An evidence-based review of poorly differentiated thyroid cancer

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Abstract

Background   Poorly differentiated thyroid cancer (PDTC) presents the endocrinologist and surgeon with challenges of recognition and treatment given the lack of consensus on histopathologic definition and limited literature on surgical and nonsurgical treatment.

Methods   We offer an operational pathologic definition for PDTC, which should help guide future work in this area. Poorly differentiated thyroid cancer should include insular and trabecular variants but should not include solid type lesions (included by other workers) or more differentiated tumors that may have poor prognosis such as tall cell, columnar, diffuse sclerosing, and oncocytic lesions. Systematic evidence-based literature reviews focusing on two questions were carried out: (1) is PDTC associated with an intermediate prognosis relative to anaplastic and WDTC? and (2) What are the postoperative treatment options for poorly differentiated thyroid cancer?

Conclusions   We have found level IV evidence that PDTC is intermediate between WDTC and anaplastic cancers in terms of prognosis. It represents a disease where appropriate administration of aggressive treatment not typically necessary for routine WDTC and not effective for anaplastic disease may uniquely result in substantial benefit. Limited level IV data show conflicting results regarding ^{131}I treatment benefit. Given lack of morbidity and potential for benefit, we recommend that ^{131}I therapy be considered in all patients postoperatively. Recommendation regarding external beam radiotherapy (XRT) is based primarily on extrapolation from studies in forms of poor-prognosis WDTC where substantial data exist regarding treatment benefit. We recommend that external beam treatment be considered in all patients with PDTC with T3 tumors without distant metastasis, all patients with T4 tumors, and all patients with regional lymph node involvement.

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Poorly differentiated thyroid cancer (PDTC) is a rare and variously defined diagnosis which is felt to carry a poorer prognosis than well differentiated thyroid cancers (WDTC). Poorly differentiated thyroid cancer presents the surgeon and endocrinologist with challenges in its recognition and in the consideration of aggressive treatment options. There is no consensus on the histopathologic definition of PDTC. Some series include variants of WDTC that also tend to have a poor prognosis, such as tall cell, columnar, diffuse sclerosing, and oncocytic lesions. Some subset of patients with PDTC may be misdiagnosed with undifferentiated tumors. If only insular, trabecular, and solid variants of PDTC are included, 2%–3% of thyroid cancer patients in North America (but up to 15% of thyroid

cancer patients in Northern Italy) are affected. Poorly differentiated thyroid cancer is thought to be an intermediate follicular-derived tumor with a prognosis that falls somewhere between that of WDTC and that of anaplastic thyroid cancer. Because PDTC has a higher rate of local invasion than most WDTC at presentation, preoperative evaluation of vocal cord function is extremely important, allowing for optimal surgical planning and the best chance for complete resection of all gross disease, which in turn has substantial favorable prognostic implications.

There is limited literature on postsurgical treatment options of PDTC. Most of the current literature is retrospective with very small patient numbers. We have provided an evidence-based review both to evaluate prognosis in PDTC and to investigate the optimal treatment modalities. We considered two important questions: Does PDTC have an intermediate behavior between well differentiated and anaplastic cancers? and What is the therapeutic benefit of external beam radiation, ^{131}I, and chemotherapy in patients with PDTC? To answer these two questions we must first define histologically PDTC.

Part I

Pathology of poorly differentiated thyroid carcinoma

The concept of an intermediate grade carcinoma between papillary/follicular and anaplastic makes sense if one compares thyroid tumors to cancers of other systems [1, 2]. However, for many years the recognition and definition of this group of neoplasms was not clear. Indeed, many pathologists diagnosed them under the rubric of follicular carcinomas. Others considered them a variety of anaplastic carcinoma and classified some as small-cell carcinomas.

Because of the confusion about the pathologic definition of this group of tumors, their treatment and prognosis remain unclear. This produces problems because no evidence-based decisions are possible without clear and uniform definitions.

In the middle 1980s two seminal papers appeared that began to address the problem in terms of the pathologic definitions of these tumors. In 1983 Sakamoto et al. published the Japanese experience and described an intermediate group of lesions in terms of prognosis [3]. However, their article and others from Japan [4, 5] included in the poorly differentiated carcinomas, lesions that are recognized as variants of papillary carcinoma: tall cell, diffuse sclerosing, columnar cell, and solid subtypes [6–8]. The classification also included Hurthle cell carcinomas under the poorly differentiated classification [4]. In 1984, Carcangiu et al. described a clinicopathologic study of a thyroid tumor they termed ''insular'' carcinoma, based on its his-

tologic growth pattern. They pointed out the aggressive clinical course of these lesions, which in their series of 25 cases showed a 60% 5-year mortality rate [9]. It should be noted that their series was a retrospective analysis, and many of the lesions were extrathyroidal and metastatic at diagnosis. Subsequent articles reported smaller numbers of cases and indicated that if such tumors were identified when still gland confined, the outlook was somewhat better. In a few series, the identification of this tumor by fine-needle aspiration biopsy suggested that early diagnosis was possible and the outlook with aggressive therapy could be better than the initial study reported [10]. Nevertheless, the mortality rate was still significantly higher than well-differentiated papillary and follicular carcinoma [11].

