Warsaw. Due to the early stage of the disease, lack of hormonal activity of the tumour, the patient was not qualified for adjuvant therapy, and, instead, regular imaging tests were ordered. In the abdominal CT with contrast, performed annually during follow-ups, the patient did not show any alarming symptoms. After 5 years of asymptomatic course of the disease, an abdominal CT from August 2016 revealed lymph node package with desmoplastic reaction, located anteriorly to the aortic bifurcation, in the adipose tissue of the mesentery. After 3 months the patient was hospitalised due to abdominal pain – ileus was ruled out. A CT showed possible recurrence of the neoplastic process. In February 2017 [^{68}Ga]-DOTATATE PET/CT was performed and it revealed multiple metastases and increased expression of somatostatin receptors in the heart, skeleton, muscles, mesentery and intraperitoneally (fig. 1, fig. 2).

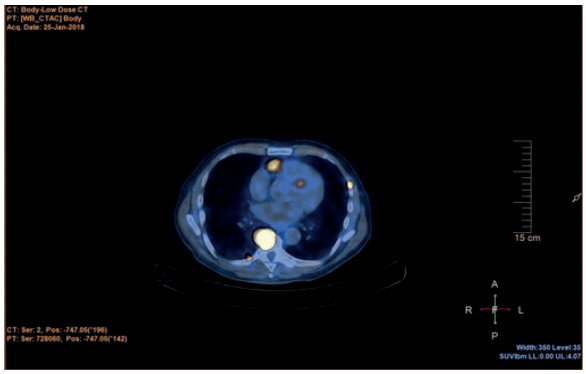

Figure 2. [^{68}Ga]-DOTATATE PET/CT before treatment with long-acting somatostatin analogues: pathological concentration of SST receptors in the area next to the pulmonary trunk, right heart ventricle and in the spine

The patient was qualified for palliative treatment with long-acting somatostatin analogue – octreotide – (Sandostatin LAR), which was administered once each 28 days subcutaneously with a dosage of 30 mg. The treatment was well tolerated, 12 cycles overall were administered. Control [^{68}Ga]-DOTATATE PET/CT performed after one year showed progression of the disease, including an increase in the number of metastases and SST receptors (fig. 3). Due to the concurrent increase in CgA levels (91,87 ng/ml – 6th cycle, 162,9 ng/ml – 12th cycle) the treatment with Sandostatin LAR was terminated and the patient was qualified for peptide receptor radionuclide therapy with radiolabelled somatostatin analogues (PRRT). In July 2017 [^{177}Lu]-DOTATATE 3,7 GBq treatment was started, post-therapeutic scintigraphy revealed pathological accumulation of the marker in multiple locations with a CgA level of 523,1 ng/ml. The same treatment was repeated in October 2018, but the disease showed no sign of regression and CgA levels remained high (443,9 ng/ml) (fig. 4). A thoracic CT showed intrapericardial tumours near the pulmonary trunk (34 x 34 mm), in the right ventricle (26 x 20 mm) and on the border between the right atrium and the right ventricle (32,5 x 20 mm) (fig. 5).

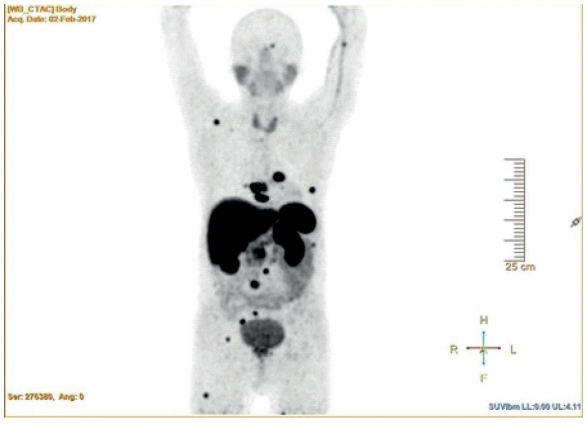

Figure 1. [^{68}Ga]-DOTATATE PET/CT before treatment with long-acting somatostatin analogues: numerous metastases, multiple localisations with increased expression of SST receptors in heart, skeleton, muscles, mesentery and intraperitoneally

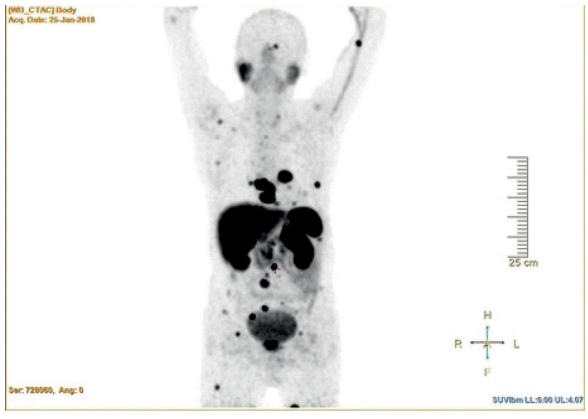

Figure 3. [^{68}Ga]-DOTATATE PET/CT after 12 cycles of treatment with long-acting somatostatine analogues – progression of the disease, new metastases

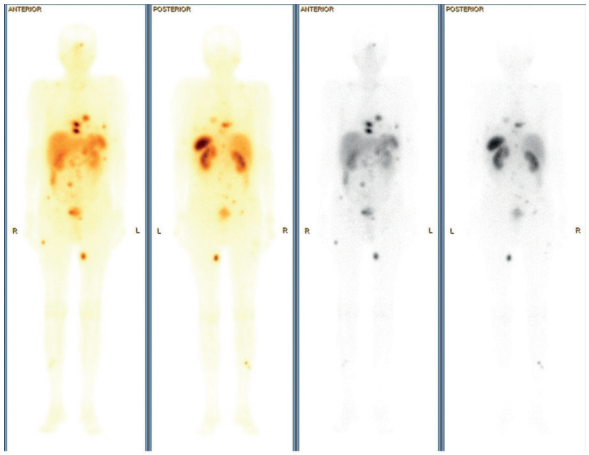

Figure 4. Post-therapeutic scintigraphy after [^{177}Lu]-DOTATATE treatment: pathological accumulation of the marker in the left paranasal region, near both sternoclavicular joints, in the right scapula, along the axis of the thoracic spine, in the right iliac bone, left pubic bone, sacral bone, right femur bone, on the left side of the thorax, left side of the abdomen and medially on the proximal end of the thigh

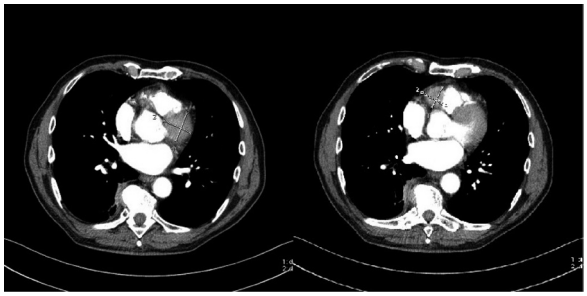

Figure 5. Thorax CT with contrast after 2 cycles of radionuclide therapy: intrapericardial tumours near pulmonary trunk and in the right ventricle

Metastases were found in the spleen and epigastric peritoneum. Fibrous scarring was present in both lungs, sternal manubrium and Th9 and Th10 vertebral bodies. An echocardiography (ECHO) revealed a pathological mass in the heart wall, on the border of the right ventricle wall and the right atrium, with possible right fibrous ring infiltration. The patient did not show any signs or symptoms of carcinoid heart disease. He died two months afterwards due to cardiological complications after the electrical conduction system was infiltrated.

