Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review

B Jarząb, D Handkiewicz-Junak and J Włoch¹

Department of Nuclear Medicine and Endocrine Oncology and ¹Clinic of Oncological Surgery, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Wybrzeże Armii Krajowej 14, 44-100 Gliwice, Poland

(Requests for offprints should be addressed to B Jarząb; Email: bjarzab@io.gliwice.pl)

Abstract

Well under 15% of differentiated thyroid carcinoma (DTC) is diagnosed at ≤ 18 years of age. The population is heterogenous and the differences between prepubertal children and pubertals and adolescents are to be considered. Although very little has been reported on children with sporadic DTC under the age of 10 years, juvenile DTC has at least some undeniable differences with adult DTC: (1) larger primary tumor at diagnosis; (2) metastatic pattern and features, namely: (a) greater prevalence of neck lymph node and distant metastases at diagnosis, (b) lungs almost the sole distant metastatic site, (c) pulmonary metastases nearly always functional; (3) closer-to-normal and more frequent sodium-iodide symporter (NIS) expression; and (4) higher recurrence rate but longer overall survival. These differences are especially distinct in prepubertal children. The goals of primary treatment of juvenile DTC are to eradicate disease and extend not only overall, but recurrence-free survival (RFS). Extending RFS is itself a desirable goal in children because it improves quality-of-life, alleviates anxiety during psychologically formative years, reduces medical resource consumption, and may increase overall survival. Primary treatment of DTC generally comprises a combination of surgery, radioiodine (^{131}I) ablation, and thyroid hormone therapy applied at varying levels of intensity. Therapeutic decision-making must rely on retrospective adult and/or pediatric outcome studies and on treatment guidelines formulated mostly for adults. Differences between juvenile and adult DTC and physiology dictate distinct treatment strategies for children. We, and many others, advocate a routine intensive approach because of the more advanced disease at diagnosis, propensity for recurrence, and greater radioiodine responsiveness in children, as well as published evidence of significant survival benefits, especially regarding RFS. This intensive approach consists of total thyroidectomy and central lymphadenectomy in all cases, completed by modified lateral lymphadenectomy when necessary and followed by radioiodine administration. However, absence of prospective studies and of universal proof of overall cause-specific survival benefits of this approach have led some to propose more conservative strategies. Most European centers give radioiodine ablation to the vast majority of juvenile DTC patients. Ablation seeks to destroy any residual cancer, including microfoci, as well as healthy thyroid remnant. Large studies have documented the procedure to decrease cause-specific death rates and, in children, to significantly lessen locoregional recurrence rates (by factors of 2–11) independent of the extent of surgery. There is universal agreement on treating inoperable functional metastases with large radioiodine activities. Treatment is especially effective in small tumor foci up to 1 cm in diameter, and should be administered every 6–12 months until complete response, loss of functionality, or attainment of cumulative activities between 18.5–37 GBq (500–1000 mCi). Radioiodine therapy is generally safe. Short-term side effects include nausea and vomiting (more frequent in children than in adults), transient neck pain and edema, sialadenitis (<5% incidence), mild myelosuppression (~25%), transient impairment of gonadal function both in females and males (sperm quality in boys), or nasolacrimal obstruction (~3%), with most cases generally being asymptomatic–moderate, self-limiting, or easily prevented or treated. If pregnancy is ruled out before each ^{131}I administration, and conception avoided in the year afterward, radioiodine therapy

appears not to impair fertility. However, therapeutic ^{131}I carries a small but definite increase in cancer risk, particularly in the salivary glands, colon, rectum, soft tissue and bone. To better guide primary treatment, different therapeutic combinations should be prospectively compared using RFS as the primary endpoint. Efforts also should be made to identify molecular signatures predicting recurrence, metastasis and mortality.

Endocrine-Related Cancer (2005) **12** 773–803

Introduction

This review evaluates the role of ^{131}I -iodine (^{131}I) therapy of differentiated thyroid cancer (DTC), i.e., papillary or follicular thyroid cancers, in children, defined as patients ≤ 18 years old. Unless noted otherwise, the adjectives ‘juvenile’ or ‘pediatric’ refer to prepubertal, pubertal and adolescent patients collectively. Simultaneously, it should be borne in mind that the clinical DTC course in prepubertal children shows distinct differences in comparison to pubertals and adolescents and these differences will be referred to whenever necessary. We use the term ‘therapy’ to comprise radioiodine ablation of healthy thyroid remnant, treatment of local or metastatic disease, or both. We begin by summarizing juvenile DTC epidemiology. Next, we evaluate the characteristics and natural history of this entity, highlighting putative differences with the adult disease, many of which, in our opinion, dictate a distinct treatment strategy for children, especially those ≤ 10 or 15 years old. We then look at primary treatment outcomes and strategies, emphasizing differences between conservative and intensive approaches, in an effort to place the role of radioiodine ablation in context. A discussion of radioiodine treatment of metastatic disease follows, after which we focus on specific radioiodine therapy-related issues, namely safety, thyroid-stimulating hormone (TSH) stimulation, dosimetric considerations, ‘stunning,’ and low-iodine diets. We close by summarizing future directions and the current status of radioiodine therapy.

Epidemiology of juvenile DTC

Juvenile thyroid cancer is rare, with well under 15% of DTC cases diagnosed at age ≤ 18 years. However, it does account for $\sim 10\%$ of malignant tumors and $\sim 35\%$ of carcinomas in children (Bernstein & Gurney 1999). In the US, ~ 350 people age < 20 years are diagnosed with thyroid carcinoma each year (Bernstein & Gurney 1999). In Europe, annual numbers of new sporadic pediatric cases are less well characterized (Storm & Plesko 2001).

DTC comprises 90–95% of all childhood thyroid cancers (Harach & Williams 1995, Hassoun *et al.* 1997, Bernstein & Gurney 1999, Yusuf *et al.* 2003). Medullary thyroid cancer is diagnosed in 5–8%, however, with more thorough screening, higher incidences have been registered (Harach & Williams 1995). Undifferentiated tumors, i.e., insular and anaplastic cancer, are extremely rare (Hassoun *et al.* 1997).

Thyroid carcinoma occurrence is negligible in very young children, although the literature contains isolated clinical cases in 4–6-month-old infants or even neonates (Harness *et al.* 1992, Newman *et al.* 1998, Schlumberger *et al.* 2004a). Age-specific incidence rates diverge for males and females starting at age 10 years, and increase substantially for females from age 13–14 years (Harach & Williams 1995, Bernstein & Gurney 1999) (Fig. 1). Although the very low thyroid cancer incidence in children precludes a definitive evaluation, most authors agree that from 1975 to 1995, incidence rates in the < 20 -year-old population remained rather stable in the US, Great Britain and Germany (Harach & Williams 1995, Bernstein & Gurney 1999, Farahati *et al.* 2004), though not completely without fluctuation (Niedziela *et al.* 2004, Leenhardt *et al.* 2004).

However, over the past ~ 60 years, pediatric thyroid cancer incidence has had two distinct peaks. The first, in the mid-20th century, was due to use of irradiation to treat benign childhood conditions including tinea capitis, acne, chronic tonsillitis and thymus

Figure 1 Differentiated thyroid cancer in 235 patients diagnosed when ≤ 18 years of age at the Maria Skłodowska Memorial Cancer Center and Institute of Oncology, Gliwice Branch, between 1973 and 2002. Distribution by age at diagnosis and sex.

enlargement (Ron *et al.* 1995, Lubin *et al.* 2004). In these cases, thyroid cancer onset was delayed an average 10–20 years, and elevated risk persisted up to 40 years post-exposure. When the causal relationship between external neck irradiation and thyroid cancer became evident and such therapy was abandoned in benign conditions, thyroid cancer incidence rates decreased (Harness *et al.* 1992). This experience led to recognition of ionizing radiation exposure as the best-established risk factor for DTC (Catelino *et al.* 2004). For obvious reasons, external irradiation of childhood tumors continues contributing to thyroid cancer risk in survivors of other malignancies (Blatt *et al.* 1992, Black *et al.* 1998, De Vathaire *et al.* 1999, Acharya *et al.* 2003, Gow *et al.* 2003).

The second peak in pediatric thyroid cancer incidence occurred in the early 1990's in some Eastern European countries. It stemmed from environmental contamination with radioactive iodine from the 1986 Chernobyl nuclear power plant catastrophe (Mahoney *et al.* 2004, Murbeth *et al.* 2004, Parfitt 2004). The peak started just 4–5 years after exposure, reaching its maximum in the mid-1990s, and the disease developed mainly in children <5 years old at exposure, with onset before age 14 years (Farahati *et al.* 1997, 2000, Tronko *et al.* 1999, Mahoney *et al.* 2004). The accelerated onset relative to external irradiation-induced disease (Ron *et al.* 1995) may be attributable to radiation dose rate differences and to endemic iodine deficiency in Eastern Europe (Mahoney *et al.* 2004). The Chernobyl experience confirmed the thyroid's markedly higher sensitivity to the effects of ionizing radiation during early childhood vs adulthood (Michel & Donckier 2002).

As may be inferred above, juvenile DTC may be classified as sporadic or radiation-induced. These two forms do not appear to have major clinical differences (Samaan *et al.* 1987, Viswanathan *et al.* 1994, Gow *et al.* 2003). Very frequent extra-thyroidal local invasion and distant metastases initially were believed to be peculiarities of Chernobyl-induced pediatric DTC. However, the majority of clinically evident Chernobyl-related tumors were diagnosed at ~10 years of age (Nikiforov & Gnepp 1994, Farahati *et al.* 1997, Tronko *et al.* 1999), an age at which these disease characteristics also occur very frequently in sporadic DTC (Harach & Williams 1995, Newman *et al.* 1998).

Characteristics and natural history of juvenile DTC

Putative unique features of childhood DTC provide important rationales for a separate treatment strategy

and for given therapeutic approaches in the pediatric population, particularly children <15 years old. Juvenile DTC appears to have up to six notable contrasts with adult DTC (Table 1).

First, even in recent years, mean papillary tumor volume at diagnosis has been much larger in patients <20 years old than in those age 20–50 years (Mazzaferri & Kloos 2001). Zimmerman *et al.* (1988) found that newly diagnosed papillary thyroid tumors were >4 cm in 36% of children vs 15% of adults, and <1 cm in 9% of children vs 22% of adults. Just 1.5% and 3.0% (Dottorini *et al.* 1997, Chow *et al.* 2004a, respectively), of the two pediatric papillary thyroid cancer (PTC) series presented with tumors <1 cm. However, in populations undergoing intensive screening and thus presumably diagnosed earlier, e.g., children exposed to Chernobyl fallout, pediatric PTC is mostly detected as a 1–2 cm tumor (Tronko *et al.* 1999). It should also be considered that the thyroid gland is smaller in children than in adults, which can lead to earlier involvement of the thyroid capsule and surrounding tissues (Farahati *et al.* 1999). Thus, the distinct staging category of microcarcinoma, necessary in adults, should be avoided in children or restricted to very small cancers, since a tumor 1 cm in diameter may already constitute a significant clinical finding in a child, especially a prepubescent. At this point it is also worth considering the question of multicentricity of childhood DTC. In general, thyroid cancer and especially its papillary histotype appear as multiple foci (Katoh *et al.* 1992, Pasieka *et al.* 1992) and recent reports (Sugg *et al.* 1998) indicate that these foci may be polyclonal. It is generally accepted that juvenile DTC is more frequently multicentric, although detailed comparisons are hampered by technical differences. This offers an argument for the resection of the whole thyroid gland (Miccoli *et al.* 1998).