Many of the tumor types included in the Japanese classification scheme as poorly differentiated (including tall cell and diffuse sclerosing variants of papillary carcinoma and Hurthle cell carcinoma) are discussed in other articles in this issue. Here, we focus on the solid variant of papillary carcinoma, which most thyroid pathology experts do not consider a poorly differentiated tumor. We then describe recent work to define the group of poorly differentiated thyroid carcinoma pathologically. Such a definition is needed in order to begin the approach to studies of the clinical features, pathologic features, epidemiological aspects, and molecular biological correlates of these lesions and to place PDTC into a larger overall classification scheme of thyroid tumors of follicular cell derivation.

Solid variant papillary thyroid carcinoma

The solid variant of papillary disease has been best defined in studies of the thyroid cancers occurring in children living in the countries of the former Soviet Union affected by the Chernobyl nuclear accident [12, 13]. Pathologists studying these thyroid tumors found that about 30% showed a solid pattern of growth. Harach and Williams examined pediatric thyroid cancers from the United Kingdom and also found tumors with this histology in young children [14]. It appears that this type of lesion is a form of thyroid cancer that has a propensity to occur in childhood and that it may be related to radiation exposure and/or dietary iodine deficiency [6, 15]. These tumors are characterized by a nested pattern of growth with the nests separated by a delicate capillary network (Fig. 1). The nuclei are those of papillary carcinoma, although they may show a more crinkled nuclear membrane. The study of Nikiforov and Gnepp indicated that in the post-Chernobyl group these tumors were usually extrathyroidal with 42% showing vascular invasion [12].

Do these tumors occur in adults? The work of Nikiforov et al. published from the Mayo Clinic patient database indicates that they do [16]. In their study 20 patients among
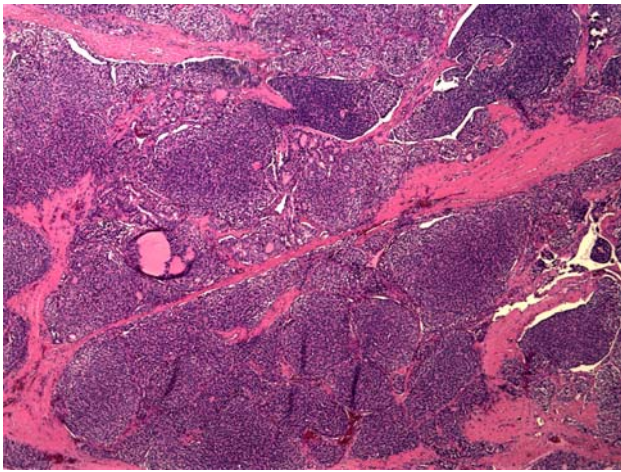
Fig. 1 Poorly differentiated thyroid cancer (PDTC)

almost 800 cases of papillary carcinoma were diagnosed with the solid variant. In this subset, there was a 10% mortality from this tumor as compared to 0% mortality in the classic papillary carcinoma group. However, a set of tumors classified as ''poorly differentiated'' based on tumor necrosis showed a greater than 50% tumor-related mortality rate. Nikiforov et al. concluded that solid variant papillary carcinoma behaves in much the same way as classic papillary cancer and should not be considered poorly differentiated. In the experience of one of the authors of the present paper (V.A.L.), solid variant papillary carcinoma in adults seems to arise most often against a background of severe chronic lymphocytic thyroiditis, and in patients with systemic autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis. The tumors seem to behave as usual papillary carcinomas (unpublished observations). As a corollary, in the experience of the post-Chernobyl thyroid cancers, very few children have died of thyroid cancer, and there does not appear to be excess mortality in those children with solid subtype [13].

The pathological definition of poorly differentiated thyroid carcinoma

In 2004, the entire annual meeting of the Endocrine Pathology Society was devoted to poorly differentiated thyroid carcinoma. The definitions were as varied as were the speakers (who were expert pathologists from different geographic areas of the world). It was concluded that although many experienced endocrine pathologists say that they ''know it when they see it,'' there was a need for a pathologic definition of poorly differentiated carcinoma of the thyroid. In 2006 in Turin Italy, a consensus conference was convened to that purpose. Pathologists with expertise

in thyroid cancer from all over the world participated, and a first attempt at establishing diagnostic criteria for this group of tumors was developed [17].

A search of the literature indicates that only a few articles on these tumors have been published, and they have been retrospective. Most have been published from Italy and northern alpine regions of central Europe, suggesting either genetic or environmental factors or both in the etiology of this disease. It is noteworthy that in the northern half of Italy about 15% of thyroid cancers are poorly differentiated whereas in North America the poorly differentiated form comprise only 2%–3% of thyroid malignancies [4, 18–23]. If these numbers are valid, and such lesions are uncommon in North Americans of Italian descent, then it appears that environmental factors may play a significant role in the genesis of these lesions (possibly related to dietary factors, including iodine).