Discussion

In most patients, small intestine NENs are well-differentiated and grow slowly [5]. Hormonally inactive NENs are associated with a variety of localised symptoms. Patients usually report chronic, non-specific abdominal pain, which can suggest some other functional disorders and therefore delay the actual diagnosis [6]. This particular case relates to a small intestine NEN of G1, showing no hormonal activity and causing no carcinoid syndrome, manifesting itself only as intermittent subileus.

The desmoplastic reaction, which could be observed in the patient's mesentery, is typical in NETs and could exacerbate the pain by impairing intestinal blood circulation. This reaction is associated with a more advanced grade of disease and poorer prognosis [7, 8]. Patient did not report any "red flag" symptoms and did not present typical carcinoid syndrome, even during progression, which suggested a stabilisation of the illness. The asymptomatic course of the disease played a major role in withdrawing from measuring the plasma chromogranin A concentration,a prognostic factor that allows for monitoring the course of the illness [8, 9]. According to the Polish Endocrine Society standards, when looking for a primary tumour site and grade, somatostatin receptors imaging (SRI) in correlation with multi-phase CT or MRI should be performed, due to its higher sensitivity in comparison to radiological methods [10]. After 5 years in remission [^{68}Ga]-DOTATATE PET/CT was preformed, due to the suspicion of a recurrence of the neoplasm in lymph nodes. The examination showed extensive metastases in the structures of the heart, bones, muscles, mesentery and intraperitoneal space. Those changes were not revealed in the contrast CT [11]. On the basis of the results stated above, systemic treatment was implemented. The patient was given 12 cycles of long-acting somatostatin analogue – 30 mg octreotide IM (Sandostatin LAR), which is the first-line treatment for patients with well-differentiated small intestine NENs [12]. After 12 cycles of treatment, a progression of the disease, an increase in CgA concentration and a progression in [^{68}Ga]-DOTATATE PET/CT were observed. ECHO revealed intrapericardial tumours located near the right ventricle and between the right ventricle and the right atrium. Their size was approximately 30 mm in diameter.

Carcinoid heart disease can occur in up to 50% patients with carcinoid syndrome and although there were no signs of this syndrome in the patient, intrapericardial tumours turned out to be a life-threatening problem [13]. Such localisation of metastases in the course of NENs is uncommon [14]. The patient was referred to cardiosurgical consultation and died from cardiovascular complications associated with arrhythmia during preparation for surgery.

Conclusion

The following case of a well-developed small intestine NEN is an example of an oligosymptomatic neoplastic disease. CgA concentration should be checked after the diagnosis and also during each follow-up visit, altogether with performing the abdominal CT [15]. [^{68}Ga]-DOTATATE PET/CT, if performed right after tumour resection, could be of great diagnostic value, even with a low grade tumour with a low chance of metastasis. This examination would allow to determine the success of the surgical treatment and could reveal metastases in lymph nodes or bones – tissues more difficult to examine in CT [1, 15]. A complete resection of the primary site of the neoplasm significantly improves the overall prognosis but does not guarantee full recovery – even after a few years in remission [5]. Regularly performed tests would increase the chances of discovering

the neoplasm progression, especially with an asymptomatic course of the disease. Due to the atypical metastases in cardiac structures, not corresponding with typical Hedinger syndrome, performing an ECHO after surgical treatment in the case of no active tumours should be considered as well.

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Well-differentiated neuroendocrine neoplasms (NENs) of the digestive system – a diagnostic and therapeutic problem

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The WHO classification system has emerged to distinguish between well-differentiated and poorly differentiated neuroendocrine neoplasms (NENs) in order to prognostically stratify the neuroendocrine tumors (NETs) that are further classified according to the TNM classification [1].

Typically, well-differentiated NETs are slow growing malignancies, of which about 30–60% are metastatic at diagnosis and even approximately 30% of patients with completely resected localized disease develop metastases during follow-up [2]. Except for rare cases of radically resected liver metastases, distant dissemination of NENs inevitably results in patient death. However, in some patients, death is related to heart failure in the course of carcinoid heart disease or a massive unresectable retroperitoneal desmoplastic reaction.

Surgery is the only curable treatment for NENs. However, the expression of somatostatin receptors on the tumor cell surface makes NENs accessible for diagnostic and therapeutic approaches (theranostics) using radiolabeled peptides. The first somatostatin receptor imaging (SRI) was performed in 1989 with a gamma camera using somatostatin analogs radiolabeled with iodine 123 in a patient with a pancreatic neuroendocrine tumor. Since that time, SRI has developed and numerous studies have demonstrated the superior sensitivity of Ga-68-based PET/CT (around 90–100% in most NEN localizations except for insulinoma). As a result, the current 2017 ENETS guidelines for radiological, nuclear medicine, and hybrid imaging [3] and follow-up of NET [4] guidelines consider SSA-PET/CT, if available, as the first-line diagnostic procedure for staging and NEN follow-up. A positive SRI scan means lesion uptake that is equal to or greater than the liver uptake and is a good predictor factor for effective biotherapy and radiolabeled therapy with somatostatin analogs [5,6].

In the present issue of *Nowotwory. Journal of Oncology* Tyrybon et al. presented a case of a patient with low-grade NEN of the small intestine who underwent surgery due to subileus. Although emergency surgery could suggest an aggressive disease, a retrospective study did not show that the signs of bowel obstruction before surgery were a prognostic factor of death in small-intestine NET (SI-NET) patients [1, 7]. However, emergency surgery is related to a lower number of resected lymph nodes and the risk of inappropriate staging [1]. This underlines the need for adequate postoperative staging using CT and SRI, which is in line with our opinion. Leaving the metastatic lymph node and a severe desmoplastic reaction may have resulted in relapse in this patient.

When well-differentiated NETs recur with distant metastases, somatostatin analogs (SAs) are the first-line options in most patients except for fast growing tumors or with the risk of visceral crisis. For patients with oligometastatic disease, SA is the most reasonable treatment option, which results in disease stabilization of 12 months. Since SI-NETs have a poor response to chemotherapy, TOR inhibitors [8, 9] or radiolabeled

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somatostatin analogs are the second line of therapy [10]. mTOR inhibitors are not reimbursed in Poland. Therefore, radiolabeled somatostatin analogs (PRRT) are the only available option with an estimated median time of disease stabilization of about 3 years. High radiopeptide uptake in metastatic disease is the predictive factor for long-term response [6].

Of note, during treatment, progression occurs in some lesions despite isotope accumulation. If it occurs in a vital organ, a patient must be carefully monitored and consulted in terms of the possibility of using other cytoreductive therapies. In the presented case, progression of recurrence in the heart may have resulted in the patient's death. In oligometastatic disease without the symptoms of the carcinoid syndrome other causes are unlikely.