Second, children differ from adults in their pattern and features of metastases. Pediatric patients are more likely to present with cervical lymph node or distant metastases (Farahati *et al.* 1997, Robie *et al.* 1998). For example, among 1039 consecutive PTC patients treated at the Mayo Clinic, neck node involvement was found in nearly 90% and distant metastases, in almost 7% of children, versus in 35% and just over 2% of adults, respectively (Zimmerman *et al.* 1988). In fact, one of two peaks in the rate of PTC metastases at diagnosis occurs in children (the other, in patients >60 years old) (Mazzaferri & Jhiang 1994b). In addition, distant metastases outside the lungs are very rare in children, albeit they should be sought in cases of unexplained thyroglobulin (Tg) elevation. The

Table 1 Putative differences between juvenile and adult DTC: possible mechanisms and clinical implications in children and adolescents

Differences in Juvenile vs adult DTC	Possible mechanism(s)	Clinical implication(s) in children and adolescents
Larger tumor volume at presentation	More aggressive growth, i.e., faster clinical onset, DTC diagnosis at a later stage, or both	Makes routine intensive primary treatment desirable
Extent and pattern of metastases: <ul style="list-style-type: none">• More frequent cervical lymph node and distant metastases• Distant metastases almost always in lungs• Lung metastases almost always miliary and functional at presentation	More aggressive tumor growth, decreased local immune response, or both Pathophysiological differences with focal, frequently non-functional metastases seen in older adults	Makes routine intensive primary treatment desirable; radioiodine treatment is particularly likely to be effective
Tumor NIS expression less reduced compared to healthy thyroid cells and less often absent		Radioiodine treatment is particularly likely to be effective
Higher recurrence rate	More aggressive disease, less intensive treatment, or both	Makes routine intensive primary treatment desirable
Longer overall survival	Tumors of rapid clinical onset but easily exhaustible proliferation	May be at least partially an artifact of limited observation time relative to life span; cited as an argument against routine intensive treatment
More frequent papillary histology	Belief based on frequent papillary histology in radiation-induced DTC	Not evident from a review of the sporadic DTC literature; even if true, has minimal if any clinical impact

DTC, differentiated thyroid carcinoma.

literature contains only scattered reports of bone lesions — which ultimately led to death (Schlumberger *et al.* 1987, Newman *et al.* 1998). Just a few cases of brain or other soft tissue metastases have been described in children (Hay 1987, Newman *et al.* 1998). Further, unlike adult lesions, pediatric pulmonary DTC metastases are overwhelmingly miliary and seldom nodular, and when detected radiographically, are almost always functional (Vassilopoulou-Sellin *et al.* 1993, Schlumberger *et al.* 1996a, La Quaglia *et al.* 2000, Reiners *et al.* 2002, Ronga *et al.* 2004). For example, among 95 Byelorussian children with Chernobyl-induced DTC lung metastases, 92 (97%) had disseminated, and only 3 (3%), nodular pulmonary radioiodine uptake (Reiners *et al.* 2002). Lung metastases were functional in 40 (95%) of 42 children with pulmonary DTC involvement seen at our institution from 1973 to 2002 (B Jarzab, unpublished observations).

The high prevalence of functional metastases in pediatric DTC relates to a third difference with the adult disease: although sodium iodide symporter (NIS) expression is reduced compared with that of healthy thyroid cells, childhood tumors appear to have greater

and more frequently detectable expression than do adult tumors (Ringel *et al.* 2001, Patel *et al.* 2002, Faggiano *et al.* 2004). In the absence of TSH stimulation, NIS expression is undetectable in ~65% of papillary and ~56% of follicular cancers in patients <20 years of age (Patel *et al.* 2002). In contrast, NIS expression is absent or below normal in ~90% of adult DTC, as assessed by reverse transcription PCR (Ringel *et al.* 2001) or immunohistochemistry (Mian *et al.* 2001, Gerard *et al.* 2003). Expression of other iodine transport-related molecules, pendrin and apical iodide transporter (AIT), also has been found to be reduced in pediatric (M Wiench and M Kovalska, unpublished observations) as well as in adult DTC (Gerard *et al.* 2003, Lacroix *et al.* 2004), but it is unclear if expression is greater in childhood DTC.

The greater NIS expression in juvenile than in adult DTC implies greater differentiation and radioiodine responsiveness in the former, which may be relevant to outcome. In young patients, recurrence risk was increased in NIS-negative vs NIS-positive tumors, even when Tumor Node Metastasis (TNM) status and treatment were similar (Patel *et al.* 2002). The degree of NIS expression in primary DTC lesions correlated

with subsequent radioiodine uptake in metastases (Castro *et al.* 2001) and the clinical response of recurrences (Min *et al.* 2001).

A fourth major characteristic of juvenile vs adult DTC is a generally higher recurrence rate (Mazzaferri & Massoll 2002). With 16.6 years' follow-up, this rate approaches 40% in patients with PTC diagnosed when <20 years old, vs ~20% in patients diagnosed at age 20–50 years (Mazzaferri & Kloos 2001).

Fifth, overall survival seems to be distinctly better in children than in adults. The contrast between the generally advanced disease at diagnosis and frequent recurrences and the low mortality is particularly striking. Not more than 35 cause-specific deaths occurred among some 2000 recently reported children and young adults (Table 2A).

Lastly, PTC prevalence is assumed to be greater in children than in adults with DTC (Leboulleux *et al.* 2004). However, the literature appears not to fully support this statement, although follicular thyroid cancer (FTC) occurs as a rule mainly in older children (Hung & Sarlis 2002). Only some centers (Schlumberger *et al.* 1987, Harness *et al.* 1992, Newman *et al.* 1998, Landau *et al.* 2000, Grigsby *et al.* 2002, Borson-Chazot *et al.* 2004) report FTC prevalence in their pediatric DTC series of <5% to 10%; others observe 15–20% prevalence, similar to the adult range.

Many differences between pediatric and adult DTC, namely the larger size and wider extent at presentation, more limited distant metastatic sites and greater propensity for recurrence, seem undeniable and presumably have a biological explanation. One such possible explanation relates to onset delay. Nearly all *RET* PTC-initiating mutations presumably occur in childhood; after puberty, they would not be transmitted to later generations of cells, given that the division potential of thyroid cells expires early (Williams 1995, Dumont *et al.* 2003). Thus the PTCs with the fastest clinical onset become detectable in children.

It remains unclear how much of the explanation for these differences lies in DTC molecular biology. To date, little has been determined about this area in children. In PTC, mutation of any of at least four genes, *RET*, *NTRK*, *BRAF*, or, much less frequently, *RAS*, activates the MAP kinase cascade, thereby initiating tumorigenesis via increased transcription of growth and proliferation genes (Viglietto *et al.* 1995, Kimura *et al.* 2003, Fagin 2004). Many studies suggest that distribution of the four mutated genes may differ between children and adults, with higher prevalence of *RET* rearrangements (Bongarzone *et al.* 1996, Nikiforov *et al.* 1997, Fenton *et al.* 2000b, Wiench

et al. 2001) and absence of *BRAF* (Kumagai *et al.* 2004) mutations in children, but contradictory data have been reported (Motomura *et al.* 1998, Elisei *et al.* 2001). There are suggestions that particular gene mutations may serve as prognostic markers (Nikiforov *et al.* 1997). For example, in adults, *RET* rearrangements appear to be associated with development of relatively indolent microcancers, and never with anaplastic tumors, notwithstanding these tumors' frequent PTC origin (Fagin 2004). However, early suggestions of more advanced disease in *RET*- (Sugg *et al.* 1996) or *RET*- and *NTRK*-positive cases (Bongarzone *et al.* 1998), were not confirmed in a later study (Fenton *et al.* 2000b) that addressed recurrences but had a relatively short, 3.6-year median follow-up. Other data (Elisei *et al.* 2001, Basolo *et al.* 2001) also fail to support any relationship between *RET* immunopositivity and PTC prognosis.

Other differences include lack of mutations seen in adults, for example in *G(s)alpha* gene (Waldmann & Rabes 1997). Regarding genes known for prognostic significance in non-thyroid cancers, one study (Ramirez *et al.* 2000) suggests that over-expression of *MET* alone, or, especially, together with the gene for this tyrosine kinase receptor's ligand, hepatocyte growth factor/scatter factor, is associated with a heightened PTC recurrence risk in children and young adults. However, other groups' (Wasenius *et al.* 2003, Finley *et al.* 2004) and our studies (Jarzab *et al.* 2005) suggest that *MET* over-expression characterizes the majority of PTCs, at least at the RNA level. Limited numbers of studies have correlated over-expression in PTC cells of vascular endothelial growth factor and its receptor with tumor size in children (Fenton *et al.* 2000a), of all tyrosine kinases with PTC recurrence risk in young adults (Patel *et al.* 2000) or of telomerase with advanced disease in children and adolescents (Straight *et al.* 2002). Much additional study is needed to verify these putative relationships and elucidate their mechanisms of action, and to establish any prognostic utility for these markers.

In the case of follicular thyroid cancer (FTC), two genes involved in neoplastic transformation should be mentioned, *RAS* and *PPARG*, the rearrangement of the latter triggering transformation of follicular adenoma to follicular carcinoma (Nikiforova *et al.* 2003). However, even less is known about the possible prognostic importance of mutations in these genes or about their distribution in children than is known with the analogous PTC mutations. Some authors (Nikiforova *et al.* 2003) claim that the *PPARG* rearrangement is more frequent in FTC occurring at a younger age.