The tumors have been described pathologically under terms such as insular, primordial cell, intermediate type, or just poorly differentiated [9, 18–25]. Grossly, such lesions are usually large (average 4–5 cm), may be partially encapsulated, and show foci of necrosis (see Fig. 1). In some cases, obvious vascular invasion involving large veins has been noted [11].

The Turin consensus has proposed a definition of PDTC: The lesions are of follicular cell origin (medullar carcinoma is not included in the group); they can produce thyroglobulin although by immunohistochemistry, the staining tends to be focal and weak [17]. The avidity of these tumors to take up and respond to radioactive iodine is unclear [24]. Pathologically, they are composed of nests, insulae, or trabeculae of tumor cells that appear primitive with scant cytoplasm and a high nuclear to cytoplasmic ratio (Fig. 2). Occasionally pleomorphic tumor cells may
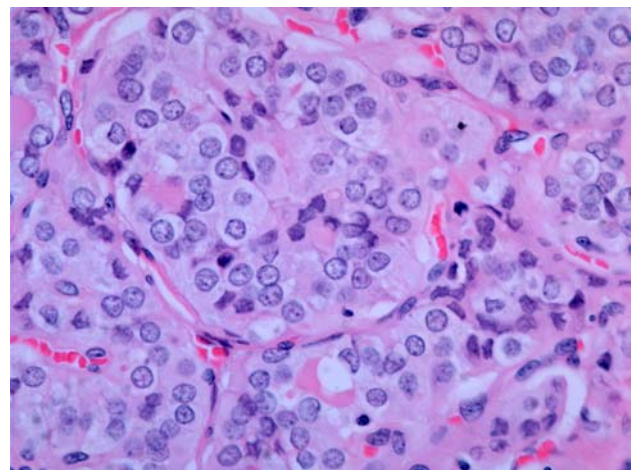

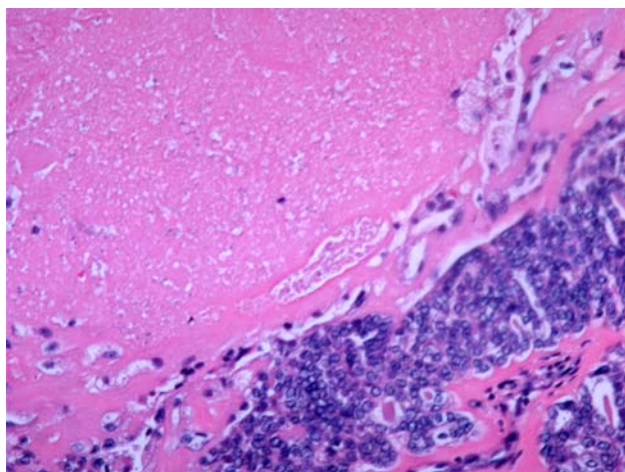Fig. 2 PDTC: Note high nuclear to cytoplasmic ratio

Fig. 3 PDTC: Note necrosis coagulation

be present, but these are usually randomly scattered within the tumor or comprise small clusters of cells. One important pathologic feature is the presence of tumor necrosis, which is not geographic or related to preoperative biopsy. It is what has been considered in other tumor systems as ''coagulative necrosis'' (Fig. 3). Mitotic activity including the presence of abnormal mitotic forms is easily identified. Lymphovascular invasion and obvious invasion of surrounding thyroid or extrathyroidal soft tissue is common [17].

The relationship of this group of tumors to differentiated thyroid carcinomas has also been studied. At least anecdotal cases of transformation from and/or association with a differentiated thyroid cancer, usually papillary, have been reported. The poorly differentiated carcinoma may occur in a recurrence of a previously treated well differentiated cancer (as is illustrated in the last edition of the Armed Forces Institute of Pathology (AFIP) fascicle, 7); or, at the time of diagnosis of the poorly differentiated lesion, parts of the tumor may show characteristic nuclear features and growth pattern of papillary carcinoma (more rarely follicular carcinoma).

On the opposite end of the spectrum, some cases of association of poorly differentiated lesions with undifferentiated or anaplastic carcinomas have been described [7, 26]. This form of the disease may occur as a poorly differentiated carcinoma, which in recurrence or metastasis undergoes anaplastic transformation, or the two characteristics may coexist at the time of initial diagnosis.

The molecular biological correlates of these tumors and their relationships to other follicular cell derived neoplasms is difficult to discern because of the definitional issues stated above. A few studies do seem to indicate that, at least for insular carcinoma, p53 mutations occur in up to 25% of lesions, suggesting a genetic middle ground between WDTC and the anaplastic form [26–30]. These fundamental molecular alterations and the interrelationships among the various tumors will, we hope, become clearer once studies of sets of tumors having the defined pathologic features are performed.