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Rectal NET treatment – current approach

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The estimated incidence of rectal neuroendocrine tumours (NET) is 1.04 per 100,000 people although the real incidence may be higher. Recent epidemiological studies report higher incidence of rectal NETs in Asia comparing to Europe or North America [1, 2]. Most NETs are asymptomatic neoplasms diagnosed in screening colonoscopy, which could be one of the reasons for the increasing occurrence. Less than 1% of rectal NETs produce serotonin; this explains why there is no manifestation of carcinoid syndrome. In cases of NET located in the rectum, the size of the tumour is strictly associated with its behaviour. The risk of metastases increases with the lesions' diameter [3, 4].

The current guidelines established by the European (ENETS) and North American (NANETS) Neuroendocrine Tumor Societies show detailed treatment algorithms that support the decision-making process following the diagnosis. The most important criteria for therapy are tumour size and the histopathological risk factors for metastases. For well-differentiated rectal neuroendocrine neoplasms <1 cm, local endoscopic or surgical excision is recommended. Endoscopic resection is sufficient in most cases: conventional polypectomy or endoscopic mucosal resection (EMR) for smaller lesions or endoscopic submucosal resection with a ligation device (ESMR-L), cap-assisted EMR (EMR-C) and endoscopic submucosal dissection (ESD) [5].

Rectal NETS with a tumour diameter greater than 2 cm show a very high frequency of lymph node metastasis (58–76%), and therefore these tumours are indications for rectal resection plus lymph node dissection. Either low anterior resection with total mesorectal excision (TME) or abdominoperineal resection are possible treatment options (APR) [6, 7]. Moreover, recent studies show that the resection of the primary tumour may lead to the prolonged survival of patients with GI-NETs associated with metastases [8].

Zubaryev et al. in the article *Local excision vs. radical surgery in treating rectal nets considering the biology of neuroendocrine tumors (NETs)* raised a very important subject [9]. Due to the lack of evidence, tumours sized 1–2 cm represent a grey area for prognosis and treatment. It is crucial to apply the right therapy for this group of patients. Choosing the right treatment might be a challenge in these cases. We need to determine when minimally invasive treatment with endoscopy or TEM is sufficient. We should be careful while considering radical surgery, particularly when there are no clear indications after we have performed tumour staging. Surgeons should always have in mind the potential risks associated with colorectal surgery. There is no doubt that radical surgical treatment such as APR is mutilating by definition. But even laparoscopic rectal resections may carry significant risk. The most frequent postoperative surgical complications after colorectal resections are surgical site infections, anastomotic leakages, intra-abdominal abscesses, ileus and bleeding. What is more, between 25 and 80% of patients undergoing low or very low anterior resections suffer postoperatively. There are a plethora of long-term post-operative complications including faecal urgency, frequent bowel movements, bowel fragmentation and incontinence, collectively referred to as low anterior resection syndrome (LARS) [10].

In order to avoid potential trauma related to surgical treatment, we should consider treatments which are as minimally

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invasive as possible, while, at the same time we should also have oncological indications on our mind.

We should appreciate that the authors have tried to determine independent factors helping clinicians to make the right choice of therapy to reach a satisfactory oncological outcome. The impact of invasion's depth of primary NETs has been confirmed to be the most important factor before planning treatment strategy. The authors also deserve praise for including a large group of patients in the study.

According to the current state of knowledge, regarding tumours with a diameter of 1–2 cm, the guidelines recommend local resection if neither muscularis propria invasion nor lymph node metastasis is suspected. The reported predictors of lymph node metastasis for rectal NETs present the following characteristics: tumour diameter >1 cm, ulcerations, presence of vascular invasion. It therefore seems that patients with tumour diameters of 1 cm or smaller and muscularis propria invasion or without suspicion of lymph node metastasis should undergo local minimally invasive resection. If a histopathological report reveals vascular/muscularis propria invasion, positive surgical margins, then rectal resection with TME should be introduced [11].

We agree with the authors' conclusions. It is certain that more prospective randomised studies are required to discover other prognostic factors regarding rectal NETs that might have an influence on treatment strategies. However, they may be challenging to conduct due to the limited number of cases, the relatively large sample size and the long-term follow-up period needed.

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Colon cancer in the older population

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Fifty percent of new diagnoses of colorectal cancer are made in patients aged over 70 years, and 25% are aged 80 years or over. Older patients tend to have locally advanced colon cancer, with negative lymph nodes and without distant metastasis. Frequently the colon cancer is located on the right side. There is still a belief that older patients can not manage curative treatment regimens. This is based on the results of older studies showing higher rates of short-term morbidity and mortality. At present, we are observing significant improvements in the outcomes of older patients with colon cancer in high volume centers. This could be due to better preoperative staging, increased use of minimally invasive techniques, better anesthesiology and perioperative care, awareness of complications, expertise and high-volume care. A standardized pre-operative diagnostic approach, individualized surgical technique selection and tailored postoperative care are essential for the successful treatment of older patients. Furthermore, counseling and shared decision-making should be based on modern insights in surgical outcomes rather than outdated data.

Key words: older oncologic patients, elderly, colon cancer, frailty

As the population aged 65 years and more increases worldwide and about 50% of all cancers occur in this group, 70% of them will die as result [1]. The third most common neoplasm worldwide is colorectal cancer (CRC) and its global incidence also continues to increase. 50% of new diagnoses of CRC are made in patients aged over 70 years, and 25% are aged over 80 years [2, 3]. Therefore, the problem of CRC in older patient is very topical and it will gain even more importance over time.

Characteristics of colon cancer in older patients

Among older patients, more women than men develop colon cancer due to their longer life expectancy. The incidence of right-sided colon cancer increases with age. Older patients tend to have locally advanced colon cancer. The frequency, however, of lymph nodes and distant metastasis is lower compared to younger patients. Furthermore, more often, the CRC is well differentiated and less often the cells mucinousmobile or signet ring [4, 5].

Preoperative assessment and treatment decisions

As was mentioned before, the population of older patients is very heterogeneous with regard to co-morbidity, physical reserves, cognitive function and social support. The current routine pre-operative assessments also cannot adequately identify patients at risk. Therefore, the Comprehensive Geriatric Assessment (CGA) was introduced and should be performed before the beginning of treatment. The CGA helps to determine the primary status of the older patient, to diagnose frailty syndrome and to identify how to optimize the patient's condition before surgery. Surgery is one of the

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primary triggers for disability in older patients. In this age group, it is more important to be mobile independent than to prolong life.

This is particularly true in patients with frailty syndrome, or decreased physiological reserves, which arise from cumulative deficits in several physiological systems and result in a diminished resistance to stressors. Therefore, a standardized pre-operative diagnostic approach, individualized surgical technique selection and tailored postoperative care are essential for successful treatment of older patients. This concept is also in agreement with the definition of health proposed by the World Health Organization; it is not a lack of disease or ailment but rather a state of well-being that encompasses physical, mental and social welfare. It is pivotal to preserve a patient's functional status and independence whilst at the same time minimizing the morbidity and mortality risks that they might be exposed to [6–8].

