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# The clinical course of poorly differentiated thyroid carcinoma (insular carcinoma) — own observations

## Przebieg kliniczny niskozróżnicowanego raka tarczycy (*ca insulare*) — obserwacja własna

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### Abstract

**Introduction:** Poorly differentiated thyroid carcinoma (PDTC, insular carcinoma) occurs rarely. It is described with more aggressive behaviour, poorer prognosis, and higher mortality than well differentiated thyroid carcinoma (WDTC).
The aim of this study was to evaluate the clinical course of patients with PDTC, in addition to frequency, clinical stage at the time of diagnosis and the possibility of radical surgical resection, the necessity and kind of complementary treatment, occurrence of distant metastases, and the survival of patients.
**Material and methods:** The study involved 14 patients (9 females, 5 males) diagnosed and treated for PDTC between 2000 and 2009, aged 38 to 78 years. The medical records of patients with PDTC were analyzed to estimate assumed parameters according to the purpose of the study.
**Results:** PDTC was diagnosed in 14 among 801 patients with thyroid carcinoma (1.75%). Clinical stages (UICC 2002) at the time of diagnosis were as follows: 3 patients — $pT_{1-2}N_{o-x}M_x$ (21.5%); 10 patients — $pT_{3\,4}N_{x\,o\,1}M_{x-1}$(71.4%); and 1 was unresectable — $T_xN_1M_1$ (7.1%). Total thyroidectomy was achieved in 9 patients (64.3%), and 4 patients (28.6%) received non radical surgery. Complementary radioiodine treatment was given to 12 patients (85.8%). Radiation therapy of the neck was applied to 7 patients, palliative radiotherapy of the brain to 1 patient, and chemotherapy to 1 patient. Distant metastases to the lung and to the brain at diagnosis were observed in 2 patients (14.3%). During follow-up of 3–62 months lung metastases were observed in 4 patients (28.6%), three patients were observed above 5 years as disease-recurrence free (21.5%), but in one patient after 5 years and 2 months distant metastases were diagnosed. Three patients died after 2–30 months (21.5%), 2 patients were lost for control, and in the remaining 6 follow-up lasted for less than 5 years.
**Conclusions:** Poorly differentiated thyroid carcinoma is still a challenge both for pathologists and clinicians. Infrequent prevalence, more aggressive course, and poorer prognosis constitute major problems for the clinicians.
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***Key words:*** *poorly differentiated thyroid carcinoma, insular carcinoma, prognosis, therapy*

### Streszczenie

**Wstęp:** Niskozróżnicowany rak tarczycy (PDTC, *poorly differentiated thyroid carcinoma*) występuje rzadko, charakteryzuje się bardziej agresywnym przebiegiem, gorszym rokowaniem, większą śmiertelnością niż wysokozróżnicowane raki tarczycy (WDTC, *well differentiated thyroid carcinoma*).
Celem pracy była analiza przebiegu choroby u pacjentów z PDTC z uwzględnieniem częstości występowania, zaawansowania klinicznego przy rozpoznaniu, możliwości chirurgicznego leczenia radykalnego, konieczności i rodzaju leczenia uzupełniającego, wystąpienia przerzutów odległych, przeżycia chorych.
**Materiał i metody:** Badaniem objęto 14 chorych (9 kobiet, 5 mężczyzn) z PDTC, zdiagnozowanych i leczonych w latach 2000–2009, wiek 38–78 lat. Przeanalizowano dokumentację medyczną pacjentów z PDTC, oceniając założone w celu pracy parametry.
**Wyniki:** Niskozróżnicowanego raka tarczycy zdiagnozowano u 14 chorych spośród 801 z rakiem tarczycy (1,75%). Zaawansowanie kliniczne (UICC 2002) przy rozpoznaniu 3 chorych: $pT_{1-2}N_{o-x}M_x$ (21,5%), 10: $pT_{3-4}N_{x-o-1}M_{x-1}$(71,4%), 1 nieoperacyjny: $T_xN_1M_1$(7,1%). Radykalnie operowano 9 chorych (64,3%), nieradykalnie 4 (28,6%), jednego (7,1%) zdyskwalifikowano. Leczenie uzupełniające — terapia $^{131}I$: 12 (85,8%), 1 zdyskwalifikowany, 1 nie zgłosił się; radioterapia szyi: 7 (50%), paliatywna OUN: 1 (7,1%); chemioterapia: 1 (7,1%).
Przerzuty odległe przy rozpoznaniu stwierdzono u 2 chorych (14,3%), po 3–62 miesiącach: u 4 (28,6%). Przeżycie: 3 chorych ponad 5-letnie (21,5%), u jednego po 62 miesiącach zdiagnozowano przerzuty do płuc; 3 zmarło (21,5%), 2 zaprzestało kontroli, u 6 obserwacja poniżej 5 lat.
**Wnioski:** Niskozróżnicowany rak tarczycy wciąż stanowi wyzwanie zarówno dla patologów, jak i klinicystów. Rzadkie występowanie, bardziej agresywny przebieg i gorsze rokowanie nie ułatwiają opracowania dla tej grupy chorych jednolitych zaleceń terapeutycznych, które mogłyby poprawić przeżycie. Część z nich może wymagać wielokierunkowego intensywnego leczenia, a ustalenie wskazań do takiego postępowania nadal pozostaje przedmiotem badań i obserwacji. **(Endokrynol Pol 2010; 61 (5): 467–473)**