What are the clinical implications of the diagnosis of poorly differentiated thyroid carcinoma? Studies in this area are scanty and, again, confused because of difficulties in pathological definitions. The available data imply that certain pathologic features of PDTC are associated with a bad outlook—lack of encapsulation, extrathyroidal growth, necrosis, and excess mitotic activity [7, 17].

It is hoped that with acceptance of the proposed definition of PDTC, classic clinicopathologic and immunohistochemical studies can produce a morphological classification of this heterogeneous group of neoplasms that will be reproducible by practicing pathologists. Then studies to assess the molecular–morphologic correlates can be performed (and because these tumors are so unusual, multi-institutional studies may be needed), and prognostic and therapeutic implications can be identified that would be scientifically valid and evidence based.

Evidence-based analysis

Is poorly differentiated thyroid cancer associated with prognosis that is intermediate between anaplastic and well differentiated?

We performed an electronic search of the Medline database search from January 1983 until June 2006. Only articles published in English were used. No case reports or review articles were considered. We also limited our study to include only patients with nonanaplastic, insular, trabecular, and solid variants. Excluded from our search were patients with including anaplastic, tall cell, columnar, diffuse sclerosing, or oncocytic variants. We then performed a focused review attempting to determine whether patients with PDTC have a significantly different prognosis than patients with well-differentiated or anaplastic thyroid carcinoma. For this question, we further focused only on studies that included survival as the primary outcome measure (see Table 1).

The level of evidence for each publication was ranked according to the classification of Sackett et al. [31] Level I evidence includes large randomized trials. Level II evidence includes small randomized trials with moderate to high risk of errors. Level III evidence includes nonrandomized trials with contemporaneous controls. Level IV is a retrospective or cohort study. Level V includes expert opinion or case series without controls.

Only four studies met the inclusion/exclusion criteria as described above. All were retrospective in nature, and none

Table 1 PDTC: Prognostic studies

Reference	Volante et al. [22]	Wreesman et al. [32]	Luna-Ortiz et al. [33]	Sakamoto et al. [3]
Level (design)	IV (case series)	IV (case series)	IV (case series)	IV (case series)
Total no. patients	357	42	84	258
No. of PDTC	183	12	13	35
No. of WDTC	139	15	71	186
No. of ATC	35	9	0	25
OUTCOMES				
Survival measure	Overall survival, univariate analysis	5-year disease-free survival; 5-year cause- specific survival; overall survival	3-year survival	5-year survival; 10-year survival; 15-year survival
Survival	PDTC: 85% 5-year; 67% 10-year	PDTC 70% 5-year;WDTC 100% 5-year; ATC 0% 5-year	ITC: 62% 3-year WDTC 91% 3-year	5-year. 10-year 15-year % ATC: 0, 0, 0 % PDTC: 65, 34, 0 % WDTC: 95, 86, 81
p Value, survival	< 0.0001, PDTC vs WDTC, ATC	Not reported	< 0.05	< 0.01, PDTC vs WDTC
Conclusion, survival	PDTC has a mortality rate intermediate between WDTC and ATC	PDTC carries an intermediary prognosis between WDTC and ATC	PDTC survival rate worse than WDTC	PDTC survival rate worse than WDTC
Secondary outcome measures	Multivariate analysis of potential prognosticators on survival	WDTC, PDTC, ATC Extrathyroidal: 33%, 73%, 100% Tumor > 4 cm: 13%, 73%, 69% +Lymph nodes: 47%, 64%, 100% Distant metastases: 0%, 50%, 87%	Metastases: ITC = 53.8% WDTC = 5.3%	None reported
p Value, secondary measures	Age < 0.007; necrosis < 0.0001; mitosis < 0.01	Extrathyroidal Tumor: < 0.0001 Lymph node metastases: < 0.0007 Distant metastases: < 0.001	Metastasis p = 0.001	None reported
Conclusion, secondary measures	Three different prognostic categories, patient age (≥ 45), the presence of necrosis, and mitotic count, are of independent value	PDTC has an intermediate chance of having extrathyroidal extension, tumor > 4 cm, positive lymph nodes, and distant metastasis when compared to WDTC and anaplastic	ITC has higher level of metastases and mortality than WDTC	None reported
Follow-up time	2–30 years	43 months	2–144 months	15 years
STUDY DESIGN				
Database	2,900 patients with malignant thyroid tumors who underwent surgery from 1960 to 2002 from the Department of Pathology of the University of Turin and of the Mauriziana Hospital	All patients treated at Memorial Sloan- Kettering Cancer Center, New York, between 1940 and 1999	Patient treated at Nacional de Cancerplogia, Mexico, from 1986 to 2002	Cancer Institute Hospital, Tokyo 1965–1980
Inclusion criteria	The presence of either focal (10%–40%), extensive, or predominant PDTC, including oxyphilic variants	Patients in database treated for PDTC and ATC between 1940 and 1999 at Memorial Sloan-Kettering Cancer Center, New York	Patient in database with diagnosis of ITC and control group	Only patients treated from the onset of their illness at the cancer institute