In general, based on the CGA, we can differentiate three groups of older patients:

1. Fit: patients without any deficits in CGA domains and less than 80 years. In this group standard oncologic treatment can be offered and the postoperative outcomes are comparable with young patients.
2. Pre-frail: patients with one deficit in the CGA domains or who are more than 80 years old. In these patients, prerehabilitation should be recommended before surgical treatment with standard intention.
3. Frail patients: patients with two or more impaired domains in the CGA or 80 years old with one deficit in the CGA. If these patients do not improve after prerehabilitaion, the tailored approach should be discussed in a geriatric multidisciplinary team meeting [9].

Treatment of colon cancer in older patients

Surgery plays a key role in the treatment of patients with CRC. In cases of stage I–III disease, surgery represents the main treatment option: most patients with stage I or II disease are treated by surgery alone; in the case of stage III, upfront surgical resection of the tumor along with adjuvant chemotherapy is the recommended treatment approach. A selected group of patients (potentially resectable metastases or symptomatic diseases: bleeding, obstruction) with stage IV disease may also take advantage of the surgical approach [10].

There is still a belief that older patients can not manage curative treatment regimens. This is based on the results of older studies that showed an association between chronological age and high rates of postoperative morbidity and mortality. At present, we can observe a significant improvement in the outcomes of older patients with colon cancer in high volume centers. Possible explanations could be better staging, increased use of minimally invasive techniques, better anesthesiology, better perioperative care, awareness of complications, expertise and high-volume care [10].

Therefore, colectomy with primary anastomosis is mostly well tolerated not only by the fitter older patient, but also by the pre-frail and not-severe frail patients when they are operated on by an experienced surgeon. There is no difference in the surgical complications rate between younger and older patients, with higher rate of medical complications. However, the mortality rate in the first six months postoperatively can be even 25% among frail patients and functional recovery must be closely monitored. This is mainly due to body changes related to perioperative trauma and their influence on all aspects of well being, which in turn, further increase the risk of new complications [11].

Therefore, perfect surgery, in the case of older patients, is not the end of the battle for a better outcome, but instead just the beginning. Diagnosing frailty is not only a qualitative aspect but the severity of frailty can be quantified. However, its influence on perioperative decisions must be further explored (e.g. the importance of total mesocolic excision in frail patients, etc.)

In selected patients with early cancers, an endoscopic resection can be offered. An endoscopic submucosal dissection is ideal because of its *en bloc* resection. Although significantly less invasive than surgery, it still carries the risk of perforation and bleeding. Therefore, the procedures must be performed with caution [12, 13].

Minimal invasive colon cancer surgery is safe and has comparable oncological results as open surgery [6, 14]. What is of paramount importance in older patients, is that minimal invasive surgical techniques evoke a less intensive immune response in comparison to open surgery, thus reducing the effects of perioperative trauma [16]. This could be an explanation for the improved recovery seen after minimal invasive surgery with less postoperative pain, shorter hospital admissions and less postoperative and cardiopulmonary complications [5, 15, 17, 18] – a key element in the recovery of older patients [14–18].

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Personalised medicine in lung cancer

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Personalised therapy is currently a promising method of treatment for cancer patients. The dynamic development of molecular biology enabled identification of molecular subtypes of neoplasms, allowing determination of the optimal therapeutic management for the patient. Molecular diagnostics is also essential for cancer diagnosis, predicting disease development and prognosis. In the case of lung cancer, which is one of the most common malignant neoplasms, the main candidates for targeted treatment are patients with stage III and IV of the disease and with no possibility of radical local treatment. In clinical practice, the most proven therapeutic agents are inhibitors of tyrosine kinase, i.e. a receptor of the epithelial growth factor (TKI-EGFR), inhibitors of ALK, ROS1, BRAF and others, as well as immunotherapy applying monoclonal antibodies against immunological system checkpoints in cases of high level expression of programmed death receptor type 1 (PD-1) or its ligand (PD-L1), but also in cases of the high tumour mutational burden (TMB). As compared to chemotherapy, targeted therapy undoubtedly improves the treatment outcomes and, due to its lower toxicity, improves the quality of life of advanced non-small cell lung cancer patients. The aim of this paper is to characterise molecular tests which are currently applied in qualification of non-small cell lung cancer patients for targeted therapies.

Key words: lung cancer, NSCLC, FISH, NGS, targeted therapy, TKI

Introduction

Personalised therapy in oncology relies on the close relationship between molecular changes in cancer and treatment. Patients with the same diagnosis, but with different tumour molecular profiles, may undergo different course of the disease and react differently to the applied therapy. The most common action points for targeted drugs are proteins that are involved in the control of tumour cell activity, including control of various signalling pathways. These proteins show abnormal activity or function in tumour cells, leading to tumour-promoting events such as excessive cell proliferation, impaired angiogenesis, inhibition of apoptosis, and other dysfunctions of the cell cycle [1, 2]. The purpose of characterising molecular subtypes is to determine the optimal therapeutic management for the patient.

Lung cancer is one of the most common malignant neoplasms, and five-year survival is achieved only in 10–15% of patients [3]. Worldwide, over 1.5 million people a year develop non-small cell lung cancer (NSCLC), which accounts for 80–85% of all lung cancer cases. In 2018, over 2 million new cases of NSCLC were diagnosed and over 1.7 million deaths were registered [4]. There is a two-fold prevalence of cases among men compared to women (13,798 *vs.* 7,747 – in 2017 in Poland), but this difference is decreasing year by year. For 15 years, a tendency has been recorded of decreased incidence and mortality of lung cancer in men, while in 2017 for the first time, the number of women who died of lung cancer exceeded the number of patients who died of breast cancer (17.4% of deaths *vs.* 14.8% of deaths). In men, lung malignancies are still

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the dominant cause of deaths (about 30%) due to neoplastic diseases [4]. The risk of developing NSCLC is strongly correlated with smoking: 85–90% of lung cancer cases are associated with this addiction [5]. The classification of 2015 by the World Health Organization (WHO) included:

- small cell lung cancer (SCLC), which accounts for 15% of primary lung cancers,
- non-small cell lung cancer (NSCLC), which is diagnosed in 85% of cases [6].

Histopathologically, NSCLC is divided into:

- adenocarcinoma (45% of all diagnosed primary lung cancers),
- squamous cell carcinoma (about 30%),
- large cell carcinoma (10%) and
- other rare morphological types (<1%) [6].

The lung cancer is rarely diagnosed at early stages. In Poland, this diagnosis is most often made at stage IV (47–62%, depending on the voivodeship) and stage III (24–38%) [7]. In patients with advanced NSCLC, chemotherapy treatment results in a 25–30% objective response rate (ORR), while the median overall survival is 10–12 months [8]. Only about 15% of patients survive 5 years from the diagnosis [9].

In the early stages, of lung cancer the basic method of treatment is surgery (in approximately 15–20% of NSCLC patients). In stage III of the disease, tumour resection is rarely possible, and patients are treated with radiotherapy, chemotherapy or a combination of these two methods, supplemented with adjuvant immunotherapy [10]. Patients with stage III and IV of the disease, in the absence of radical local treatment, are candidates for targeted therapy [6, 11].

The knowledge of molecular background of NSCLC is improving, but still in about half of the patients the molecular target remains undefined. However, numerous studies of the subpopulation of patients with various molecular changes in the neoplastic tissue allow for constant improvement of characterisation of this tumour [5, 12, 13].