Table 2A Recently reported experience^a with sporadic pediatric DTC: overview

Row No. and Reference	Population			Treatment % (no.)			Outcome			
	No. of Patients	Upper age limit, years (other age data)	Histology, % (no.)	Median follow-up (reported time span) [other follow-up data]	Total thyroidectomy	Radioiodine ablation	Cause-specific mortality rate (no. deaths)	Recurrence rate	Survival: Overall cause-specific	Survival: Disease-free or related
Multicenter series:										
1. (Newman <i>et al.</i> 1998)	329	21	P: 90 (297) F: 10 (32)	11.3 y (1946–91)	54 (178)	43% (143)	<1% (2)	NR	10-y: 100%	PFS: 10-y: 67% 20-y: 60% RFS: 10-y: Stage 1: 83% Stage 2: 58% NR
2. (Welch Dinauer <i>et al.</i> 1998, Robie <i>et al.</i> 1998, Powers <i>et al.</i> 2003a)	170	21 (median: 19 y, 24% ≤16 y)	P: 81 (137) F: 19 (33)	6.6 y (1953–96) [> 10-y FU in 32%]	49 (84)	58% (98)	<1% (1)	19%	NR	
3. (Storm & Plesko 2001)	165	14 (13% <10 y)	NR	NR (1978–89)	NR	NR	4% (6)	NR	5-y: 97%	NR
4. (Farahati <i>et al.</i> 1997)	114	18	P: 78 (89) F: 22 (25)	3.9 y (NR)	NR	NR	NR	NR	NR	NR
5. (Harach & Williams 1995)	108 ^b	14 (mean: P: 12.4 y, F: 11.5 y)	P: 77 (83) F: 23 (25)	NR (1963–92)	NR	NR	10% ^c	NR	NR	NR
Single-center series encompassing > 50 DTC patients:										
6. (Jarzab <i>et al.</i> 2000, Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z & Jarzab B, unpublished observations) ^d	235	18 (median: 13.5 y, 13% <10 y)	P: 82 (193) F: 18 (42)	6.9 y (1973–2002) [> 10-y FU in 25%]	73 (172)	74% (174) ^e	0% (0)	14%	10-y: 100%	10-y TBRFS ^f LTT: 86% TT: 99% 10-y LNRFS ^f : 90%
7. (La Quaglia <i>et al.</i> 1988)	103	17 (mean: 13.3 y, 26% <10 y)	P: 84 (87) F: 7 (7) Not specified: 6 (6)	20.0 y (1949–86) [> 6-y FU in 75%]	46 ^g (46)	22% (22)	0% (0)	35%	100%	67%
8. (Harness <i>et al.</i> 1992)	89 ^a	17	P: 93 (83) F: 75 (6)	NR (1936–1990) [FU range: 0.5–18 y; > 10-y FU in 82%]	94 (79)	27% (24) [73% since 1971]	2% (2)	24% ^h	NR	NR
9. (Dottorini <i>et al.</i> 1997)	85	17 (mean: 14.7 y, 8% <10 y)	P: 85 (72) F: 15 (13)	9.25 y (1958–1995)	54 (46)	88% (75)	0% (0)	7%	100%	NR
10. (Borson-Chazot <i>et al.</i> 2004, Causeret <i>et al.</i> 2004)	74	19 (median: 17 y, 35% <15 y)	P: 95 (71) F: 4 (3)	5 y (1985–2001)	61 (45)	34% (25)	0% (0)	LN: 14% T: 4%	100%	RFS: 38% ^h 90% ⁱ
11. (Schlumberger <i>et al.</i> 1987)	72 ^b	16	P: 69 (50) F: 6 (4) PDF: 25 (17)	13.0 y (1945–1984) >20 y FU: 28%	40 (29)	6% (4) ^j	8% (6)	10-y: 17% 20-y: 34%	10-y: 98% 25-y: 78% (95% CI, 56%–90%)	NR
12. (Segal <i>et al.</i> 1998)	61	19 (mean: 15.8 y)	P: 79 (48) F: 21 (13)	14.8 y (1952–95)	84 (51)	100% (61)	3% (2)	30% after <TT 0% and after TT	20 y: 97%	NR

Table 2A continued

Row No. and Reference		Population			Treatment % (no.)			Outcome			
		No. of Patients	Upper age limit, years (other age data)	Histology, % (no.)	Median follow-up (reported time span) [other follow-up data]	Total thyroidectomy	Radioiodine ablation	Cause-specific mortality rate (no. deaths)	Recurrence rate	Survival: Overall cause-specific	Survival: Disease-free or related
13.	(Chow <i>et al.</i> 2004a)	60 ^b	20 (mean: 17 y, 3% <10y)	P: 82 (49) F: 18 (11)	14.0 y (1960–97)	82 (49)	60% (36)	3% (2)	25%	98%	LNRRFS: 79% ^k DRFS: 91% NR
14.	(Zimmerman <i>et al.</i> 1998)	58	16	P: 100	28 y (1946–1975)	36 (21)	20 (12)		local 12% distant 7%	97%	
15.	(Grigsby <i>et al.</i> 2002)	56	20 (mean: 15.8 y)	P: 95 F: 5	11 y (1970–2000)	89 (48)	82% (46)	2% (1)	34%	98%	PFS: 10-y: 61% 20-y: 46%
Combined data from smaller studies											
16.	(Mizukami <i>et al.</i> 1992, Fassina <i>et al.</i> 1994, Millman & Pellitteri 1995, Stael <i>et al.</i> 1995, Massimino <i>et al.</i> 1995, Danese <i>et al.</i> 1997, Sykes & Gattamaneni 1997, Hallwirth <i>et al.</i> 1999, Alessandri <i>et al.</i> 2000, Landau <i>et al.</i> 2000, Bingol-Kologlu <i>et al.</i> 2000, Giuffrida <i>et al.</i> 2002, Kowalski <i>et al.</i> 2003, Haveman <i>et al.</i> 2003, van Santen <i>et al.</i> 2004)	439	17–19 for 273 (62%) 14–16 for 166 (38%)	P: 84 F: 16	Median > 10 y for 175 (40%)	66 (239)	72.5% (247)	1.6% (7)	21%	Studies with 20-y data: (Landau <i>et al.</i> 2000) 86% (Alessandri <i>et al.</i> 2000) 100% (Kowalski <i>et al.</i> 2003) 90%	Studies with 20-y data: (Landau <i>et al.</i> 2000) 65% (Alessandri <i>et al.</i> 2000) 32%

CI, confidence interval; DRFS, distant recurrence-free survival; F, follicular well-differentiated; FU, follow-up; LN, lymph nodes; LNRRFS, lymph node recurrence-free survival; LTT, less than total thyroidectomy, NR, not reported; P, papillary; PDF, poorly-differentiated follicular; PFS, progression-free survival; RFS, recurrence-free survival; T, thyroid; TBRFS, thyroid bed recurrence-free survival; TT, total thyroidectomy.

^aExcludes reports on <15 patients and series in which >25% of the patients had radiation-induced DTC (Tronko *et al.* 1999, Gow *et al.* 2003, Spinelli *et al.* 2004), as well as series related to disseminated DTC exclusively (Vassilopoulou-Sellin *et al.* 1993, Samuel *et al.* 1998, Brink *et al.* 2000, Reiners *et al.* 2002). However, one paper (Harness *et al.* 1992), who reported 1 radiation-induced DTC case among 33 (3%) patients treated since 1971 and 32 (57%) radiation-induced DTC cases among 56 patients treated before 1971, was included.

^bFrom larger series also including adults or patients with other forms of thyroid cancer.

^cExcluding deaths from medullary thyroid carcinomas, teratomas and malignant teratomas, all recorded in n=34 patients with 20-yr follow-up available.

^dShorter follow-up on 102 of these patients was reported in (Jarzab *et al.* 2000).

^eTherapeutic radioiodine given for thyroid remnant ablation, treatment of distant metastases; or both.

^fRefers to locoregional recurrence (independent of distant metastases status at presentation) and excludes patients with recurrence appearing as distant metastases only.

^gTotal or subtotal thyroidectomy.

^hIn patients with enlarged lymph nodes at diagnosis.

ⁱIn patients without enlarged lymph nodes at diagnosis.

^jAblation applied in cases of incomplete excision; therapeutic ¹³¹I also given to 12 patients for distant metastases.

^kIn patients without distant metastases at diagnosis.

Table 2B Recently reported experience^a with sporadic pediatric DTC: key findings and recommendations on treatment

Reference	Type of statistical analysis	Key findings of statistical analysis of the influence of treatment related factors on DTC prognosis	Recommendations:	
			Total Thyroidectomy	Radioiodine Ablation
(Newman <i>et al.</i> 1998)	Univariate	No	Not recommended	Radioiodine therapy not recommended except in patients with distant metastases
(Welch Dinauer <i>et al.</i> 1998, Robie <i>et al.</i> 1998)	Univariate	No	Recommended	Recommended
(Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z & Jarzab B, unpublished observations) ^b (La Quaglia <i>et al.</i> 1988)	Multivariate	Radical surgery and radioiodine ablation were significant independent predictors of local or lymph node recurrence-free survival	Recommended	Recommended for all patients but those given total thyroidectomy and appropriate lymph node surgery and not showing radioiodine uptake or stimulated serum Tg increase post surgery
	Multivariate	Thyroid surgery type was non-significant while age at diagnosis and histologic subtype were significant independent predictors of recurrence	Not recommended	Not addressed
(Borson-Chazot <i>et al.</i> 2004)	Univariate	Not evaluable, treatment was related to the initial staging	Recommended, though not performed by the authors in their low-risk patients	Not addressed
(Schlumberger <i>et al.</i> 1987)	Univariate	Significant association between less than total thyroidectomy and recurrence ($P<10^5$)	Recommended	Radioiodine therapy not recommended except in patients with residual disease
(Chow <i>et al.</i> 2004a)	Univariate	Radioiodine ablation significantly ($P=0.04$) increased the locoregional failure-free survival in patients without distant metastases at diagnosis, as well in a subgroup with complete thyroid surgery and without distant metastases at diagnosis ($P=0.014$)	Not addressed	Recommended
(Zimmerman <i>et al.</i> 1988)	Univariate	No	Not recommended	Not recommended
(Grigsby <i>et al.</i> 2002)	Multivariate	No	Recommended	Recommended except in patients with unilateral disease and no lymph node metastases
(Alessandri <i>et al.</i> 2000)	Multivariate	Total thyroidectomy, radioiodine therapy and TSH suppression were not significant predictors of time to recurrence	Recommended	Not addressed (number of treated patients too low)
(Kowalski <i>et al.</i> 2003)	Univariate	No	Recommended	Recommended
(Landau <i>et al.</i> 2000)	Multivariate	TSH suppression ($P=0.0003$) was a significant independent predictor of DTC recurrence while extent of surgery and radioiodine therapy were not significant. Recurrence itself was a significant risk factor for cause-specific mortality ($P=0.02$)	Recommended	Recommended for all patients except those T1 or T2 N0M0 and node-negative and age > 10 yrs at diagnosis

FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; Tg, thyroglobulin.

^aExcludes studies listed in Table 2A that did not statistically evaluate treatment-related issues. Non-significant effects on univariate analysis are not mentioned. Both positive and negative results of multivariate analysis are described.^bMultivariate analysis on 102 of these patients was reported in (Jarzab *et al.* 2000).

In explaining the distinct natural history of childhood DTC, not only tumor molecular biology but differences between the juvenile and adult thyroid gland and host organism must be addressed. Age-related thyroid gland differences are not yet well-characterized molecularly, however, some investigations became possible in healthy thyroid glands obtained surgically from *RET* mutation carriers (Faggiano *et al.* 2004). These data suggest that children have more metabolically active and functional thyroid glands than do adults. Follicles <100 µm, considered active, were prevalent in children <12 years old, while follicles >200 µm, considered hypofunctioning, were more frequent in older individuals including adults up to age 40 years. In addition, younger patients had a higher proportion of thyroid cells and follicles immunopositive for iodide-transport- and organification-related molecules, among them NIS, pendrin, thyroid peroxidase and dinucleotide phosphate oxidase (Duox; thyroid H₂O₂ generator), but not AIT. The degree of NIS, pendrin and Duox expression also was independently associated with younger age, regardless of follicular size.

The key host organism difference might be in immune response to thyroid cancer (Boyd & Baker 1996, Mitsiades *et al.* 1999). A variety of observations support the importance of that response in preventing PTC metastasis or recurrence in adults (Matsubayashi *et al.* 1995, Loh *et al.* 1999, Modi *et al.* 2003) and children (Gupta *et al.* 2001). Gupta found that the pediatric PTC patients with the greatest number of proliferating lymphocytes in thyroid infiltrates had the longest disease-free survival. Of interest, intense tumor expression of the B7-2 antigen has been correlated with a greater propensity for recurrence in children and adolescents with DTC (Shah *et al.* 2002).

Some differences between pediatric and adult DTC may to at least some degree be artifacts of the observation period. For example, the purported low mortality rate of pediatric DTC may reflect relatively short follow-ups compared with patients' lifespans. As seen in Table 2A, most reports on DTC diagnosed in childhood have a median follow-up of ≤15 years. However, a high proportion of cause-specific deaths may take place longer-term (Vassilopoulou-Sellin *et al.* 1998). For example, in the analysis of Harach & Williams (1995), mortality was 10% in the subgroup of 34 patients with ≥20-year follow-up. In one of the largest single-institution series, that of the Institut Gustave Roussy (Schlumberger *et al.* 1987), 15% (6/40) of patients diagnosed with DTC at age <12 years succumbed to their

tumor 12–33 years after initial treatment. The two cause-specific deaths in a 329-patient multi-institutional study with an 11.3-year median follow-up (Newman *et al.* 1998) took place 16 and 18 years post-diagnosis. In another series, DTC mortality was noted as late as 59 years after presentation (Landau *et al.* 2000).