Table 1 continued

Reference	Volante et al. [22]	Wreesman et al. [32]	Luna-Ortiz et al. [33]	Sakamoto et al. [3]
Exclusion criteria	Medullary thyroid cancer; anaplastic focus	If specimen contained less than 70% of PDTC or anaplastic or nonfollicular-derived thyroid cancers	All pathology slides in which immuno- histochemical studies were positive for calcitonin, chromogranin, and CEA	Recurrent cases treated before 1964
Age	Mean age 56.3 years	PDTC were over 45 years; 1 anaplastic < 45 years; 4 WDTC < 45 years	27–74 years	Mean 55.2
Interventions	Surgery ± ^{131}I	Not specified	^{131}I (12); external beam (1); surgery (5)	Lobectomy; subtotal or total thyroidectomy
Treatment	^{131}I between 3,700 and 7,400 megabecquerels after total thyroidectomy in 83% of patients for whom postsurgical treatment information was available	Not discussed	Not discussed	Not discussed

ATC anaplastic thyroid carcinoma; *CEA* carcinoembryonic antigen; *ITC* insular thyroid cancer; *PDTC* poorly differentiated thyroid carcinoma; *WDTC* well differentiated thyroid carcinoma

were case-controlled studies. One study from the University of Turin, Italy, by Volante et al., reviewed 183 patients with focal or predominant PDTC. The investigators found that PDTC overall followed a more aggressive course compared with WDTC, irrespective of whether PDTC was focally or diffusely present (overall survival, $p < 0.0001$) [22]. It also noted that age (over 45), the presence of necrosis, and a mitotic count greater than 3 per high-power field were also associated with a poorer outcome. The drawback of this study, other than being retrospective, was that it included oxyphilic (Hurthle cell) variants as part of the group of poorly differentiated thyroid cancers.

Wreesmann et al. reviewed all patients treated at the Memorial Sloan-Kettering Cancer Center for poorly differentiated thyroid cancer and anaplastic thyroid cancer between 1940 and 1999 [32]. Cases of WDTC were randomly selected from a search of the pathology department. These investigators performed comparative genomic hybridization analysis. This analysis suggests a sequential accumulation of chromosomal abnormalities progressing from well differentiated thyroid cancer to anaplastic thyroid cancer. They also showed increasing rates of extrathyroidal extension ($p < 0.0001$), tumor size ($p < 0.0001$), lymph node metastasis ($p < 0.0007$), distant metastasis ($p < 0.0001$) as one progressed from well differentiated, to poorly differentiated, to anaplastic cancer. The 5-year disease-free interval ($p < 0.0001$), 5-year cause-specific survival ($p < 0.0001$), and overall survival ($p < 0.0001$) were best for WDTC intermediate for PDTC and worse for anaplastic.

Luna-Ortiz et al. from Mexico studied 13 patients with PDTC and compared to patients with WDTC [33]. They concluded insular thyroid carcinoma, which overlapped well with our definition of PDTC, is more aggressive than WDTC. The average follow up time was 44.7 months. The outcome measures which show statistical difference include survival ($p < 0.05$), and presence of metastasis ($p < 0.05$). There was no statistical difference in tumor size ($p > 0.05$).

Sakamoto et al. from Tokyo from 1983 studied 258 WDTC and anaplastic patients and compared them to 35 patients with PDTC [3]. They found differences in survival among WDTC, PDTC, and anaplastic carcinoma which were statistically significant ($p < 0.01$). As mentioned earlier in this paper the definition of poorly differentiated thyroid cancer included scirrhous and other subtypes which we feel would be best not to include within the PDTC rubric.

Due to the rarity of PDTC, no randomized control trials are available in the literature. The evidence thus far present in the literature is level IV evidence and indicates that PDTC has a prognosis that falls between that of WDTC and anaplastic thyroid cancer. Three of four studies show statistically significant difference in prognosis with this cellular variant (versus WDTC or anaplastic), while the fourth shows a trend toward the same result. All of this evidence is retrospective [3, 22, 32, 33], with variable small sample sizes. Because of the relative infrequency of this disease, it would be very difficult to perform a prospective comparative study with standardized treatment regimens. The largest retrospective study, for example, took 42 years at one institution in order to accumulate 183 cases of PDTC. Given that high-level randomized controlled trials are unlikely, these retrospective data may re-

main the highest level of evidence regarding this specific clinical question in the years to come (Table 1).