***Słowa kluczowe:*** *niskozróżnicowany rak tarczycy, rak wyspowy, rokowanie, leczenie*

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## Introduction

Thyroid carcinoma (TC) is the most frequent neoplasm of endocrine glands. Well differentiated thyroid carcinomas (WDTCs) account for up to 90% of all thyroid carcinoma cases and are characterized by favourable prognosis when modern treatment is applied [1]. Undifferentiated (anaplastic) thyroid carcinoma (UDTC) occurs rarely, but it presents a very aggressive clinical course with a fast local growth, distant metastases, and definitely bad prognosis [1]. A 5-year survival is so rare that after obtaining such a treatment effect, primary diagnosis revision is usually required [3].

Among patients diagnosed with thyroid carcinoma, a small group with distinct histopathological and clinical features has been noticed which does not suit either WDTCs or UDTC. The term 'poorly differentiated thyroid carcinoma' (PDTC) was suggested for the group of TCs with intermediate features [4]. According to various authors, the incidence of PDTC among patients with thyroid carcinomas is estimated at the level of 2–3% in the USA and up to 15% in northern parts of Italy, with an average of 4–7% for all thyroid carcinomas [5, 6]. Genetic factors are thought to explain the relatively high prevalence of PDTC in northern Italy and other Alpine regions of Central Europe [5]. Genetic and/or environmental factors are suggested in the aetiology of PDTC (including dietary factors, e.g. iodine) [5].

Gene p53 mutations are detectable in approximately 70–85% of UDTCs and 20–30% of PDTCs, but they are not found in WDTCs. Thus, mutated p53 is a molecular marker of thyroid tumour dedifferentiation, signalling poor prognosis [7–10]. The mutations are mostly spontaneous but they may be also a result of previous radiotherapy or $^{131}$I treatment [7].

K-, H-, and N-RAS mutations are other genetic factors which appear to play a role and are found in nearly 10–20% of WDTCs, in 50% of PDTCs, and in a similar percentage of UDTCs [7, 11]. The role of $\beta$-catenin mutations is still controversial. There are data on the occurrence of $\beta$-catenin mutations in thyroid carcinomas associated with worse and bad prognosis, observed in 32% of PDTC and 80% of UDTC [7, 12]. However, Rocha et al. described 17 PDTCs of which none presented $\beta$-catenin mutation, and suggested that loss of membrane E-cadherin is the crucial event in determining the dedifferentiation rather than $\beta$-catenin mutations [13].

The activating mutation in the *BRAF* gene was detected in a fraction of poorly differentiated thyroid carcinoma developing from differentiated papillary thyroid carcinoma (PTC) having some residual foci of papillary carcinoma. Therefore, the presence of BRAF mutation may appear as a prognostic factor of transition from PTC to PDTC [14, 15]. It is worth noticing that in a recent study *BRAF* mutation has been associated to $^{18}$FDG PET-positive radioiodine refractory metastases of PDTC [16].

PDTCs are characterized by a more aggressive clinical course than WDTCs. They are often more clinically advanced at diagnosis, tend to recur locally, and develop metastases to regional lymph nodes, lungs, and bones [6]. The prognosis is worse than for WDTCs, but it is not as bad as for UDTCs. The mean 5-year survival of patients with PDTCs is approximately 50% while patients with UDTCs have a mean survival of 6–8 months [6, 17].

The rarity of PDTCs and equivocal diagnostic criteria are the causes of difficulties in establishing uniform recommendations concerning the therapeutic procedure for this type of tumour. Postoperative $^{131}$I treatment, radiotherapy, or chemotherapy are decided on the basis of individual indications [18, 19].