Of interest, the relatively short follow-up in many studies also may lead to underestimation of the recurrence rate in patients diagnosed as children. In a large mixed young adult and pediatric series (~25% patients <17 years old), Welch Dinuer *et al.* (1998) observed 90% of recurrences within 7 years of diagnosis. However, in a similar-sized purely pediatric series, La Quaglia *et al.* (1988) observed only 50% of recurrences within 1–6 years after primary treatment. Relapses have been noted as long as 25 years after primary treatment (La Quaglia *et al.* 1988) or 44 years after diagnosis (Landau *et al.* 2000), and among DTC patients diagnosed at any age, Mazzaferri found 15% of locoregional and 24% of distant recurrences more than two decades after initial therapy (Mazzaferri 2004).

Within the pediatric DTC population, some investigators found an association between younger age at diagnosis and a higher rate of (Landau *et al.* 2000) or shorter time to (La Quaglia *et al.* 1988) recurrence. Alessandri *et al.* (2000) identified age at diagnosis as the major determinant of recurrence risk in pediatric DTC: 20-year recurrence-free survival (RFS) was 10.1% in patients diagnosed at age <10 years, vs 48.3% in patients diagnosed at ages 10–18 years ($P = 0.008$). However, the statistical significance of the association was not evident in multivariate analysis.

Our own work with larger series confirms this pattern. Univariate analysis of our original series of 103 pediatric DTC patients (Jarzab *et al.* 2000) revealed a poorer RFS when patients were diagnosed at age ≤10 years vs at age 11–13 or 14–17 years (0% vs 70% vs 88% respectively, $P = 0.05$). However, age was non-significant in a multivariate analysis including treatment-related factors. With respect to locoregional recurrence, we now have extended these results to a larger population of 235 juvenile DTC patients, more than 100 diagnosed at age <15 years, and to our knowledge, the largest group yet reported of children followed according to a detailed, standard protocol (Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z & Jarzab B, unpublished observations). In our opinion, previous observations of worse outcome in the youngest patients were biased by a sometimes less intensive treatment approach in this group.

Table 3 Goals and Rationale for Radioiodine Ablation in DTC, with special emphasis on juvenile DTC

Goal of Ablation	Rationale
Ablate any residual cancer, including microfoci	Ablation decreases cause-specific death risk independently of extent of surgery (Mazzaferri & Kloos 2001) In large pediatric studies, ablation decreased DTC locoregional recurrence risk by a factor of 2.1 ($P<0.0001$)(Newman <i>et al.</i> 1998), and thyroid or lymph node recurrence risk by factors of 11.0 ($P<0.03$) and 3.2 ($P<0.03$), respectively (Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z & Jarzab B, unpublished observations) Extra layer of primary treatment confers “peace of mind” for patients and families
Ablate healthy thyroid remnant	Ablation destroys sources of residual serum Tg secretion, enabling Tg to be a sensitive and specific marker of DTC persistence or recurrence, particularly when measured after TSH stimulation (Ladenson <i>et al.</i> 1997, Mazzaferri & Kloos 2002, Haugen <i>et al.</i> 2002, Mazzaferri <i>et al.</i> 2003) Ablation eliminates high remnant uptake that can obscure radioiodine uptake in lymph node or lung metastases on WBS Ablation eliminates sources of thyroid hormone that may prevent endogenous TSH increase after thyroid hormone withdrawal, precluding withdrawal-aided Tg testing or diagnostic WBS
Enable sensitive post-ablation WBS	In ~20%–50% of affected pediatric DTC patients, only post-ablation WBS allows complete detection of lung metastases (Mazzaferri & Jhiang 1994a, Samuel <i>et al.</i> 1998, Hung & Sarlis 2002, Reiners <i>et al.</i> 2002, Bal <i>et al.</i> 2004a,b, Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z & Jarzab B, unpublished observations).

DTC, differentiated thyroid carcinoma; Tg, thyroglobulin; WBS, whole-body scan.

Primary treatment of juvenile DTC

Overview

Despite differences between PTC and FTC in molecular biology, histology and clinical picture, especially lymph node involvement at diagnosis, interventions are similar for both (Reynolds & Robbins 1997, Newman *et al.* 1998, Mazzaferri & Massoll 2002, Ringel & Ladenson 2004). As with adult disease, primary treatment of pediatric DTC generally comprises some combination of three modalities, surgery, radioiodine ablation, and thyroid hormone therapy, applied at varying levels of intensity.

Surgery may range from lobectomy to total thyroidectomy. According to the recent guidelines of national and international societies and recent publications, total thyroidectomy is the preferred operation in cancers >pT_{1a} (Mazzaferri & Kloos 2001, Ringel & Ladenson 2004, Watkinson 2004) and is routinely accompanied by en bloc dissection of the central compartment with clearing of lymphatic and soft tissue. Modified lateral neck dissection is advocated in cases of metastases to lateral lymph node compartments. The main potential complications include persistent hypoparathyroidism and recurrent laryngeal nerve injury of varying clinical relevance (van Santen *et al.* 2004, Schneider *et al.* 2004). After total or near-total thyroidectomy, thyroid remnant volume should be <2ml on sonography performed no earlier than 1 month after the procedure (Maxon 1999, Mazzaferri & Massoll 2002).

Even after total thyroidectomy and negative postoperative sonography, some ¹³¹I uptake usually appears in the thyroid bed, particularly if scintigraphy is performed with an activity higher than that normally used for diagnostic whole-body scan (WBS) (Zidan *et al.* 2004). Most often, this residual uptake is attributable to healthy thyroid remnant cells. However, as tumor multifocality is frequent in DTC, especially PTC, and metastatic spread common in pediatric patients, the presence of cancer microfoci must be considered. In most European centers, as recommended by most guidelines (Reynolds & Robbins 1997, Mazzaferri & Massoll 2002, Haugen 2004), thyroid remnant ablation is routinely given to the vast majority of, if not all DTC patients to destroy every source of uptake, for several reasons which do play even a more prominent role in juvenile DTC (Table 3). However, adjuvant radioiodine should be given to complete, not to replace total thyroidectomy: ablation success rates are significantly lower when patients have less extensive thyroid surgery (Maxon 1999), and our multivariate analysis in a large series of young DTC patients (Table 4) shows that the two maneuvers are independent predictors of RFS, as previously reported in a general PTC population (Mazzaferri & Kloos 2001).

‘Successful ablation’ usually is defined using relatively short-term ‘surrogate markers’, namely, absent or <0.1–1.0% uptake on a diagnostic WBS performed 6–12 months after the procedure (Leung *et al.* 1992, van Wyngaarden & McDougall 1996, Pacini *et al.*

Table 4 Potential predictors of recurrence-free survival in 274 DTC patients diagnosed at age <28 Years^a: results of multivariate analysis

Potential Predictor (categories analyzed)	Relative Risk, Mean (95% CI)	P, Cox multiple regression analysis
Extent of thyroidectomy (less than total vs total)	6.2 (2.8–13.7)*	<0.001*
Radioiodine ablation (no vs yes)	5.8 (2.4–14.1)*	<0.001*
Lymph node metastases at DTC diagnosis (present vs absent)	3.1 (1.3–7.2)*	0.027*
Age at diagnosis (19–28 years vs ≤18 years)	0.99 (0.92–1.0)	0.964
Gender (male vs female)	0.97 (0.38–2.4)	0.959
Histopathology (follicular vs papillary)	0.51 (0.23–1.1)	0.160

CI, confidence interval; DTC, differentiated thyroid carcinoma.

*Statistically significant at $P < 0.05$.

^aIncludes 103 children ≤18 years old and 171 adults 19–28 years old.

Adapted from (Handkiewicz-Junak *et al.* 2001), with permission of Nowotwory Journal of Oncology, Warsaw, Poland.

2002, Zidan *et al.* 2004), or, increasingly, undetectable TSH-stimulated serum Tg at the same timepoint (van Wyngaarden & McDougall 1996, Reynolds & Robbins 1997, Mazzaferri & Kloos 2002, Mazzaferri & Massoll 2002). Typically, one course of radioiodine therapy achieves successful ablation defined in this manner (Zidan *et al.* 2004), however, the procedure sometimes must be repeated, usually after 6–12 months (Leung *et al.* 1992, van Wyngaarden & McDougall 1996, Pacini *et al.* 2002). Approaches for choosing an ablative activity are discussed in detail in the *Dosimetric Considerations* section below.

Ablation also should entail performance of a ‘post-therapy’ or ‘post-ablation’ WBS, generally 3–7 days after radioiodine administration. Detection or confirmation of functional metastases on this scan implies further radioiodine treatment, sometimes in combination with surgery.

The third modality in DTC primary treatment is thyroid hormone therapy with levo-thyroxine (T_4). This modality is termed thyroid hormone suppressive therapy (THST) when supraphysiological doses are used to suppress serum TSH to subnormal levels, thereby reducing the risk of the TSH stimulating tumor growth and proliferation (Mazzaferri & Jhiang 1994b, Pujol *et al.* 1996). At present, many authors propose slightly suppressed, low–normal or even normal TSH levels as endpoints for thyroid hormone therapy (Mazzaferri & Massoll 2002, Barbaro *et al.* 2003, Schlumberger *et al.* 2004a,b).

A number of long-term safety issues surround THST, particularly in growing patients who are likely to receive the modality for a very long time (Muller

et al. 1995, Shapiro *et al.* 1997, Horne *et al.* 2004, Botella-Carretero *et al.* 2004). Potential THST side effects may include osteoporosis (Schneider & Reiners 2003), and of special concern, cardiovascular complications, particularly ventricular hypertrophy (Biondi *et al.* 1993, Fazio *et al.* 1995, Matuszewska *et al.* 2001). In addition, target serum TSH levels need to be adjusted very carefully in children to avoid impairing physiological growth and development.

Primary treatment strategies

The goals of primary treatment of DTC are to eradicate disease and extend not only overall, but recurrence-free survival. Though sometimes — and, we believe, curiously — overlooked in debates on treatment strategies, maximizing RFS is, in our opinion, an important and desirable endpoint in and of itself (Mazzaferri & Kloos 2001). Extending RFS spares patients morbidity and anxiety, an especially important benefit in children and adolescents, who are in their psychologically formative years. Further, with sufficient follow-up, avoiding recurrence may decrease mortality. In one study (Landau *et al.* 2000), the risk of death was significantly higher in recurrent patients (hazard ratio 9.9, 95% CI, 0.98–100.0, $P = 0.02$), even though their median survival was 30 years. Additionally, anecdotal reports exist of patients diagnosed in childhood succumbing to recurrent DTC 22–35 years later (Tubiana *et al.* 1985). Lastly, extending RFS may lessen medical resource consumption, e.g., avoid re-operation for local recurrence (Harness *et al.* 1992).

When formulating primary treatment strategies for juvenile DTC patients, the first question that arises is whether distinct strategies are required from those employed in adult patients (Ringel & Levine 2003). We, and many others (Zimmerman *et al.* 1988, Harach & Williams 1995, Dottorini *et al.* 1997, Newman *et al.* 1998, Hung & Sarlis 2002, Reiners 2003) believe that the answer is affirmative, particularly in patients <10 or <15 years old.