Part II

External beam radiation therapy

There has been little published on the role of XRT in PDTC; most reports are on differentiated thyroid cancer or anaplastic disease. There is increasing evidence that patients with differentiated thyroid cancer who are at high risk of local or regional recurrence can benefit from external beam radiotherapy [34]. Extrathyroidal extension is a poor prognostic factor in differentiated thyroid cancer, especially among patients older than 45 years. Radioactive iodine is less likely to reduce the risk of recurrence in these patients than in younger patients or those with nodal disease [35]. Therefore lessons learned from patients with poorer prognosis differentiated thyroid cancer can probably be applied to those with PDTC, which we know responds poorly to radioactive iodine and is more likely to have more extensive extrathyroid extension compared to papillary or follicular cancers of similar size in patients of similar age [36]. In one study at the Princess Margaret Hospital (PMH), patients who underwent external radiation therapy for microscopic residual disease after surgery for papillary thyroid cancer had a better 10-year actuarial local control rate than those who did not (93% versus 78%; $p = 0.01$) [38]. A follow-up to this review found a higher 10-year cause-specific mortality (81% versus 65%), and local-regional relapse-free rate (86% versus 66%) among patients over age 60 with extrathyroidal extension but no gross residual disease who were treated with external beam radiation. Many investigators have reached similar conclusions in retrospective reviews on the role of external beam radiotherapy in differentiated thyroid cancer [38–43]. In many of these studies not all patients were at high risk of recurrence in the thyroid bed or had what would be considered now to be conventional treatment with total thyroidectomy and radioiodine in addition to external radiotherapy. In a study from Germany of 137 patients over 40 years of age with extrathyroidal extension, all of whom had total thyroidectomy and radioiodine, 85 patients received radiotherapy (50–60 Gy) to the thyroid bed and cervical and upper mediastinal lymph nodes. The patients in the radiotherapy group had fewer local and regional recurrences ($p = 0.004$) [44].

Patients with WDTC older than 45 years with extensive extrathyroid extension (T4a or T4b lesions) and grossly complete resection and patients with WDTC with postoperative gross residual disease are at high risk of local recurrence and may benefit from adjuvant external radia-tion therapy after surgery and radioiodine treatment. It therefore follows that patients with PDTC who are at high risk of local regional recurrence, especially if they have extrathyroid extension and are less likely to take up RAI will benefit from XRT in addition to surgery [37, 45]. Although differentiated thyroid cancer patients with minimal extrathyroid extension (now defined as AJCC/UICC T3 disease) probably do not benefit from XRT, this therapy should probably be considered in patients with poorly differentiated T3 carcinoma. Similarly, in WDTC, lymph node involvement is not in itself an indication for XRT because regional control is usually achieved with initial neck dissection in combination with postoperative radioiodine. It may be of value in PDTC, however, especially in patients who have extracapsular extension of their lymph node disease or extensive lymph node involvement.

It is necessary to consider distant metastases in deciding whether to use XRT to the neck for PDTC. Given that PDTC distant metastases are much less likely to respond to radioactive iodine as compared to those from differentiated thyroid cancer, there is probably no advantage to adjuvant XRT to the neck in PDTC in patients with distant metastasis. In the presence of distant metastases the role of XRT is limited to palliation of metastases or uncontrolled disease in the neck.

Patients with grossly palpable disease after surgery for differentiated thyroid cancer benefit from XRT. In a series of 126 patients, those that had external beam radiotherapy (69 patients) had a significantly better local regional control than those that did not (56% local regional control at 10 years with external radiation versus 24% without; $p = 0.002$ [38]. Other authors have reported disease control rates of 30%–65% [37, 46, 47]. Therefore patients with unresectable PDTC should have external beam radiotherapy to prevent uncontrolled disease in the neck.

The U-shaped volume of the thyroid bed presents a challenge for adequately treating the volume at risk of recurrence while sparing the spinal cord. Prior to the era of intensity modulated radiotherapy (IMRT) many techniques were described to overcome these difficulties, but all required some degree of compromise [48]. Intensity modulated radiotherapy, however is undoubtedly the best technique in terms of adequate planning target volume (PTV) coverage and minimizing dose to spinal cord [49, 50].

Well-planned XRT produces acceptable levels of acute toxicity, rarely produces serious complications, and does not preclude future surgical intervention, although it may make surgery more difficult. During the course of radiation therapy, moderate skin erythema develops, with higher doses causing dry or, rarely, moist desquamation. Mucositis of the esophagus, trachea, and larynx can occur toward