Molecular testing in the qualification of NSCLC for personalised therapy

Molecular diagnostics of neoplastic tissue is essential for tumour classification, predicting disease development and prognosis, as well as choosing the optimal therapy. In the case of lung cancer, the tissue material obtained from the patient is usually small, which significantly limits the diagnostic possibilities and determines the choice of the diagnostic algorithm (Thunnissen et al., 2012) [5].

The continuous development of the molecular markers, mainly related to the application of the next generation sequencing technique (NGS) into routine laboratory practice, enables better and wider selection of NSCLC patients for targeted therapies [14–16]. Currently, multi-gene molecular profiling studies are included in the diagnostic standard in lung cancer. They allow detection of specific mutations or rearrangements of genes that are of predictive importance. Identification of these changes enables individualisation of therapy and improves treatment with an acceptable degree of toxicity. In clinical practice, the widest used drugs are inhibitors of tyrosine kinase (via a blockage of epithelial growth factor (TKI-EGFR) receptor), the inhibitors of ALK, ROS1, BRAF, NTRK, as well as immunotherapy applying monoclonal antibodies against immunological system checkpoints – mainly against the programmed cell death receptor type 1 (PD-1) or its ligand (PD-L1) (tab. I) [17].

NGS is a promising and state-of-the-art, precise and sensitive technique that allows detecting changes in the genetic material. NGS is one of the difficult diagnostic methods that require staff with high manual skills, but also with analytical and interpretative competencies. However, NGS enables analysis of many genes and, depending on the type of equipment and reagents used, many patients may be tested at the same time. The available diagnostic kits for NGS are usually designed for individual tumours and allow for a complete molecular characterisation of the examined tissue according to modern knowledge in one reaction. This significantly shortens the examination time and enables reduction of the amount of tissue necessary for its performance [13].

Molecular tests in NSCLC can be performed on formalin-fixed postoperative material (only 15–20% of primary lung cancers referred for molecular tests), in cytological material obtained during fine-needle biopsy or in the material of the so-called liquid biopsy, which is based on the use of the cell-free circulating tumour DNA (ctDNA) and RNA released from tumour cells. Recently, the increasing use of liquid biopsy to monitor therapy has been recorded [1]. Before performing molecular test in tissue, cytological material and fine needle

Table I. Genetic changes important in the molecular profiling of non-small cell lung cancer [11, 18]

No.	Gene	Change	Percentage of NSCLC
1	*KRAS*	point mutations	15–25
2	*EGFR*	amplification	20
3	*EGFR*	point mutations	10–15
4	*PTEN*	point mutations	4–8
5	*DDR2*	point mutations	4
6	*ALK*	rearrangement	3–7
7	*HER2*	point mutations	4
8	*MET*	fusion and exon 14 skipping	2–4
9	*BRAF*	point mutations	1–3
10	*PIK3CA*	point mutations	1–3
11	*AKT1*	point mutations	1
12	*MEK1*	point mutations	1
13	*NRAS*	point mutations	1
14	*RET*	rearrangement	1
15	*ROS1*	rearrangement	1

biopsy, a pathomorphological assessment of the percentage of neoplastic cells in the preparation is required [1]. In Poland, the National Health Fund (Narodowy Fundusz Zdrowia – NFZ) refunds genetic diagnostics for NSCLC patients.

Genetic changes in non-small cell lung cancer important for qualification for targeted therapy

EGFR

Mutations (pathogenic variants) in the *EGFR* (epidermal growth factor receptor – ERBB1) gene are the described as driver mutations for NSCLC and occur in approximately 10% of Caucasian patients [19]. *EGFR* belongs to the family of genes that code for receptor tyrosine kinases (RTKs). Its protein product participates in the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK pathways. The most common *EGFR* mutations are found in adenomatous type cancers [3].

Most pathogenic variants of *EGFR* are activating deletions in exon 19, which do not interrupt read-out frame (in-frame deletions) – and do not modify the three-nucleotide genetic code, hot-spot point mutations in exon 21 (e.g. L858R), and also the resistance mutation at exon 20 (T790M) [13].

If an activating *EGFR* mutation is found in the tumour tissue, treatment implemented as first line includes EGFR tyrosine kinase inhibitors (TKIs). We currently have several generations of tyrosine kinase inhibitors: the first including erlotinib, gefitinib, the second: afatinib, dacomitinib, and the third: osimertinib. In addition, it has been shown that for the less frequent *EGFR* deletions and point mutations in exons 18–21, therapy with selected TKI inhibitors can be used with good outcomes, too [13]. Rare mutations in the *EGFR* gene may coexist with common mutations of this gene. Then, it is possible to obtain a therapeutic response after the use of first-line TKI. It is an exceptional situation if an inactivating mutation (most frequently T790M) which determines TKI therapy resistance is detected to coexist with another primary activating mutation. This means that the tested neoplastic cells are insensitive to first- and second-generation TKI therapy and the patient will not benefit from such therapy, but a response to third-generation TKI treatment can be achieved [13]. However, it should be remembered that the material must be collected at the time of disease progression. In Poland currently, from 1 January 2021, the first-line treatment with osimertinib and afatinib is reimbursed in the lung cancer drug programme. In the second line treatment is reimbursed osimertinib and failure of previous treatment with other TKIs and with the presence of the T790M mutation in the *EGFR* gene. Erlotinib and gefitinib are available in the catalogue.

The methods used to detect pathogenic variants of *EGFR* include qPCR (real-time PCR, qPCR – quantitative polymerase chain reaction) or NGS. The former allows for diagnostics of a selected set of mutations (usually about 30–40 mutations in exons 18–21) and it is relatively easy among methods used in genetic diagnosis of neoplasms – usually it is performed with validated CE IVD-certified ready diagnostics sets and the result is described with fluorescence chart for particular mutations and with numerical values. The qPCR technique enables detection of mutations present even in only 1% of neoplastic cells in the examined tissue, with the use of small amounts of DNA (e.g., at a concentration of 10 ng/µl). Real-time PCR is the recommended technique for the determination of EGFR mutations. This is currently a standard method at molecular laboratories which perform genetic testing of neoplastic material. The sensitivity of the applied method should ensure reliable evaluation of the tissue material containing at least 50% of tumour cells [20].

The second technique that is used to detect variants in both the *EGFR* gene and other relevant genes, usually in combined multigene panels, is NGS. Its advantage over qPCR is the ability to detect all pathogenic and potentially pathogenic variants of all exons of gene. The standard threshold of detection of somatic mutations for NGS is defined at ≥ 5% of variant allele frequency (VAF), but it is actually possible to detect mutation at lower VAF [21].

A different diagnostic procedure is used for the T790M inactivating mutation (60% of all *EGFR* mutations). The applied techniques enable monitoring of occurrence of this mutation based on the liquid biopsy sample, i.e., on the relevantly sampled venous blood used to isolate cell-free circulating tumour DNA. In this case, the mutational status is usually assessed using qPCR but also digital PCR droplet (ddPCR) designed to study known single mutations in a very small quantity of genetic material [22]. Determination of ct*EGFR* (circulating tumour – EGFR) in liquid biopsy is also possible thanks to an automated method based on ready-to-use Idylla™ (Biocartis) cartridges, in which both the isolation process and qPCR occur in one place [23].