The aim of this study is to present our own observations of the clinical course of PDTCs in patients who were diagnosed and treated during 9 years in one clinic — the Department of Endocrinology and Nuclear Medicine in cooperation with the Department of Surgical Pathology, Hollycross Cancer Centre (Świętokrzyskie Centrum Onkologii, SCO) in Kielce.

## Material and methods

The study involved a group of 14 patients diagnosed histologically with poorly differentiated thyroid carcinoma (PDTC): nine female patients with ages ranging from 38 to 78 (mean age 63.2 years) and five males with ages ranging from 51 to 75 (mean age 63.8 years), who were treated in SCO in Kielce between 2000 and 2009.

The patients' medical documentation was analyzed retrospectively and the frequency of PDTC among all the thyroid carcinoma patients was taken into consideration. Moreover, the clinical course of PDTC (clinical stage at the moment of diagnosis, the possibility of radical surgical treatment, the necessity and type of the complementary treatment applied, occurrence of distant metastases, and survival of patients) was evaluated.

The first diagnosis of PDTC originates from November 2000. The period of patient follow-up was ranged from 2 to 76 months. The study finished in December 2009.

The clinical advancement at the moment of diagnosis was evaluated during the first diagnostics and the initial treatment - preoperatively, postoperatively, after complementary $^{131}$I treatment with the post-therapeutic scintigraphy results, in accordance with the recommendations of the Polish Group of Endocrine Tumours, including the TNM classification dating from 1992, modified in 2002 [18, 20, 21].

All histopathological examinations of the patients operated in SCO were evaluated by two pathologists from the Department of Surgical Pathology, SCO, Kielce. Histopathological material taken from two patients after first surgical treatment performed beyond SCO was consulted in our centre. The whole complementary and/or palliative treatment, including $^{131}$I treatment, radiotherapy, and chemotherapy, was administrated in SCO in Kielce. Among 801 thyroid carcinoma patients 14 were diagnosed with PDTC, 1.75% of our material. It occurred more often among females (64.3%); the female:male ratio (F:M) was 1.8:1. Most patients were ≥ 50 years old at the time of the diagnosis: thirteen patients (92.9%) including five males and eight females. During analysis of the anamnesis preceding the diagnosis, 11 patients (78.6%) were diagnosed with nodular goiter including two patients with recurrence after strumectomy. One patient was administered 11.1 mCi $^{131}$I because of subclinical hyperthyroidism in the course of postoperative regrowth of goiter 5 years before thyroid carcinoma diagnosis. Five patients (35.7%) were characterized by quite fast growth of tumour on the neck, ranging from a few weeks to 4–5 months. Three patients (21.5%) were diagnosed preoperatively with thyroid carcinoma because of lymph node metastases.

## Results

### *Clinical advancement at the moment of diagnosis*

At the moment of thyroid carcinoma diagnosis, three patients presented $pT_{1-2}N_{o-x}M_x$ stage (21.5%) and ten patients $pT_{3-4}N_{x-o-1}M_{x-1}$ stage (71.4%). One female patient presented inoperable disease from the very beginning and was in rather poor general condition with metastases to the regional, mediastinum, and left supraclavicular lymph nodes and distant metastases to the lung and brain ($T_xN_1M_1$).

One female patient was primarily diagnosed with right thyroid lobe papillary carcinoma at the clinical stage of pT1aNoMx. As well as the diagnosed microcancer, the presence of a *hyalinising trabecular tumour* (diameter of 46 mm) in the left thyroid lobe was found in the specimen. The occurrence of metastases after a year and surgical removal of these metastases led to verification of the diagnosis. Finally, the left thyroid lobe carcinoma and metastasis to the lungs were diagnosed as poorly differentiated thyroid carcinoma foci.

The TNM classification of our patients is presented in Table I.

**Table I.** *Clinical stage at the time of diagnosis PDTC — TNM*
**Tabela I.** *Zaawansowanie kliniczne w chwili rozpoznania PDTC — TNM*

| TNM feature | n | % |
|---|---|---|
| pT1 | 1 | 7.1 |
| pT2 | 2 | 14.3 |
| pT3 | 6 | 42.9 |
| pT4 | 4 | 28.6 |
| Tx non-operative | 1 | 7.1 |
| N1 | 4 | 28.6 |
| M1 | 2 | 14.3 |

### *Surgical treatment*

Thirteen patients (92.9%) were qualified for operative treatment. One female patient (7.1%) was disqualified because of very poor condition since the beginning of the disease. Nine patients (64.3%) underwent radical surgery: total thyroidectomy and lymphadenectomy. Some patients from this group (4/9; 44.4%) required surgical radicalisation after the first operative treatment, including two patients after the first operation not performed in our centre.