Table 2 Postoperative and nonsurgical treatment options for PDTC

Reference	Lai et al. [53]	Auersperg et al. [51]	Justin et al. [52]
Level (design)	IV	III	IV
Total no. of PDTC patients	82	34	5
No. of patients in radiation protocol	14	27	
No. of patients in ^{131}I protocol	23	0	4
No. of patients in chemotherapy protocol	Not mentioned	30	0
Intervention	^{131}I ± XRT	Chemotherapy ± XRT ± surgery	^{131}I
OUTCOMES			
Survival measure	5-year and 10-year	Overall survival	Not reported
Survival	5-year was 72.2%; 10- year was 52%	24.5% died during study: 6 of tumor; 1 of secondary tumor; 1 of hepatitis	Not specified
p Value, survival	Gender (p = 0.287); tumor size (p = 0.0689); extrathyroidal invasion (p = 0.996); lymph node metastasis (p = 0.699); age over 45 years (p = 0004); distant metastasis (p < 0.0001)	Not performed	Not performed
Additional outcome measures	^{131}I treatment survival; ^{131}I with or without external beam radiation survival	56% had no evidence of disease 11 ± 72 months after treatment 50% of inoperable tumors became operable	80% (n = 4/5) showed postoperative ^{131}I localization; 20% (n = 1/5) not studied
p Value, additional measures	^{131}I treatment (p = 0.9789); ^{131}I with or without external beam radiation (p = 0.2172)	Not performed	Not performed
Conclusion	Although often used after operative treatment, the efficacy of ^{131}I is not yet established	Chemotherapy and XRT can cause up to a 50% response for regression of tumor	^{131}I localization and treatment should be offered to all patients with insular cancer
Follow-up time	1–468 months	11 ± 72 months	7–38 months
STUDY DESIGN			
Database	Medline search (1984–2005) and Taipei Veterans General Hospital (1991–2005)	The Institute of Oncology Ljubljano, Yugoslavia 1983–1989	Patients with slides previously diagnosed as anaplastic or insular at the University of Iowa College of Medicine 1968–1988
Inclusion criteria	Insular thyroid cancer	Patients with inoperable PDTC	Insular after re-evaluation by pathologist
Exclusion criteria		WDTC & operable tumors on presentation	Anaplastic thyroid cancer
Age	Mean age 82 years	39–81 years	40–75 years
Surgical intervention	72 total thyroidectomize; 4 lobectomies	Patients were operated on only if response to treatment modality caused tumors to become operable. Total thyroidectomy ± RND	3 total thyroidectomy 1 with RND; 1 subtotal thyroidectomy 1 hemithyroidectomy

RND radical neck dissection; *WDTC* well differentiated thyroid carcinoma; *XRT* external beam radiation therapy

the end of the irradiation and may require a soft diet and use of analgesics. Esophageal or tracheal stenosis is extremely rare. Tsang and colleagues reported no Radiation Therapy Oncology Group (RTOG) grade IV toxic effects. Similarly Farahati and colleagues observed no irreversible late toxic effects among 99 patients given doses of 50–60 Gy in 1.8- to 2.0-Gy fractions to a large volume [37, 44].

Evidence-based analysis

What are the postoperative and nonsurgical treatment options for poorly differentiated thyroid cancer?

We performed an electronic search of the Medline database search from January 1983 until June 2006. Only articles published in English were used. No case reports or review articles were included. We also limited our study only to include patients with only nonanaplastic, insular, trabecular, and solid variants. Excluded from our PDTC search were anaplastic, tall cell, columnar, diffuse sclerosing, or oncocytic variants. We sought to decide what postoperative and nonsurgical treatment options were optimal for patients with PDTC. For this question, we focused on studies that (1) had intervention with XRT, radioactive iodine (RAI), and/or chemotherapy and (2) outcomes measured in terms of survival or clinical response to any treatment (see Table 2). Only three studies met the inclusion/exclusion criteria as described above. Two were retrospective in nature, and one was prospective but not case-controlled.

Auersperg et al. reported from Osaka University Medical School in Japan on a series of patients with either anaplastic or poorly differentiated thyroid cancer [51]. From 1983 to 1989 only 34 patients with inoperable poorly differentiated thyroid cancer were given chemotherapy. The agents used were a combination of methotrexate, adriamycin, bleomycin, and vinblastine. Patients were given further more aggressive treatment if the tumor responded. External beam radiation was offered if the chemotherapy response was poor (in an attempt to render the patients suitable for surgery) or postoperatively if surgery was performed. The investigators found that anaplastic tumors rarely if ever responded to chemoradiation. The poorly differentiated group had a 56% response to the chemo-rads protocol with some not requiring surgery.

Justin et al. at the University of Iowa College of Medicine reviewed 35 histology cases of anaplastic or PDTC between 1968 and 1988 [52]. Chart review was performed of each patient to determine overall survival and treatment regimen. He found that 80% of insular variants had uptake of ^{131}I. This study did not include survival analysis.

Lai et al. from Taipei veterans General Hospital in Taiwan reviewed all patients from 1991 to 2005 with insular thyroid cancer [53]. They found 9 patients out of a total of 1,042. They then did a Medline search from 1984 to 2005 using English literature only. Cases with individualized description of treatment and follow-up were added to the review. They combined this search with their previous 9 patients for analysis, making a total of 82 cases. The mean follow-up time was 84.5 months, with 26 men and 56 women. The rate of lymph node metastasis was 49%, and distant metastasis was 57.5%. Disease-specific death rate was 37.8%. The 5-year and 10-year survival rates for insular cancer were 72.2% and 52%, respectively. The review found that use of ^{131}I and XRT did not prolong survival ($p = 0.9789$ and 0.2172, respectively) (Table 2).

Conclusions

We focused discussion and evidence-based analysis on two topics we thought were important in understanding patients with PDTC:

(1) What is the pathologic definition of PDTC and is it in fact a disease intermediate between WDTC and anaplastic cancer prognostically?
(2) What evidence exists regarding nonsurgical and postsurgical treatments for PDTC ?