There are, we feel, two main rationales for distinct pediatric strategies. First, as discussed above, childhood DTC appears to behave differently from the adult disease: its large tumors, frequent metastasis, responsiveness to radioiodine, and above all, propensity for recurrence should influence decision-making (Newman 1993, Hung & Sarlis 2002, Orsenigo *et al.* 2003). Second, juvenile patients of course are, unlike adults, physically and psychologically developing and if cured, will have longer survival. Therefore both short- and long-term safety are extremely important considerations, and the clinician should, as always, aim to apply the minimum interventions likely to achieve treatment goals.

In formulating distinct pediatric treatment strategies, a conventional evidence-based approach is not possible. Given DTC's frequent curability and relatively low mortality, large sample sizes in a relatively rare disease and an unusually long follow-up would be required to detect intergroup differences in overall survival. Therefore no randomized, prospective studies in either pediatric or adult DTC have compared the effect of different therapeutic options on this endpoint, or, for that matter, with respect to RFS (Dragoiescu *et al.* 2003).

Three main sources of published guidance are available for devising pediatric primary treatment strategies: 1) the adult DTC outcomes literature (Schlumberger *et al.* 1986, DeGroot *et al.* 1990, 1994, Samaan *et al.* 1992, Mazzaferri & Jhiang 1994b, Sherman *et al.* 1998); 2) DTC treatment algorithms (Mazzaferri 1999, 2001a,b, Vini & Harmer 2002, Harris 2002, Phillips *et al.* 2003, Watkinson 2004 and other recent guidelines, among them EANM2003, AACE/AAES 2001a and Polish Guidelines 2001b) based overwhelmingly on adult experience, and with few exceptions, not considering children separately; and, of greatest relevance, 3) the pediatric outcomes literature. Tables 2A, B summarize recent experience in children and young adults with DTC, published in the last 15 years in outcome studies reporting ≥ 15 patients. Several major papers of the late 1980's summarizing the largest centers' earlier experience also are included (Schlumberger *et al.* 1987, La Quaglia *et al.* 1988,

Zimmerman *et al.* 1988). Because it currently is likeliest to be seen in most clinical practices, sporadic pediatric DTC is emphasized and studies with >25% of patients with radiation-induced DTC (Tronko *et al.* 1999, Gow *et al.* 2003, Spinelli *et al.* 2004) have, with one exception (Harness *et al.* 1992) been excluded, as have those devoted only to distant metastatic cases (Vassilopoulou-Sellin *et al.* 1995, Brink *et al.* 2000, Reiners *et al.* 2002).

Three limitations of the pediatric outcomes literature should be borne in mind. First, because studies are retrospective and treatment intensity was generally greater in patients with more extensive disease, it often is difficult if not impossible to fully untangle the independent influence on outcome of tumor and host biology and different treatment options. Second, the rarity of DTC in children caused many authors to include young adults, sometimes >20 years old, in their analyses to increase statistical power. In the majority of publications, it is impossible to fully separate data on younger patients. Third, a large part of the reported experience took place before the era of sonography, computed tomography (CT) and recombinant human TSH (rhTSH)-stimulated Tg measurement, i.e., when disease or recurrence tended to be detected later than they are currently. Therefore, this experience may not be fully applicable to the present.

Nonetheless, some general comments may be made based on the recent juvenile DTC literature. First, the majority (~60%) of reported children and adolescents were treated with total or near-total thyroidectomy, while the policy towards radioiodine therapy is more varied (~50% use). However, few investigators favor less extensive surgery followed by radioiodine; post-operative ^{131}I is given mostly by authors agreeing that both modalities improve final outcome. There is no clear relationship between treatment strategy and the recurrence rate, which averages about 25%. However, as seen in Fig. 2, a trend towards less recurrence seems to emerge as the proportion of patients in a series receiving both total thyroidectomy and radioiodine ablation increases.

The absence of prospective or universal retrospective proof of recurrence-free or overall survival benefits of different treatment modalities or intensities in the adult or pediatric literature has engendered considerable controversy over primary treatment strategies for DTC, specifically, over whether a routinely conservative or intensive approach is appropriate (Cady 1998, Landau *et al.* 2000, Mazzaferri & Kloos 2001, Ringel & Levine 2003). Investigators advocating conservatism have included the Mayo Clinic group, who cited a 1.7% death rate after a 28-year median

Figure 2 Relationship between intensive primary treatment and recurrence rate. Analysis of juvenile differentiated thyroid carcinoma (DTC) outcomes from selected published studies, providing information on 1420 patients, suggests that as the prevalence of patients with both total thyroidectomy and radioiodine ablation increases, DTC recurrence rate decreases. Dot size for each study reflects its population: larger dots denote a larger series. Numbers refer to the row numbers in Table 2A where the papers are described. The fitted surface was approximated using least squares method. It should be noted that the obtained model is not a formal meta-analysis approach and is not weighted according to the population size.

follow-up and a 3.4% 30-year recurrence rate in 58 patients <17 years old, of whom 90% had neck node metastases and only 38% received total thyroidectomy, and 17%, radioiodine ablation (Zimmerman *et al.* 1988). In a separate publication (Brink *et al.* 2000), the Mayo investigators described 14 children and adolescents (mean age at diagnosis: 13.5 years, range 9.8–17 years) with pulmonary PTC metastases at presentation, treated from 1937 to 1998. All but one patient had abnormal chest radiography, 12 received ^{131}I , and one each, external beam irradiation or suppressive T_4 only. Excluding three recent patients, median follow-up was 27 years (range, 1–45 years). All patients remained alive, including the two without ^{131}I therapy, who were followed for ~24 years. The individual given only T_4 remained clinically stable during this time, but was not tested for pulmonary function. No patients developed extra-pulmonary disease, although two suffered from local recurrence and 50% from persistent disease. These results led the authors to ask whether an aggressive surgical strategy might be replaced by less intensive treatment, a question which we find hard to understand in light of their substantial percentage of incomplete remission. However, a recent review from this center (Thompson

& Hay 2004) advised total thyroidectomy and radioiodine in children with DTC.

Less extensive surgery and omission of radioiodine ablation have been supported by the analysis of Newman *et al.* (1998) of determinants of DTC progression in an American multi-institutional cohort of 329 patients diagnosed when <21 years old. Progression-free survival did not differ significantly in relation to the extent of surgery or use of radioiodine ablation, while complications were more frequent after extensive operations (also van Santen *et al.* 2004). However, total thyroidectomy was more often applied to later-stage patients, calling into question the claim of no benefit from more intensive treatment. In addition, the inclusion of a substantial number of patients of age 18–21 years, in whom the prognosis is usually excellent, might influence their conclusions.

The conservative primary treatment strategy entails so-called stage-oriented, risk-based algorithms (Newman *et al.* 1998, Powers *et al.* 2003b), which are widely accepted in adult DTC. Regarding radioiodine ablation, advocates of the conservative approach propose that beyond patients with functional distant metastases, the procedure be restricted to selected high-risk patients (Wartofsky *et al.* 1998). Implementing this algorithm is, however, complicated by the lack of consensus on the definition of high-risk patients, excluding the relatively rare stage IV cases at presentation. The numerous staging systems do not solve the problem (Sherman *et al.* 1998, Voutilainen *et al.* 2003), especially as the majority are based on overall survival rather than the much more appropriate endpoint of RFS (Mazzaferri & Massoll 2002). Staging is especially vexing in children, who have a high recurrence risk but very good overall survival. Based on the frequent extrathyroidal invasion, lymph node metastases and distant metastases, and above all, on the recurrence likelihood, most children should be included in the high-risk group, while because of good overall survival, most staging systems classify them as stage I, and only as stage II when they have distant metastases.

The main arguments favoring intensive primary treatment are its significant associations with improved RFS in many studies, especially those with longer follow-up (Tables 2A, B). For example, with respect to radioiodine ablation in children, a recent paper based on a large group of patients ($n = 60$) is very conclusive on the procedure's recurrence-related benefits. In univariate analysis, Chow *et al.* (2004a) demonstrated that local DTC relapse was reduced in children from 42.0 to 6.3% when ^{131}I was administered postoperatively ($P = 0.001$). Ten-year locoregional

failure-free survival in children without distant metastases at diagnosis was 86.5% with, vs 71.9% without ablation ($P = 0.04$). The distant failure-free rate was also reduced with adjuvant radioiodine: 100% vs 94%, albeit this difference did not reach significance. In addition, our own previously mentioned multivariate analysis of a large pediatric series found that ablation significantly reduced recurrence risk in both the thyroid bed and neck lymph nodes, independent of the influence of total thyroidectomy or adequate lymph node resection (Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z & Jarzab B, unpublished observations); thus, adjuvant radioiodine had an additive benefit to that of extensive surgery. The results of Chow *et al.* (2004a) and our group echo those of the recent meta-analysis of remnant ablation outcomes in DTC patients of all ages, which determined that this intervention reduced locoregional and distant recurrence risk (Sawka *et al.* 2004).

Radioiodine treatment of metastatic DTC

In contrast to the controversy over routine radioiodine ablation in children, there is universal agreement that ^{131}I treatment should always be administered for inoperable functional distant metastases. Such treatment is especially important in that Landau *et al.* (2000) clearly documented association of distant metastases at diagnosis with poorer survival in children (hazard ratio: 29, 95% CI, 2.5–334, $P < 0.001$).

Both clinical experience and theoretical considerations indicate that response relates to tumor dimensions. Radioiodine treatment usually completely eradicates tumor deposits, especially when their diameter is ≤ 1 cm (Schlumberger *et al.* 1986, 1996a, Reynolds & Robbins 1997, Hindie *et al.* 2003). However, Monte Carlo simulations suggest that when tumor diameter is very small, especially < 0.1 mm, therapeutic results may be distinctly poorer, as $> 90\%$ of ionizing energy emitted during ^{131}I decay will be absorbed outside the tumor focus (the maximal range of beta particles is 2.4 mm) (Reynolds & Robbins 1997, Maxon 1999). A 0.1 mm lesion will receive only 8.6% of the radioactivity dose received by a 5 mm lesion (Van Nostrand *et al.* 2002). This phenomenon may contribute to the failure of complete remission seen in some children with metastatic DTC detected only by post-therapy scan.

Pediatric metastatic DTC appears to be more radioiodine-sensitive than adult disease, resulting in better survival in children. In publications to date, this modality achieved complete remission in the majority of children with lung metastases (Schlumberger *et al.* 1986, 1987, Vassilopoulou-Sellin *et al.* 1993, Sisson

et al. 1996) and even partial responders rarely subsequently progressed (Brink *et al.* 2000, Jarzab *et al.* 2000, Reiners *et al.* 2003). Over a 20-year follow-up, La Quaglia *et al.* (1988) observed few if any cause-specific deaths in pediatric patients with lung metastases, which contrasts favorably with the 30–60% 10-year mortality rate in their adult counterparts (Samaan *et al.* 1992, Casara *et al.* 1993a, Pacini *et al.* 1994a, Schlumberger *et al.* 1996a).