ALK

Rearrangements (fusions) of the *ALK* (anaplastic lymphoma kinase) gene leading to its permanent activation occur in approximately 3–6% of patients with adenocarcinoma and belong to the main alteration [24, 25]. The most common one is the fusion of *ALK* with *EML4* (echinoderm microtubule-associated protein-like 4), which results from inversion of the short arm of chromosome 2, where both genes are located, and leads to the expression of the chimeric protein EML4-ALK [25]. In addition, *ALK* fuses also with *TFG* (trafficking from ER to Golgi regulator) and *KIF5B* (kinesin family member 5B). If an *ALK* rearrangement is detected in tumour tissue of patients that are qualified for therapy with ALK inhibitors of the first (crizotinib), second (alectinib, ceritinib, brigatinib) or third generation (lorlatinib). However, occurrence of another mutation in *ALK*, or activation of other pathways: EGFR or PI3 causes resistance to this therapy [25]. In NSCLC, when an *ALK* rearrangement occurs, there is an increased predisposition for the patient to develop brain metastases.

In Poland, from January 2021, crizotinib, alectinib and ceritinib in the first line of treatment are reimbursed by National Health Fund, and so are therapies with crizotinib in the second and third lines after failure of prior chemotherapy. In addition, alectinib, ceritinib and brigatinib are reimbursed after failure of therapy with another ALK inhibitor.

Immunohistochemical testing is a cheap and fast screening method for detection of expression of the EML4-ALK fusion protein in cancer cells. Under physiological conditions, ALK plays an important role in the maturation of neurons and is not expressed in normal lung tissue, so its expression in a tumour means that it has rearranged [26]. The performance of this study to qualify a patient for targeted therapy is annually evaluated externally under the European Quality Control Program. It should be emphasised that an equivocal IHC result in the form of a weak, heterogeneous ALK protein cytoplasmic test should be confirmed by testing the *ALK* gene rearrangement with (FISH) [1]. Assessment of *ALK* gene rearrangement with FISH technique applies two-colour fluorescent probes – one for the 5' end and the other for 3' end of *ALK*. If there is no rearrangement, both probes are located close to each other (the test shows them as a single, two-coloured signal), while in the case of *ALK* rearrangement, the probes for at least one copy of the gene are separated and two discrete signals (break-apart probes) or signal deletion for the gene's 5' end can be observed in the nucleus, indicating presence of the rearrangement [25]. In this test, a minimum of 50 interphasic nuclei are analysed (100 by default, but this is not always possible due to technical difficulties and a small amount of tissue material), and the cut-off limit for a positive result is the presence of rearrangements in >15% of the analysed cells, found by two examiners in independent analyses [25]. Patients with rearrangement of the *ALK* gene present in at least 15% of nuclei may be eligible for therapy with ALK inhibitors [1].

For a patient to be qualified for the drug programme, *ALK* gene rearrangement in tumour cells should be identified by IHC, FISH or NGS using a validated test.

Another *ALK* testing method is qPCR reverse transcription. This method allows identification of fusion partners and fusion variants of this gene, but requires obtaining good quality RNA from FFPE tissue (formalin-fixed paraffin-embedded tissue), which is not always possible due to degradation of the genetic material [27, 28]. Moreover, it is not possible to detect all *ALK* fusion variants with the qPCR technique. This method is not recommended in Poland in qualifying patients for therapy and therefore it is not widely used.

ALK gene rearrangements can also be tested with the NGS technique, with both *ALK* test-only kits or kits for testing several different genes in one sample. This significantly reduces the time of the analysis, and also allows to obtain more data, including not only information on the rearrangement, but also on other pathogenic variants, e.g., point mutations which are very important for the patient, determining insensitivity to therapy. Using NGS is cost-effective for a larger number of samples and not economical for single markings [13–15]. Performing this test in patient selection for targeted therapy, similarly to IHC and FISH testing, is annually evaluated outside the lab within the European quality control system.

ROS1

Rearrangements of the *ROS1* gene (ROS protooncogene-1, tyrosine kinase receptor) occur in 1–2% of NSCLC patients and determine the response to therapy with *ROS1* inhibitors (e.g., crizotinib). Similar as in the case of *ALK*, point mutations occur in the *ROS1* gene causing insensitivity to this therapy despite the occurrence of rearrangements [13]. Analogically to the *ALK* gene, diagnostics can apply FISH and NGS methods, and selection for treatment is possible based on results obtained from a laboratory that has received positive evaluation within the annual control of the European quality control system.

PD-1 and PD-L1

PD-L1 (programmed death-ligand 1) is a cell surface ligand and its overexpression in neoplastic cells is conditioned by loss of the *PTEN* gene and induction of the PI3K-AKT pathway. In turn, PD-1 (programmed cell death protein 1) is a receptor on the surface of CD81+ T cells, and its expression increases during tumour cell infiltration [29]. This reduces the lymphocytes' ability to produce cytokines and proliferate, which disrupts the immune system. If an IHC test using DAKO PD-L1 IHC 22C3 antibodies concentration or Ventana PD-L1 SP263 antibodies confirms presence of PD-L1 in 50% or more cancer cells, patients are qualified for treatment with anti-PD-1 antibodies in monotherapy (pembrolizumab), restoring lymphocytes' cytotoxic activity. On the other hand, when PD-L1 expression is below 50%, patients benefit from treatment with immunotherapy in combination with chemotherapy (currently reimbursed in the Polish drug program from January 2021).

It should be remembered that expression of PD-L1 in neoplastic cells is not essential for the immunotherapy treatment to be beneficial for the patient. This is the case of nivolumab, atezolizumab – in Poland reimbursed under the drug program in the second-line treatment, after failure of chemotherapy. It is not required either for application of durvalumab – as consolidation treatment after radical radiochemotherapy. However, immunotherapy is only effective in a small percentage of patients, possibly due to the highly complex immune microenvironment of the tumour.

Globally, clinical application of immunotherapy in NSCLC originated in 2015 – based on the CheckMate 017 study [30]. Clinical trials show divergent results regarding the role of PD-L1 expression as a predictive factor for immunotherapy result. This is probably due to differences in the evaluation of expression and methods of testing with immunohistochemical methods. The change in expression may be also affected by prior treatment (e.g., chemotherapy). Moreover, tumours are

characterised by heterogeneity of PD-L1 expression within the tumour as well as different expression between the primary tumour and lymph nodes [31–33].