We have offered an operational pathologic definition for PDTC, which should help guide future work in this area. There must be consensus regarding this histologic definition in PDTC, which we think should not include more differentiated tumors, which may have poor prognosis, such as tall cell, columnar, diffuse sclerosing, and oncocytic lesions, and solid type tumors. To have common agreement on the pathology is obviously an essential first step in continued work in this area.

For PDTC, etiological factors have yet to be elucidated, but the very high incidence in areas of Northern Italy implies a role for environmental factors and invites further research of the disease in these populations. Furthermore, while a great deal of work remains to be done in the genetic profiling of PDTC, it appears that PDTC may represent a unique model of malignant genetic progression from WDTC to anaplastic cancer.

We have found level IV evidence that PDTC is in fact intermediate between WDTC and anaplastic cancers in terms of prognosis. This being established, we feel that PDTC offers a significant treatment opportunity for the surgeon, endocrinologist, and oncologist. With WDTC the vast majority of patients enjoy such favorable prognosis that studies looking at extent of surgical and nonsurgical (i.e., ^{131}I) treatment do not consistently show added benefit to more aggressive treatment. Thus, the majority of WDTC patients do well, regardless of the degree of treatment. At the other end of the prognostic spectrum, in patients with anaplastic cancer, treatment intensity is also dissociated from outcome, with little treatment effect and nearly universal poor outcome regardless of aggressiveness of treatment. Poorly differentiated thyroid carcinoma represents a condition that is therefore intermediate, where appropriate administration of aggressive treatment not typically necessary for routine WDTC may result in substantial treatment benefit. We believe that for PDTC with appropriate

recognition and treatment, substantial improvements in outcome may be possible. Fine-needle aspiration cytology is generally useful in preoperative recognition of PDTC. In addition, we have shown that preoperative laryngoscopy is extremely useful in identifying extrathyroidal cancer, which is present in up to three fourths of PDTC patients [54]. Preoperative knowledge of extrathyroidal disease in patients with PDTC allows appropriate planning for extended thyroidectomy involving the airway and for preserving function of the remaining recurrent laryngeal nerve with intraoperative neural monitoring.

When vocal cord paralysis is recognized preoperatively, a presumptive diagnosis of invasive disease is made, and the surgeon then is empowered to consider several important issues. First, a more detailed regional and distant radiographic work-up including cervical ultrasonography, fine-cut neck computed tomography (CT), and chest imaging may be considered. Second, at the beginning of the thyroidectomy procedure, the surgeon may include endoscopy of the trachea and esophagus to assess for mucosal changes. The final issue raised by the diagnosis of preoperative vocal cord paralysis is that patient-specific operative planning can be carried out. It is of great value to be able to discuss issues such as tracheostomy and laryngotracheal resection and reconstruction with patients preoperatively. Without such detailed preoperative preparation, a patient may be unpleasantly surprised with a tracheostomy or a surgeon, unprepared for invasive disease, may feel pressured into rendering insufficient shave excision, leaving gross disease within the aerodigestive tract in a patient who has been insufficiently informed and concented. Studies of invasive WDTC show that completeness of resection is associated with substantial prognostic improvement in patients with WDTC and extrathyroidal disease [55].

We appreciate that control of invasive disease of the central neck is an important goal. McConahey and Tollefson have show that 36%–47 % of deaths from papillary cancers are due to uncontrolled invasive disease in the central neck base [56, 57].

Very limited information is available regarding nonsurgical treatment of PDTC. Given its rarity, controlled studies will not be forthcoming. Regarding ^{131}I, limited level IV data show conflicting results, with one study indicating a high percentage of PDTC patients with ^{131}I uptake but another study showing limited if any treatment benefit. Given the potential for ^{131}I uptake and the lack of morbidity we recommend ^{131}I to be considered in all patients with PDTC after complete surgery.

Evidence is also lacking regarding postoperative XRT treatment for PDTC. Recommendation is based primarily on extrapolation from radiation studies on forms of poor prognosis WDTC where substantial data show treatment

benefit. On this basis, for patients with PDTC, we recommend that external beam treatment be considered in T3 tumors without distant metastasis, in all T4 tumors, and in cases of regional lymph node involvement. If surgery is thought to be complete (i.e., no gross disease present in the neck postoperatively), ^{131}I should be given first. If surgery was incomplete (i.e., gross disease present in the neck postoperatively), we think it best to move forward with XRT postoperatively.

Interestingly there is level III evidence with short follow-up that in patients with inoperable PDC an intense chemotherapy regimen including methotrexate, vinblastine, adriamycin, and bleomycin with or without external beam radiation was associated with substantial treatment response, rendering some patients free of disease and others with operable disease.

Additional studies clearly are needed to investigate the long-term benefit in inoperable PDTC and whether such treatment may be applicable preoperatively in operable PDTC.

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