However, deeper inspection of the published data leads to the conclusions that long survival in radioiodine-treated children with DTC lung metastases is often unaccompanied by complete remission, and that persistent or recurrent disease can be lethal (Vassilopoulou-Sellin *et al.* 1998, Vassilopoulou-Sellin 2001). La Quaglia *et al.* (1988) noted a 31% locoregional or lung progression rate after a median 10-year follow-up among children given radioiodine for DTC lung metastases. In another large series, Reiners *et al.* (2002) noted complete remission in only 27% of children (26/95) with radiation-induced DTC, while elevated Tg levels persisted despite scintigraphic remission, albeit without clinical progression, in 37% (35/95). Other investigators (La Quaglia *et al.* 2000, Vassilopoulou-Sellin 2001), and we, have found similarly high prevalence of persistent disease in pediatric patients administered ^{131}I for DTC lung metastases. In one series, such persistent disease caused six deaths at ages 10–52 years among 112 patients (Vassilopoulou-Sellin 2001). The implication is that clinicians should avoid under-treatment of children with pulmonary DTC, notwithstanding justified optimism over their general prognosis. Hence repeated treatments are often appropriate to optimize response in children with lung foci.

It clearly would be desirable to have prospective evidence that children with DTC lung metastases have longer survival, better pulmonary function, or both with than without radioiodine. Unfortunately, lung function is only rarely determined in these patients (Ceccarelli *et al.* 1988, Samuel *et al.* 1998). Nonetheless, the survival and even response data described above do not in our opinion admit omitting ^{131}I treatment of functional lung metastases, even if anecdotal observations exist of very long survival in a few untreated affected children (Brink *et al.* 2000).

A common dilemma over the indication for radioiodine treatment arises when serum Tg levels are elevated, but the patient remains asymptomatic and all available imaging procedures have failed to localize the putative disease foci (Schlumberger *et al.* 1997, van Tol *et al.* 2003). This situation occurs in 10–15% of DTC patients, children included, and with respect to adults,

has occasioned very intense controversy (McDougall 1997, Fatourehchi *et al.* 2002, Britton *et al.* 2003). Koh *et al.* (2003) recently compared two non-randomized groups of adults with elevated serum Tg but no abnormal foci of ^{131}I uptake on diagnostic WBS, one group ($n = 28$) given ^{131}I treatment and the other ($n = 32$) untreated. Changes in Tg level did not significantly differ between groups. Nevertheless, the authors supported radioiodine administration in these cases, stressing that foci of uptake were localized by post-therapy WBS in 43% of treated patients. Of greater interest in our view, the post-therapy WBS indicated further ^{131}I therapy in only two cases (7%), in both of whom multiple lung metastases were detected; in the majority of other patients, this scan served merely to detect locoregional foci to be treated surgically. We have noted that a rising serum Tg level in children is most often the first sign of lymph node recurrence, which requires operation, not radioiodine. Attempts should be made to localize such recurrences by sonography and fine needle biopsy before turning to ^{131}I treatment (Antonelli *et al.* 2003).

Our experience in adults speaks for limited use of radioiodine treatment in asymptomatic hyperthyroglobulinemia — if post-therapy WBS is negative or shows only operable foci, we discontinue ^{131}I . We do likewise when scintigraphic remission is obtained, serum Tg decreases or even normalizes, but the lungs remain radiographically abnormal. In absence of size increase, no sure criterion exists to distinguish metastases that have lost functionality due to DTC progression from those that presumably have been rendered metabolically inactive and clinically stable by radioiodine therapy. The strategy of discontinuing ^{131}I treatment of lesions in which proliferation potential has been destroyed seems particularly important in children, in whom every unreasonable use of ionizing radiation should be avoided. Additional reasons for this strategy are the potential for the radioisotope to induce de-differentiation or for TSH increase to accelerate tumor growth. These issues have been raised mostly regarding DTC patients >45 years of age, but may well affect younger patients (Sera *et al.* 2000). However, Schaap *et al.* (2002), who specifically addressed this question, reported no such disadvantageous effects in adult patients.

Endogenous and recombinant human TSH in radioiodine therapy

TSH stimulation is required to increase NIS expression by healthy or malignant thyroid cells, the most important factor for successful radioiodine uptake

(Kogai *et al.* 1997, Castro *et al.* 2001). TSH elevations ≥ 25 or 30 mIU/l are considered necessary to provide sufficient TSH stimulation (Schlumberger 1998). Until recently, TSH stimulation usually has been attained by a 4–5 week T_4 withdrawal, often with a mixed regime including 2–3 weeks of triiodothyronine (T_3) and then 2 weeks of full thyroid hormone cessation. However, such protocols often lead to symptomatic hypothyroidism resulting in debilitation, discomfort, inability to perform activities of daily living, missed or unproductive work or study (Dow *et al.* 1997, Nijhuis *et al.* 1999, Haugen *et al.* 2002), or decreased compliance with follow-up protocols (Cohen *et al.* 2004b). In addition, prolonged hypothyroidism is related to risks of exacerbating concomitant illnesses or stimulating tumor growth, sometimes causing complications in confined anatomical spaces (Jarzab *et al.* 2003, Luster *et al.* 2005).

Use of rhTSH to provide TSH stimulation exogenously avoids many of these drawbacks (Haugen *et al.* 2002, Pacini *et al.* 2004). Based on multicenter prospective studies (Ladenson *et al.* 1997, Haugen *et al.* 1999, Haugen *et al.* 2002, Pacini *et al.* 2004), rhTSH was licensed in Europe as an adjunct to diagnostic WBS or serum Tg testing in 1999 and to radioiodine ablation in early 2005, in the US, it is licensed only in the diagnostic setting. However, in both settings, the licensing covers only adults (age ≥ 18 years), thus rhTSH administration in children is ‘off-label.’ This is probably due to the lack of pediatric patients in reported series (Luster *et al.* 2003) — to our knowledge, the youngest published rhTSH ablation patient was age 17 years. In adults, the recommended regimen is two consecutive daily intramuscular injections of 0.9 mg, followed by the ablative radioiodine activity 24 h later.

The multicenter ablation study (Pacini *et al.* 2004, Ladenson *et al.* 2004) randomized 30 patients to conventional thyroid hormone withdrawal and 33 to rhTSH administration before radioiodine ablation with an activity of 3.7 GBq (100 mCi). One hundred percent of both groups had successful ablation defined by thyroid bed uptake $<0.1\%$ on an rhTSH-aided diagnostic WBS ~ 8 months later, while 96% of evaluable rhTSH patients and 86% of evaluable withdrawal patients had successful ablation defined as rhTSH-stimulated Tg <2 ng/ml at the same time. The rhTSH group had significantly fewer hypothyroid symptoms and better quality of life, as measured by the Billewicz scoring system and Short Form-36 instrument respectively.

In addition to the multicenter study, at least 180 patients have received rhTSH-aided ablation in

open-label studies, some 140 while on thyroid hormone (Luster *et al.* 2005). In this experience, rhTSH-aided ablation using ^{131}I activities ≥ 3.7 GBq (100 mCi) has been overwhelmingly successful, however, results have been more mixed when 1.11 GBq (30 mCi) activities were employed. A prospective study at the University of Pisa (Pacini *et al.* 2002) found significantly lower ablation success rates in the rhTSH group than in the withdrawal or withdrawal+rhTSH groups (54% vs 84% vs 79% respectively, $P < 0.01$, rhTSH vs other groups). Success was defined as absence of visible thyroid bed uptake on a withdrawal-aided diagnostic WBS 6–10 months after the procedure. When success was defined as absent uptake or undetectable serum Tg, the success rates were 74% in the rhTSH group, 88% in the withdrawal group, and 95% in the withdrawal+rhTSH group (significance not reported). The results of the Pisa study may have been influenced by the fact that the study design included uptake measurements. Therefore the rhTSH groups received radioiodine 48 or 72 h after the last rhTSH injection, when serum TSH levels were declining rapidly, instead of at 24 h after the last injection (Luster *et al.* 2005).

Although not approved by European or American regulatory authorities for that purpose, rhTSH also may be considered as an adjunct to radioiodine treatment of local and, especially, metastatic DTC (Jarzab *et al.* 2003, Luster *et al.* 2005). The rhTSH-aided treatment experience published to date encompasses at least 216 patients and 266 courses, including individual activities from 1–19 GBq (27–515 mCi) and up to 6 courses (Luster *et al.* 2005). The bulk of these patients have been elderly, and only a very few juvenile patients, the youngest, to our knowledge, age 14 years, have been reported.

We have some experience with rhTSH-aided radioiodine therapy in children with DTC, as to date, we have conducted 11 therapies in six patients <18 years old (range 6–16 years, mean 13 years) after rhTSH administration. Four children received rhTSH-aided therapy once, and two, multiple times (two and five courses respectively). Indications for rhTSH were very severe hypothyroidism on previous withdrawal, suspected central nervous system metastases, or desire to decrease the whole-body radiation dose in one course each, and desire to avoid advanced DTC progression due to protracted endogenous TSH stimulation in the other courses.

rhTSH dosing was not adjusted for body weight or surface area, although some reports indicate this might be appropriate (Vitale 2003). Serum TSH levels peaked on day 3, when radioiodine was administered,

and averaged 200 ± 66 mIU/l (range 128–289 mIU/l) then, falling to a mean 4.4 ± 2.7 mIU/l on day 6. Free T_3 and free T_4 levels remained stable and a nearly ten-fold rise in serum Tg was observed on average, from 35.3 ng/ml (range, 0.2–279 ng/ml) immediately before rhTSH administration to 312.4 ng/ml (range, 0.3–1080 ng/ml) on day 6.

Two of the six patients received rhTSH-aided radioiodine therapy primarily for thyroid remnant ablation. In one of the two, brain metastases were suspected at the time of primary treatment, but excluded in further observation. The second patient exhibited not only thyroid bed but also mediastinal radioiodine uptake on post-therapy scan and was subsequently retreated on withdrawal. Both are now in remission.

The remaining four children were treated for pulmonary metastases, in one case accompanied by a mediastinal lymph node lesion. The post-therapy scan showed radioiodine uptake in metastatic lesions in three of the four, in one case, however, only after experimental retinoic acid pretreatment. This was a very rare instance of primarily non-functional lung metastases occurring in a young patient (Jarzab *et al.* 2003), in whom no progression has been observed post therapy. Two patients responded with distinct regression of metastatic foci. The fourth patient exhibited no radioiodine uptake on the post-therapy WBS which, in view of other examinations (serum Tg, chest CT) was interpreted as a proof of complete remission obtained by previous withdrawal-aided treatment.

No side effects were noted during the 11 courses of rhTSH-aided radioiodine therapy at our center, with the exception of a mild, transient skin rash seen in a patient who received her second rhTSH course. In the published experience, rhTSH also has generally been safe, with usually mild–moderate transient nausea or headache the most common side effects ($\leq 10\%$ incidence). However, a potential issue with any form of TSH elevation in patients with known or suspected lesions in confined spaces is the possibility of transient edematous or hemorrhagic tumor expansion or tumor growth and resultant compressive neurological, respiratory or other clinical complications (Vargas *et al.* 1999, Goffman *et al.* 2003, Powers *et al.* 2003a). Thus in such patients, glucocorticoid administration and caution are recommended when TSH elevation is induced. Particular care should be taken in patients with known or suspected central nervous system or spinal metastases or bulky neck lesions impairing poor pulmonary reserve. In addition, patients with osseous lesions may suffer transient bone pain

exacerbation, possibly due to tumor swelling (Lippi *et al.* 2001, Jarzab *et al.* 2003).