Other genes

Next-generation sequencing makes it possible to analyse the entire sequence of many genes in a single assay, but the amount of data obtained from such a study also carries the risk of misinterpretation and difficulties in interpreting their meaning in relation to clinical data. Therefore, according to the latest recommendations, in patients with NSCLC, the examination of tumour tissue for **diagnostic purposes** should include a specific panel of genes whose pathogenic variants are predictive or prognostic [13]. According to the recommendations by the European Society for Medical Oncology (ESMO) and the Scale for Clinical Actionability of molecular Targets (ESCAT), such genes in patients with advanced non-squamous NSCLC include:

- *MET* – which encodes the receptor for hepatocyte growth factor receptor (HGFR). The most common mutation is either exon 14 deletion (exon 14 skipping) associated with poor prognosis (approximately 3% of patients), or gene amplification (also in approximately 3% of patients) inducing resistance to EGFR inhibitors – usually a result of cell clonal selection in patients after this therapy. Application of capmatinib was an attempt to overcome this resistance. Crizotinib has been shown to be effective in patients with high amplification of the *MET* gene.
- *BRAF* – the most common V600E mutation, occurring in approximately 2% of patients. Drugs approved for first-line treatment in cases of this mutation are dabrafenib and trametinib.
- *NTRK* – 0.23–3% of patients have *NTRK/1/2/3* gene fusions, which determine formation of oncoproteins. In 0.1–1%, NSCLC does not coexist with other genetic disorders. Drugs approved for treatment in cases of these mutations are entrectinib and larotrectinib.
- *RET* – fusions occur in 0.6–0.9% of NSCLC patients, and in 1–2% of adenocarcinoma patients. Rearrangement of this gene does not usually coexist with other genetic changes in NSCLC cells. On 10 December 2020, the European Medicines Agency (EMA) approved selpercatinib in monotherapy for RET-positive non-small cell lung cancer after prior immunotherapy and/or platinum-based chemotherapy.
- *KRAS* – 12% of patients have these mutations, 97% of which are in exons 2 and 3 (mainly in G12, G13 and Q61).
- *HER2 (ERBB2)* – gene amplification and hot-spot mutations are observed in 2–5% of patients. A therapeutic effect of afatinib and dacomitinib was recorded in patients with these mutations.
- *BRCA1/2* – point mutations were observed in 1.2% of patients.
- *PIK3CA* – mainly hot-spot mutations, but also amplifications present in 1.2–7% of patients, often coexisting with mutations of other genes.
- *NRG1* – gene fusions occur in 1.7% of patients.

According to ESCAT, in patients with advanced squamous-cell NSCLC, fusions of the *NTRK* gene (present in 0.23–3% of patients), mutations of *PIK3CA* (16% of patients) and *BRCA1/2* (1.2% of patients) are diagnostically and clinically significant [13].

Tumour mutational burden (TMB)

Recently, the quantitative biomarker of TMB (tumour mutational burden) is gaining increased interest as a predictive factor in immunotherapy. The TMB test is performed with NGS technique, and the TMB value is determined by the number of mutations per million base pairs in DNA isolated from the tumour [34]. TMB result is reported as: high (TMB-high), intermediate (TMB-intermediate), low (TMB-low) or undetermined (TMB-undetermined), depending on the number of mutations detected in the tumour [35]. NSCLC patients with high TMB have been shown to benefit clinically with immunotherapy targeted at immune checkpoints (immune checkpoint inhibitors – ICIs) [16]. This effect is associated with increased expression of neoantigens induced by the presence of a mutation that mobilises the immune system to recognise and destroy cancer cells [36]. High TMB correlates with increased progression-free survival (PFS) and increased response rate in patients after immunotherapy [37].

Perspectives

In selected patients, targeted therapy undoubtedly improves treatment results and control of advanced non-small cell lung cancer, as compared to chemotherapy. The quality of life of patients treated in this way also improves because the toxicity of this therapy is lower. Application of first-generation TKI targeted at EGFR also improves PFS as compared to chemotherapy [38]. However, over time, patients inevitably develop drug resistance. The most common resistance mechanisms include appearance of the T790M mutation of *EGFR*, *RAS* gene mutation, and *MET* amplification. Resistance to first- and second-generation inhibitors has been shown to occur on average after 10–14 months [39]. In recent years, the third generation of EGFR-TKI has been developed – a drug that is active both in the first line in the presence of the *EGFR* mutation, and in the second line of treatment after other TKI inhibitors, in the presence of the T790M resistance mutation in the *EGFR* gene. Studies have shown that there is drug resistance to third generation EGFR-TKI in the form of mutations of *EGFR*, *PIK3CA*, *KRAS*, *BRAF* and *MET*. *MET* inhibitor can increase sensitivity to first-generation EGFR-TKI [40]. In general, regardless of the *EGFR* and *KRAS* mutations, approximately 5% of NSCLC patients have a rearrangement (fusion) of the *ALK* gene. A greater risk of brain metastases is observed in such cases [41]. It was also found

that the second-generation ALK inhibitor has a high intracranial efficacy compared to the first-generation ALK inhibitor [42], but with time new mutations appear, conditioning resistance to the treatment.

Other immune checkpoints besides PD-1/PD-L1 are also being sought to increase the number of patients who can benefit from this form of treatment. Another direction involves application of the combined therapy, e.g., chemotherapy with checkpoint inhibitors (such a combination of drugs is already registered and available in Poland within the drug programme – from 1 January 2021).

There are currently many clinical trials underway concerning targeted therapies in NSCLC, both alone and in combination, as well as their sequential administration. Further, there are also trials on application of molecularly targeted drugs and immunotherapy in neoadjuvant and adjuvant treatment, as well as maintenance therapy. Chemotherapy is no longer the best systemic treatment available for all NSCLC patients. Therapeutic decisions should be based on examination of the molecular characteristics of the tumour.

Expected benefits for patients, such as prolongation of overall survival and obtaining the longest possible remission in the future will probably result from finding the optimal ways of combining targeted therapy, immunotherapy and chemotherapy.

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The commercialization of research results in medicine

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The commercialization of research results, understood as their use and dissemination to other entities in a manner that allows for financial gain. In this regard, the general rules that apply to the commercial exploitation of economic and transferable intellectual property rights protecting the results of scientific activities are supplemented with specific statutory regulations. They define the procedure for the commercialization of the results of scientific activities carried out in universities and research institutes, the rights and obligations of researchers in the field of commercialization and the rules for distribution of profits from commercialization between the entity and the single author or members of the research teams.

Key words: research results, commercialization, distribution of profits from commercialization, intellectual property management policy

Introduction

Scientific research is an indispensable element of modern medicine which seeks increasingly effective ways of solving aging societies' health problems, treating civilization diseases and combating threats to public health. A lot of groundbreaking applied scientific research is carried out at medical universities and research institutes. Their results are the basis for developing new treatments, products, devices and medical technologies [1]. Apart from scientific publications, the number of patent applications and implementations based on the research results constitutes the criterion of parametric evaluation of scientific units and periodic evaluation of researchers.

Despite some freedom in the management of research results, and the acquisition of rights to them, the procedure and the distribution of profits from commercialization are subject to specific statutory regulations and/or rules applicable to funds or grants from which research activities are financed. The the knowlege of these regulations is essential for the effective and profitable management of intellectual property related to research results in scientific units, research teams and joint projects carried out by clinical departments and entities marketing medical products ready for market sales.

Model for commercialization of scientific research and development results

The protection of research results in scientific units researching the field of medical sciences is subject to the general provisions of the Act of 4 February 1993 on Copyright and Related Rights [2] and the Act of 20 June 2000 Industrial Property Law [3]. They concern, in particular, the acquisition by these units as an employer of author's economic rights and industrial property rights to intellectual creations. As regards employee's inventions, the law provides the possibility of participation of the author-employee in the benefits obtained from the use of the invention (sale or licensing of rights to the invention). The regulations also include rules of transfer and licensing of rights to such results, which, after valuation, may also constitute a contribution in kind to a capital company.