Four patients (28.6%) were operated not radically. In this sub-group, one patient (7.1%) was diagnosed with an unresectable tumour during the operation, in the other three patients (21.5%) carcinoma foci exceeded the line of the surgical cut at the histopathological assessment. In two patients (14.3%) an extensive infiltration beyond the thyroid capsule including external carotid artery, common carotid artery, larynx, and trachea was found.

### *Postoperative treatment*

After the performed surgical treatment, all patients (13/14; 92.9%) were planned for radioiodine scan and evaluation of stimulated serum Tg level. However, one patient from this group, although he was initially qualified to receive the complementary $^{131}$I treatment, did not attend. One female patient (1/14; 7.1%) was not qualified because of her very poor general health condition. The remaining 12 patients (85.8%) received $^{131}$I treatment. The endogenous TSH stimulated thyroglobulin level ranged from < 0.2 ng/ml to > 300 ng/ml, with a mean level of 84.39 ng/ml. In two patients, the thyroglobulin level was < 0.2 ng/ml, including one patient with positive antithyroglobulin antibodies.

The radioiodine activity applied for the initial treatment ranged from 2100 MBq (56.75 mCi) to 4884 MBq (132 mCi). During the follow-up, seven patients (50%) were qualified to receive further $^{131}$I treatment. Four patients were treated twice with $^{131}$I, one patient was treated three times, one was treated four times, and one was treated six times (total iodine activity 620 mCi). In the patients who were treated by means of more than one dose of $^{131}$I, the indications for successive doses of

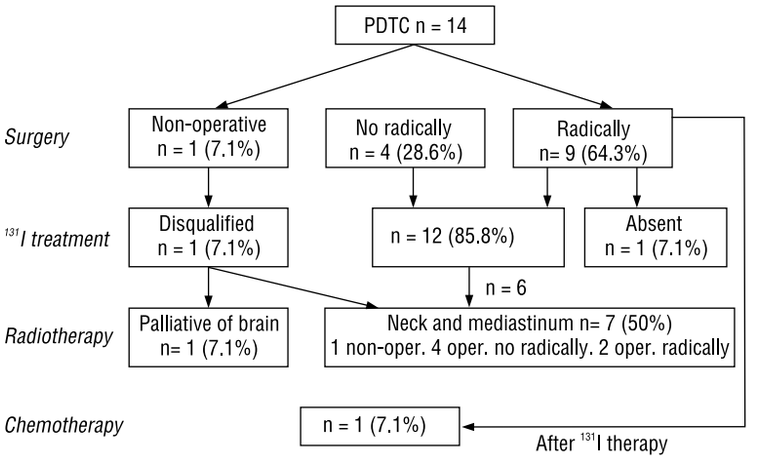


**Figure 1.** *Treatment of patients with PDTC in ŚCO in Kielce*
**Rycina 1.** *Leczenie chorych z PDTC w ŚCO w Kielcach*

**Table II.** ***Clinical course of PDTCs with distant metastases***
**Tabela II.** ***Przebieg obserwacji u chorych z przerzutami odległymi u chorych z PDTC***

| Patient gender age (year) | pTN | RtgTh | ChTh | Presence of M1 at dgn | Follow-up to presence of M1 | Total follow-up |
|---|---|---|---|---|---|---|
| S.P.♂,70 | pT4N1 | + | – | (+) lung | | 15 months |
| S.W.♂,55 | pT4N1 | + | – | (–) | 3 months | 30 months: DEATH |
| E.Ś.♂,68 | pT3N1 | + | – | (–) | 5 years 2 months | 6 years 4 months |
| L.K.♂,51 | pT3Nx | – | + | (–) | 19 months | 4 years 9 months |
| K.R.♀,56 | TxN1 | + | – | (+) lung, brain | | 2 months: DEATH |
| Z.T♀,50 | pT1No | – | – | (–) | 12 months | 20 months |

$^{131}$I resulted from persistent $^{131}$I neck uptake, and in one case radioiodine-avid lung metastases.

Seven patients (50%) were qualified to receive external beam radiotherapy, including one female patient for whom the palliative radiotherapy of neck, mediastinum, and brain areas was the only possible treatment to be applied. Six patients, in whom pT4 and/or N1 (42.9%) stage was diagnosed, were qualified to receive external radiotherapy of the neck and mediastinum after the surgical treatment and $^{131}$I therapy.