A potential benefit of rhTSH stimulation of radioiodine therapy is the decreased radiation burden to healthy tissues, due at least in part to better kidney function and twice as fast renal radioiodine clearance when patients remain euthyroid (Park *et al.* 1996, Ladenson *et al.* 1997). In the multicenter ablation study, patients given rhTSH had a one-third lower blood radiation dose than those undergoing withdrawal (Pacini *et al.* 2004); other investigators have reported similar observations (de Keizer *et al.* 2004). This safety benefit will be especially important in children. Simultaneously, any potential diminished efficacy because of a decreased pool of circulating radioiodine available for uptake by healthy or malignant thyroid cells may be less important in children due to the relatively high radioiodine sensitivity of their DTC cells (Reynolds & Robbins 1997, Hung & Sarlis 2002).

A potential issue regarding rhTSH-aided radioiodine therapy is possible iodine contamination from continued thyroid hormone, the subject of recent speculation (Massin *et al.* 1984, de Keizer *et al.* 2004). To avoid this possibility, a small study (Barbaro *et al.* 2003) used a 4-day ‘mini-withdrawal’ around administration of 30 mCi of ^{131}I . The study found that a rhTSH + ‘mini-withdrawal’ group ($n = 16$) had a numerically higher rate of ablation success, determined by rhTSH-aided diagnostic WBS and serum Tg testing 1 year after the procedure, than did a conventional withdrawal group ($n = 24$) (88 vs 75%). No hypothyroidism would be expected to develop during such a short withdrawal.

Potential safety considerations with radioiodine therapy in children

In children as in adults, potential safety risks of radioiodine therapy include short-term toxicity to healthy tissues, as well as longer-term unfavorable reproductive outcomes, carcinogenic consequences or pulmonary fibrosis. The early side effects of nausea and vomiting are clearly more frequent in children than in adults. Nausea is estimated to occur in ~30% of adults (Van Nostrand *et al.* 2002), but in our experience, is a rule in the youngest children. Similarly, vomiting is rare (<5%) in adults, while frequent, but not severe or hard to relieve pharmacologically, in children (de Keizer *et al.* 2004). Mild, transient neck pain and edema also are not uncommon, especially when radioiodine is applied after less than total

thyroidectomy, and are ameliorated by non-steroidal anti-inflammatory agents or corticosteroids. Among later side effects is impaired salivary gland function (<5% incidence), sometimes with subsequent xerostomia; however, sialadenitis is avoidable by administration of large amounts of sour liquids during therapy, increasing salivary ^{131}I clearance (Van Nostrand *et al.* 2002, Mandel & Mandel 2003). Another later side effect is transient bone marrow suppression (25% incidence), with leukocyte and/or, more often, platelet count nadirs 1–2 months post-radioiodine administration (Van Nostrand *et al.* 2002, de Keizer *et al.* 2004). Usually, the suppression resolves without therapy or clinical consequence and fatal cases have not been reported in the last 20 years. Nasolacrimal obstruction, appearing a mean 6.5 ± 1.4 months after the last ^{131}I activity, and potentially affecting 3.4% or more of patients receiving radioiodine, has been described only recently (Kloos *et al.* 2002, Burns *et al.* 2004). This obstruction results in tearing and may be treated by minor surgery.

The possibility of radioiodine-related unfavorable reproductive outcomes, namely, miscarriage, impaired fertility, or genetic damage leading to congenital malformation and malignancies, has been of concern. However, to date, no study has found a statistically significant association between ^{131}I exposure and unfavorable pregnancy outcome (LiVolsi *et al.* 1978, Casara *et al.* 1993b, Lin *et al.* 1998). The largest study (Schlumberger *et al.* 1996b) found that the miscarriage rate increased slightly after surgery, but did not vary before or after radioiodine (11% vs 20% vs 20% respectively) or with greater cumulative ^{131}I activities. No heightened risk of infertility, early menopause or congenital malformations in offspring were seen at the Royal Marsden Hospital (Vini *et al.* 2002) during a 20-year follow-up of 333 adult DTC patients age <40 years. However, other investigators have observed that precocious menopause may be a late consequence of ^{131}I treatment (Ceccarelli *et al.* 2001). Chow *et al.* (2004b) recently described more than 250 pregnancies in 104 female DTC patients and also concluded that ^{131}I therapy in young women does not hamper pregnancy outcome. However, these investigators noted some increase in the rate of preterm delivery — 16% in patients who received therapeutic ^{131}I , vs 9% in DTC patients who received only small ^{131}I activities for diagnostic scanning, and ~5% in the general population. The radiation dose to the male gonads was estimated at 5–30 cGy after administration of radioiodine during thyroid hormone withdrawal (Ceccarelli *et al.* 1999, Vini *et al.* 2002) and some transient gonadal effects of radioiodine therapy, i.e.,

oligospermia, increased follicle-stimulating hormone levels, etc., were noticeable (Pacini *et al.* 1994b, Vini *et al.* 2002, Mazzaferri 2002). In fact, the testis is even more sensitive to irradiation than is the ovary. The risk of permanent sterility increases with cumulative radioiodine activity, especially over 3.7 GBq (100 mCi), thus sperm banking in young men given repeated radioiodine activities may be prudent (Mazzaferri & Kloos 2001).

Regarding potential harmful effects of radioiodine therapy on reproduction, it should be recalled that ruling out pregnancy at each ^{131}I administration in young women is obligatory. Additionally, females of childbearing age should be instructed to avoid conception within one year after therapeutic ^{131}I , allowing for radioiodine clearance and repair of any transient post-radiation DNA damage while 6 months of contraception are sometimes recommended for male patients (Chow *et al.* 2004b).

Only rare reports exist on malignancy after therapeutic radioiodine use in children — Dottorini *et al.* (1997) described two cases, one each of breast and gastric cancer. However, studies of larger groups of DTC patients of all ages indicate an increased cancer risk due to radioiodine therapy, particularly in the salivary gland, colon and rectum, but also in soft tissue and bone (De Vathaire *et al.* 1997, Rubino *et al.* 2003, Berthe *et al.* 2004). In a European cohort of ~7000 DTC patients, among whom 62% were treated with radioiodine, a 27% risk increase for both solid tumors and leukemias was observed and, of special relevance, was related to the cumulative ^{131}I activity (Rubino *et al.* 2003).

Leukemia risk is the reason most authors advise not administering cumulative ^{131}I activities exceeding 37 GBq (1000 mCi) or, sometimes, 18.5 GBq (500 mCi), although these thresholds are rather arbitrarily chosen and consider mainly adults. Based on a recent estimate (Rubino *et al.* 2003), a 14-year-old treated with high cumulative activities has a 1–2% risk of secondary leukemia over a further lifespan of ~70 years.

Historically, the other frequently mentioned potential long-term side effect of radioiodine therapy is pulmonary fibrosis after treatment of functional lung metastases. This complication has been described principally in pre-1990 publications and carefully documented by Ceccarelli *et al.* (1988). Among recent pediatric reports, it was observed by Reiners *et al.* (2002), however, it is unclear whether these cases were attributable to radioiodine, because some children had been given bleomycin. Samuel *et al.* (1998) also were unable to completely separate between DTC-induced restrictive lung disease and radiation-induced effects. In general, pulmonary fibrosis seems to have affected

essentially only patients with very advanced lung disease and high ^{131}I lung uptake.

In conclusion, radioiodine therapy generally causes relatively mild short-term toxicity, and infrequent long-term toxicity, facilitating the modality's wide use in pediatric patients (Hung & Sarlis 2002). While the modality is not devoid of side effects, the important issue is to balance its benefits and risks, and we believe that doing so unequivocally speaks for radioiodine therapy in children with DTC.

Dosimetric considerations

To date, no consensus has been reached regarding the ^{131}I activities providing maximum efficacy with minimum toxicity for thyroid remnant ablation or treatment of functional DTC metastases. Two basic dosing strategies exist: fixed activity and dosimetry-based approaches.

To our knowledge, no prospective comparison of these strategies has been reported. However, the fixed activity approach is much more popular, particularly for ablation. This is because fixed activity administration is effective and relatively safe and avoids long, laborious dosimetric protocols, with which patient compliance is poor.

Fixed activity regimens are often incorrectly referred to as 'fixed dose regimens.' However, in radiation biology, the terms 'dose' or 'absorbed dose' are reserved to quantify ionizing energy absorbed by tissues, body compartments, or the entire body. The term 'activity' denotes the amount of radioactive isotope given to the patient. The absorbed dose is proportional to the ^{131}I activity administered, but also considerably influenced by the maximal uptake and effective half-life of ^{131}I in the particular tissue or compartment (Maxon 1999). In general, uptake is higher and half-life longer in healthy remnant than in tumor, and in more- versus less-differentiated tumor histotypes (Schlesinger *et al.* 1989), because of differences in expression of NIS and other proteins affecting iodide transport and organification.

Another, inversely proportional influence on the absorbed dose is the thyroid remnant or tumor mass (Reynolds 1993, Reynolds & Robbins 1997): when radioiodine uptake and effective half-life are constant, tumor volume increases and radiation dose decreases by the same factor. For example, given a 0.3% uptake and a 3-day effective half-life, 3.7 GBq (100 mCi) of ^{131}I delivers a dose of 150 Gy to a 1-ml focus, but only 5 Gy to a 30-ml tumor. However, this relationship is not valid in tumors <0.1–1 mm in diameter, because of issues relating to the ^{131}I beta radiation range.

In fixed activity regimens, a routine activity of ^{131}I , chosen based on institutional experience and the literature, is empirically given to all patients in a given category. For remnant ablation in adults, most centers use 3.7 GBq (100 mCi), many decide on 1.1 GBq (30 mCi), which has been suggested to be the lowest effective activity in this setting (Bal *et al.* 2004b), while others, including ours, chose intermediate activities like 2.2 GBq (60 mCi) (Leung *et al.* 1992, Reynolds & Robbins 1997, Mazzaferri & Massoll 2002, Pacini *et al.* 2002, Zidan *et al.* 2004).

Some centers (Schlumberger *et al.* 1987, Hung & Sarlis 2002) change this protocol for children by giving 3.7 MBq/kg (1 mCi/kg) of body weight (range 1.85–7.4 MBq/kg, equal to 0.5–2 mCi/kg). However, body weight-based formulas seem to produce rather low activities and body surface area-based formulas may be more appropriate. Extensively analyzing variable dosing issues in pediatric patients, Reynolds (1993) noted that red bone marrow absorbs a greater dose in children than in adults, since the same activity is distributed to smaller organs, and shorter distances between organs increase cross-radiation. According to his diagrams for calculating the appropriate activity, a 15-year-old should receive about 5/6 the adult activity. Younger children need further reductions, e.g., to 1/2 the adult activity in a 10-year-old and 1/3 in a 5-year-old.

A recent randomized, prospective study of 500 adults concluded that any activity between 0.925–1.85 GBq (25–50 mCi) appears to be adequate for remnant ablation (Bal *et al.* 2004b). However, the study evaluated only the efficacy of thyroid remnant destruction, not the impact on the detection and treatment of previously unknown micrometastases, or on recurrence rate or disease-free survival. In our opinion, the inclusion of these more clinically relevant variables as endpoints will enable more conclusive prospective trials.

Given the lower uptake and shorter retention of radioiodine in malignant thyroid tissue, higher activities usually are employed for treatment of metastases than for ablation. For example, a recent French cooperative study (Hindie *et al.* 2003) used 5.5 GBq (150 mCi) in adults. While evidence of disease persisted, this activity was re-administered every 6 months, until the cumulative activity reached 18.5 GBq (500 mCi), after which, treatment intervals were prolonged to 12 months. The range of fixed activities used to treat juvenile DTC metastases varies markedly. Brink *et al.* (2000) reported individual activities from 1.1 to 7.4 GBq (30–200 mCi) given for lung metastases, with a median cumulative activity of 15.9 GBq

(430 mCi) (range, 3.7–31.1 GBq, 100–840 mCi). Chow *et al.* (2004a) applied 5.6 GBq (150 mCi), Schlumberger *et al.* (1987), 3.7 MBq/kg (1 mCi/kg), or 0.9–2.8 GBq (25–75 mCi) in total per course. We give 2–2.5 mCi/kg, which corresponds to 1.9–2.2 GBq (50–60 mCi) in younger children and fixed activities of 3.7 GBq (100 mCi) in adolescents.