Specific rules concerning the management and commercialization of scientific activity results at universities are provi-

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ded by the Act of 20 July 2018. The Law on Higher Education and Science [4] and the Act on Research Institutes of 30 April 2010 on Research Institutes [5], apply to research institutes supervised by the Ministry of Health. The regulations as mentioned above refer to the "results of scientific research and development works and the know-how related to these results", or, a collective term "results of scientific activity", covering all types of such results. These terms also apply to inventions and copyright works resulting from development work. Results of scientific activity in this sense do not involve scientific work (scientific publications, lectures, conference speeches), as well as the following not protected by intellectual property rights: scientific findings, clinical data, discoveries, results of clinical trials "as such". These creative results are generally outside the scope of commercialization processes.

The process of transferring the results of scientific activity to practice comprises:

- direct commercialization, i.e. the sale of results, making these results or know-how available for use, in particular on the basis of a license, lease and rental agreement; and
- indirect commercialization, including the acquisition or purchase of shares or stocks in companies in order to implement the results of scientific activity in exchange for the rights to such results and to generate income from this.

Public universities can carry out indirect commercialization through a dedicated university special purpose company (e.g. SYNERGIA-WUM Sp. z o. o; the Centre for Innovative Technologies of the Pomeranian Medical University). With the consent of the Minister of Health, medical research institutes can also establish capital companies and take up or acquire shares and stocks for the purposes of commercialization, conducting activities in the field of technology transfer and dissemination of science, as well as obtaining funds for statutory activities. The units responsible for supporting the commercialization processes in research units are technology transfer centers.

Internal regulations for the management of copyright, industrial property rights and principles of commercialization are an essential tool for supporting commercialization processes. They regulate the principles, procedure for the commercialization of research results created in the research unit and in cooperation with external entities in the framework of joint research projects or commissioned work. Adoption of such regulations is the responsibility of all research units. In the case of public medical higher education institutions and research institutes, they should define:

- the rights and obligations of the units, employees and doctoral students as regard the use of copyright, related rights and industrial property rights;
- the principles of remuneration of authors;
- the principles of distribution of funds obtained from commercialization;
- the principles and procedures of commercialization of research and development results and the know-how related to these results;
- the principles of using the unit's property used for the commercialization of research results.

The rules of procedure should be effectively notified to employees and form part of their employment contracts.

Rights and obligations of the research unit and employees

The statutory model for the commercialization of research and development work in public universities covers the results of employees' scientific activity obtained in the performance of their duties, to which the research unit, as the employer, is entitled to intellectual property rights. Firstly, its essence is the obligation of the entity to decide on the commercialization of such results within a specified time. Secondly, the obligation to contractually transfer the rights to such results to the employee for a statutorily specified amount if the entity is not interested in commercialization, but the employee declares a desire to acquire them. Remuneration for the transfer of rights cannot be higher than 5% of the average salary in the national economy (about 200 PLN). This is a desirable solution for the creator--employee, who, for a small amount, can obtain the rights to research results and decide on their further commercial exploitation, e.g. as part of their business activities.

At the same time, public universities' employees have obligations related to the statutory procedure for the acquisition and commercialization of rights to research and development results. These include:

- reporting the results of scientific research and development works and the know-how related to these results in the procedure specified in internal regulations,
- transferring all available information and technical experience needed for commercialization,
- maintaining the confidentiality of these results.

Sharing commercialization revenue

An essential aspect of the statutory procedure for the commercialization of research and development results is creating a financial incentive to develop solutions that can be implemented in practice. In the case of obtaining economic benefits from the commercialization of research results at a public university (e.g. the sale or licensing of an invention resulting from scientific research), the creator-employee is guaranteed by law the right to participate in benefits obtained on this account. In this case, the employee is entitled to no less than 50% of the value of the commercialization funds. It can be reduced by no more than 25% of the costs directly related to it (Article 155 of the Act on Higher Education and Science). If a research team obtained the commercialized results, the indicated minimum share of 50% refers to the total remuneration and the allocation of these funds. In a situation where commercialization is carried out by an employee to whom the rights to research results have been transferred on the basis of an agreement, the employee is required to pay the university 25% of the value

of such benefits, reduced by no more than 25% of the costs incurred by the employee in direct relation to that activity. "Costs directly related to commercialization", include external costs, particularly the costs of legal protection, expert opinions, assessment of the value of the object of commercialization and official fees incurred to obtain protection (particularly patent protection of the invention as an ordinary object of commercialization). The right of an employee and the higher education institution to remuneration for the benefits from commercialization shall last five years from the date of the first benefit derived from commercialization. During this period, the right to claim remuneration shall be vested in the creator of the results regardless of whether or not he/she continues to have the status of an employee of the entity. Therefore the right can also be executed after the termination of employment.

The commercialization of research results financed from external sources

The described statutory rules for commercialization of research and development results laid down in the Act on Higher Education and Science do not apply to cases where the scientific activity which led to the creation of the results was conducted on the basis of an agreement with a party financing or co-financing this activity and this agreement includes an obligation to transfer the rights to the results of scientific activity to this party or to another entity. This also applies to research conducted with the use of funds, the rules of granting or use of which determine, in an autonomous way, the manner of disposing the results of scientific activities and the know-how related to these results (e.g. research funds from the National Centre for Research and Development (NCBiR), the National Science Centre (NCN), European Research Council (ERC) grants, EU research grants [6].

Conclusions

The search for new ways to effectively support health care and the treatment of civilization diseases, new possibilities of financing research in medicine, increasing cooperation between clinical units and entities marketing final medical products is conducive to the intensification of commercialization processes of research results. More and more often, they are successfully commercialized through companies dedicated to this purpose (e.g. PolTREG of the Medical University of Gdansk commercializing innovative therapy for diabetes, by using T-regulatory lymphocytes taken from the patient's blood). There are also examples of successful licensing on commercial terms (e.g. a license to iQure Pharma for a patent protecting the Jagiellonian University invention "Modified amino acid derivatives for treatment of neurological diseases and selected psychiatric disorders" [7]).

The interest of scientific employees in the implementation of their research results is also increasingly influenced by the scoring of such achievements in the periodic evaluation of scientific employees' activity and the scientific output assessed in the procedures for obtaining scientific degrees and titles.

Due to the statutory regulation of the commercialization of research and development results, public universities, research institutes and their researchers are bound by the rights and obligations arising from the applicable legislation. They can be specified or supplemented in internal regulations on the management of copyright and industrial property rights and commercialization. Compliance with these regulations is subject to control by the authorities supervising these institutions [8].

An important incentive to conduct research that has scientific value and can be applied in practice is the right to participation in the benefits of commercialization of such results. There is also the possibility to purchase rights by the employee from the university for a fixed lump sum in order to further commercialization. It can be successfully conducted through a dedicated company developing and offering medical products or services based on such results on commercial terms.

In the case of research and development results obtained under grants, multicenter or international projects or cooperation with external entities, the rules for the acquisition and commercialization of rights to such results may be the subject of autonomous regulations, which will be decisive in terms of the management of the results of such projects.

Conflict of interest: none declared

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