The scheme of the treatment performed in all the patients with PDTC is presented in Figure 1.

Distant metastases were found in two patients (14.3%) at the moment of PDTC diagnosis, in one patient there were metastases to lung and brain, and in the other there were radioiodine refractory lung metastases. During the follow-up, lung metastases were diagnosed in four other patients (28.6%). Only in one of them were the metastases characterized by low iodine uptake, and they did not accumulate radioiodine in the other three patients.

One patient (7.1%) with clinical advancement of pT3NxMo at diagnosis was referred for chemotherapy after the radioiodine refractory lung metastases were found. The patient received doxorubicin and cisplatin and achieved incomplete remission, he is currently being considered for tyrosine kinase inhibitor therapy.

In the group of patients with distant metastases to the lungs, who were diagnosed after the initial treatment, three patients were qualified for thoracic surgical treatment, in each case the histopathological confirmation of PDTC metastases to the lungs was obtained.

The observation course of the patients with distant metastases is shown in Table II.

### *Survival of patients*

Total duration of follow-up was 9 years and 2 months. The observation time of individual patients ranged from 2 months to 6 years and 4 months.

Five-year disease-free survival was acquired in three patients (21.5%). One patient was diagnosed with radioiodine refractory metastases to the lungs 5 years and

2 months after initial surgery. During the study three patients (21.5%) died. Two patients (14.3%) escaped from control after 2 and 56 months, respectively, and six patients (42.9%) have been less than 5 years in follow-up.

## Discussion

The term of 'poorly differentiated thyroid carcinoma' was proposed in 1983 by Sakamoto et al. [4]. They analyzed 258 malignant thyroid carcinomas and found that 35 of them had non-papillary/non-follicular growth pattern with poor prognosis. Five-year survival was observed in 65% of that sub-group compared to 95.1% of patients with WDTC.

Almost simultaneously, Cargangiu et al. proposed a similar definition. They reinterpreted a report originally described by Langhans in 1907 and introduced the name of insular carcinoma to a new type of thyroid carcinoma characterized by the presence of *insulae* which included small cell size, round/oval hyperchromatic nuclei, mitotic activity, and necrotic background [22].

Despite increasing acceptance of the term 'poorly differentiated thyroid carcinoma', for many years various authors around the world classified different histological types to the group of PDTC [4, 23–26]. Therefore, data in the literature were difficult to analyse morphologically, epidemiologically, and clinically. The new type of thyroid carcinoma — *poorly differentiated thyroid carcinoma* — was defined in the WHO Classification of Endocrine Tumours as recently as 2004. PDTC is defined as a neoplasm developing from thyroid follicle cell, presenting restricted differentiation to it and having both morphological and biological intermediate behaviour between well-differentiated thyroid carcinomas and undifferentiated carcinoma [27]. PDTC may develop 'de novo' or in the persistent differentiated thyroid carcinoma.

Uniform histopathologic diagnostic criteria were reached for PDTC at a consensus conference in Turin, Italy, in 2006. The proposed criteria, known as the "Turin criteria", were published in 2007. According to them, PDTC is characterised by: 1) the presence of solid/trabecular/insular pattern of growth; 2) the absence of the conventional nuclear features of papillary carcinoma; 3) the presence of at least one of the following microscopic features: convoluted nuclei; mitotic activity $\geq 3 \times$ $\times$ 10HPF; or tumour necrosis [28].

Diagnosis of poorly differentiated thyroid carcinoma should be considered an unfavourable prognostic factor for patients with thyroid carcinoma. The histopathological type of TC is an important parameter among accepted prognosis factors associated to a more aggressive clinical course in TC [29]. Doubtless, PDTC presents as a separate type in the WHO Classification of Thyroid Carcinoma; therefore, prognostic factors specific only to PDTC are still to be determined [27, 30]. A neoplasm with an intermediate morphological and biological behaviour between WDTCs and UDTC may be the result of a disturbed cell maturation process. Thus, it is possible to appreciate for PDTC the unfavourable prognosis factors known for WDTC.

Male gender is still a controversial prognostic factor, but poorer prognosis in male patients with WDTC than in female patients with the same condition predominates [29]. Since the first studies regarding PDTC, less significant female predominance has been noted in comparison to WDTCs. Women are only twice as likely to be diagnosed with PDTC as men [3, 4, 31–33]. It often occurs in older groups of patients, which may have an impact on prognosis. An age of 45 years or over is known to be an unfavourable prognosis factor both for WDTCs and PDTCs [29, 31–33]. In our study, less than two thirds of patients with PDTC were of female gender, with significant predominance of patients aged over 45 years (92.9%). Three patients, who died, were all older than 45 years (mean age 62 years) and two of them died of TC.

Volante et al. analyzed a group of 183 PDTCs with predominant *trabecular-insular-solid* growth patterns and demonstrated that the presence of distant metastases and some histopathological features, e.g. necrosis or mitotic index > 3 per 10 HPF, were statistically significant parameters associated with low 5-year survival rate, apart from age not less than 45 years [31]. Lai et al. reported similar results of a clinical analysis of a group composed of 9 of their own patients with insular carcinoma and 73 others described in other English literature reports, but without histopathological analysis [32]. The insular type of PDTC is clearly predominant, the majority of data being related to that sub-group. It is acceptable that *solid/trabecular* PDTC may come under the same diagnosis.

Consecutive studies have reported subsequent prognostic indicators associated with unfavourable outcome of PDTC, such as high TNM stage, extrathyroidal extension or infiltration of the trachea, and no post-operative $^{131}$I treatment with more than 30 mCi [33, 34]. Three patients in the study group showed intra-surgical advanced local invasion with infiltration of the trachea, and one of them died of TC after 30 months, a second one stopped follow-up after 56 months, and a third one is still being observed a little over one year later. In one patient from our group, despite satisfactory surgical management, radioiodine therapy was administered as late as almost two years after thyroidectomy.

Twelve patients in our study (85.8%) were administered with $^{131}$I therapy. Various data show that PDTCs

display the ability to uptake radioiodine in up to 80–85% of cases [3, 10]. In the literature, administration of $^{131}$I appears to be a substantially beneficial therapy if the tumour shows good radioavidity [31, 33–35]. The effects of radioiodine therapy observed in patients with insular carcinoma were more satisfactory than in patients with predominant solid or trabecular growth patterns of PDTC [35]. However, the majority of studies in the literature do not confirm the efficacy of $^{131}$I therapy to prolong 5-year survival, regardless of $^{131}$I dose or histological variant of PDTC [31–33, 35]. Thus, complementary $^{131}$I therapy ought to be considered in every patient with PDTC individually although several authors recommend it in all patients with $^{131}$I uptake [5, 18].

Seven patients (50%) in our group were treated with external radiotherapy — one with palliative radiotherapy on the neck and mediastinum as the only element of management with short survival time (7.1%). The remaining six patients (42.9%), all pT4 and/or N1, were qualified for postoperative external beam radiotherapy to the neck and mediastinum areas. In this sub-group four patients underwent not-radical surgery treatment. One of them (1/6; 16.7%) died of thyroid carcinoma after 30 months, two patients (2/6; 33.3%) have been under observation for over 5 years, and one of them presented distant metastases to the lung in the sixth year of follow-up.

External beam radiotherapy is an open question in PDTC. Individual qualification is recommended as no improvement in PDTC 5-year survival has been documented, although it was administrated significantly more frequently than in patients with WDTCs [18, 19, 32, 33]. Sanders Jr. et al. analyzed the efficacy of external radiotherapy at high risk of recurrence and recommended external beam treatment for PDTC to be considered in $T_3$ tumours without distant metastases, in all T4 tumours, and in cases of regional lymph node involvement, regardless of T [5]. He went on to say that if surgery is thought to be complete, $^{131}$I treatment should be given first, before radiotherapy, and if surgery was not radical he suggested radiotherapy postoperatively.

Most of data regarding the use of chemotherapy in thyroid cancer are based on studies performed for ATC [3]. Chemotherapy in patients with PDTCs ought to be considered individually. The available studies are usually short and concern inoperable PDTCs [3]. The administration of methotrexate, vinblastine, doxorubicin, and bleomycin in monotherapy has been proposed [3, 18, 19]. Combination therapy composed of chemotherapy and external radiotherapy at the same time is considered as an experimental treatment [18, 19]. Molecular guided therapy is the only element of controlled clinical studies [19].

One patient in our study (7.1%) with distant metastases to the lung was referred for chemotherapy. He was treated with doxorubicin and cisplatin and obtained incomplete remission.

## Conclusions

Poorly differentiated thyroid carcinoma is still a challenge both for pathologists and clinicians. Infrequent prevalence, more aggressive course, and poorer prognosis constitute major problems for clinicians.

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