Dosimetry-based protocols (Reynolds & Robbins 1997, Maxon 1999, Van Nostrand *et al.* 2002, Murbeth *et al.* 2004, Sgouros *et al.* 2004) entail administration of a diagnostic activity of ^{131}I and usually multiple measurements during the 4–5 days afterwards to estimate the maximal radioiodine uptake and effective half-life in the tissue or body compartment of interest. Much care is necessary to avoid errors (Van Nostrand *et al.* 2002).

Traditionally, two main types of dosimetry-based protocols have been employed: 1) remnant or lesion (tumor), or 2) radiation safety ('safety margin') dosimetry. With remnant or lesion dosimetry, the uptake and half-life estimates and target tissue volume measurements are used to calculate the activity that will deliver a dose considered sufficient to eradicate the remnant or tumor (Maxon 1999, Sisson *et al.* 2003, Schneider *et al.* 2004). To ablate thyroid remnants, the generally accepted minimum effective absorbed dose is 300 Gy, which is easily obtained in a totally- or near-totally-thyroidectomized patient (Reynolds & Robbins 1997), even with the lowest commonly used fixed activity, 1.1 GBq (30 mCi). To eradicate neck lymph node metastases, it is known from the excellent studies of Maxon *et al.* (1999) that doses >80 Gy are sufficient, and <35 Gy ineffective. No consensus exists regarding the minimum effective dose to destroy lung or other metastases. Samuel *et al.* (1998) presented interesting data from 14 children on the correlation between the pulmonary radiation dose, calculated using the MIRD formula, and pulmonary metastases' response to treatment, measured by chest radiography, scintigraphy, and serum Tg levels. There was wide variation in radioiodine uptake (2.7–49.4%), effective half life (8.1–120 h), pulmonary radiation dose (0.5–47 Gy) after the first treatment, and cumulative pulmonary dose after the most recent treatment (0.5–75 Gy). However, no clear dose–response relationship was noticeable, perhaps because pulmonary instead of tumor dose was measured. Consensus holds that absorbed doses <5–10 Gy/lesion generally have little if any therapeutic impact on tumor foci (Maxon 1999).

It is worth emphasizing here that the dose–response relationship of DTC to ^{131}I treatment has been much less thoroughly analyzed than that of other cancers to

external beam therapy (Suwinski & Gawkowska-Suwinska 2001). Also, the dose rate in radioiodine therapy deserves much more attention, because at <0.6 Gy/h, more and more sublethal cell damage may be repaired (Van Nostrand *et al.* 2002).

For two reasons, remnant dosimetry is far more often performed than is lesion dosimetry. First, uptake measurement is much more challenging and error-prone in tumors than in remnants. Second, multiple tumor foci create an additional level of difficulty and often render impossible the estimation of tumor mass, e.g., with miliary lung metastases. Some investigators propose arbitrarily assigning masses of 10 g to lung micrometastases not visible on plain radiography and 50 g to those barely visible (Maxon 1999).

As tumor dose determination is very difficult and even when accurate, may not predict the final therapeutic effect (Samuel *et al.* 1998), many centers choose another approach, so-called 'safety margin' dosimetry (Ringel & Ladenson 2004). This approach seeks to calculate the maximum ^{131}I activity that will not permanently harm healthy tissues (Reynolds & Robbins 1997, Dorn *et al.* 2003, de Keizer *et al.* 2003, 2004), following the old rule that the first doses of ionizing energy supplied by ^{131}I treatment have the best chance to kill cancer, and thus, should be as high as possible (Beierwaltes 1978). The MIRD formula (1988, Zanzonico 2000) is used to estimate the dose that would be absorbed by the bone marrow, the blood as its surrogate, extra-thyroidal tissues, or the whole body, and to select the administered activity accordingly (Menzel *et al.* 1996, Dorn *et al.* 2003).

The threshold dose to the bone marrow or blood, beyond which harm to the marrow ensues, is rather arbitrarily accepted as 2 Gy (Maxon 1999). To avoid pulmonary fibrosis when treating DTC lung metastases, 48-h whole body-retained activity should not exceed 2.96 GBq (80 mCi) without or 4.44 GBq (120 mCi) with dosimetry (Van Nostrand *et al.* 2002). These recommended thresholds have been little investigated in children.

Other issues: thyroid 'stunning' and low-iodine diets

Another issue related to radioiodine therapy is thyroid 'stunning' (Morris *et al.* 2003) discussed mostly regarding remnant ablation (Reynolds & Robbins 1997, Maxon 1999, Karam *et al.* 2003). Thyroid stunning occurs when a diagnostic ^{131}I activity decreases the uptake, and thus the efficacy, of a subsequent ablative activity (Dam *et al.* 2004). This phenomenon has

often been analyzed but, to our knowledge, never specifically in children. Also, not all studies confirm clinically relevant stunning. For example, Morris *et al.* (2001a), using diagnostic activities of 111–185 MBq (3–5 mCi), saw no difference in ablation success rates in patients who received a diagnostic scan and those who didn't. A recent retrospective study (Dam *et al.* 2004) observed no effect of stunning, defined as decreased activity on the post-ablation vs the diagnostic scan, on ablation or treatment efficacy, defined as no uptake on a follow-up diagnostic scan. In this 166-patient study using a diagnostic activity of 185 MBq (5 mCi) of ^{131}I , stunning was seen in 18.7% of patients. Also Lassmann *et al.* (2004) observed a mean reduction of 40% and 25% respectively in uptake and residence time after a diagnostic activity of 74 MBq. On the other hand, other authors note differences in stunning intensity related to the diagnostic activity. Muratet *et al.* (1998) reported a better ablation success rate in patients diagnostically scanned with 37 MBq (1 mCi) than with 111 MBq (3 mCi). Certain authors question the existence of stunning and speak rather about a therapeutic effect of even small, diagnostic radioiodine activities (Bajen *et al.* 2000, Luster *et al.* 2003).

Some investigators avoid possible stunning by choosing ^{123}I instead of ^{131}I for diagnostic WBS (Mandel *et al.* 2001, Geus-Oei *et al.* 2002, Gerard & Cavalieri 2002, Sarkar *et al.* 2002, Cohen *et al.* 2004a). ^{123}I seems more appropriate for children, as the radiation burden is smaller and the scan quality better. However, with the isotope's shorter half-life, ^{123}I WBS may miss a delayed uptake in distant metastases.

A second issue related to radioiodine therapy is the use of a low-iodine diet in the 2 weeks before ^{131}I administration, which augments both radioiodine uptake and effective half-life, increasing the thyroid tissue radiation dose by ~50–150% (Pluijmen *et al.* 2003). A stringent low-iodine diet was shown to significantly improve ablation success rates in Dutch DTC patients (Pluijmen *et al.* 2003), although this effect was not observed in an American study comparing the stringent diet to a regular diet plus instruction to avoid salt, seafood, and iodine-containing multivitamins (Morris *et al.* 2001b). Moreover, both these studies involved only adults, so the benefits of a low-iodine diet in children remain unconfirmed. Nonetheless, based on the adult experience, some centers prescribe the low-iodine diet for children (Antonelli *et al.* 2003). Other centers are less stringent, especially when the compliance in children may be much poorer than in adults.

Future directions and current recommendations

We believe that two research agendas should be pursued to provide better guidelines for the appropriate primary treatment intensity for individual cases of pediatric DTC. First, one or more prospective trials should be conducted comparing conservative vs intensive primary treatment. We earlier in this review, have argued the appropriateness, and Dragoiescu *et al.* (2003) recently have shown the feasibility, of conducting studies using recurrence rate or RFS as primary endpoints. Insofar as allowed by sample size requirements and ethical concerns, a multifactorial study design comparing several combinations of conservative vs intensive surgical, ablative, and THST options would be ideal. A multicenter trial would have the advantages of increasing sample size, widening relevance to more practice conditions, and overcoming the issue of a center convinced that its approach is optimal being unwilling for ethical reasons to study another approach (albeit confining treatment groups to particular centers would impair true randomization). In any event, some form(s) of prospective primary treatment study should be undertaken.

The second research agenda should focus on identifying molecular signatures of pediatric DTC recurrence, metastasis and mortality risk. These signatures could result from DNA microarray based gene expression profile studies (Huang *et al.* 2001, Wasenius *et al.* 2003, Finley *et al.* 2004, Jarzab *et al.* 2005) or future proteomic research.

It is possible that with sufficient follow-up of current patients diagnosed in the era of sonography, CT, and rhTSH-aided Tg testing, the future pediatric outcomes literature will convey a different message. Meanwhile, we believe that decision-making should rely most closely on the recent pediatric outcomes literature (Landier *et al.* 2004). The reported experience clearly indicates that: 1) children with DTC have an elevated risk of more advanced disease at diagnosis; 2) such children also have an elevated risk of persistent or recurrent disease; 3) intensive primary treatment including total thyroidectomy, appropriate lymph node resection, and radioiodine ablation significantly increases RFS and may increase overall survival; 4) as Clark (1982) has pointed out, only sufficiently radical primary treatment changes DTC from a disease with a relatively good prognosis into one that is curable; 5) a conservative approach is no more beneficial than an intensive approach. If an intensive approach is not fully supported by published experience, this should not be an argument for implementation of another, at

least equally unsupported approach. This applies particularly to omission vs inclusion of ^{131}I therapy, because its short- and long-term side effects definitely are of low impact on quality or duration of life.

In conclusion, we therefore advocate total thyroidectomy and central lymphadenectomy, with modified lateral lymphadenectomy in case of biopsy-proven metastases, followed by radioiodine ablation for all juvenile patients, except those with no or low (e.g., <0.4%) thyroid remnant radioiodine uptake and undetectable or low stimulated Tg values post-thyroidectomy. Inoperable functional metastases should continue to be treated with radioiodine. Use of rhTSH as a radioiodine therapy preparation method spares patients symptomatic hypothyroidism and its attendant drawbacks, and may decrease radiation burden to healthy tissues, thus, further studies evaluating its safety and effectiveness in comparison to classic withdrawal-aided therapy are warranted. All care of pediatric DTC should be delivered by multidisciplinary specialized teams which include both pediatricians and thyroid cancer specialists to minimize possible complications and ensure competent follow-up.

Acknowledgements

The authors thank Robert J Marlowe for editorial assistance, provided under an unrestricted educational grant from Genzyme Europe BV (Naarden, The Netherlands), Aleksandra Wrobel for literature search assistance, and Emilia Wilk for excellent general assistance. The authors declare that there is no conflict of interest.

References

- MIRD primer for absorbed dose calculations 1988 New York, The Society of Nuclear Medicine.
- 2001a Polish guidelines [Diagnosis and treatment of malignant thyroid neoplasms. Recommendations of the Scientific Committee of the 2nd Scientific Conference 'Thyroid Carcinoma 2000']. *Wiadomosci Lekarskie* **54** (Suppl 1) 443–461.
- 2001b AACE/AAES medical/surgical guidelines for clinical practice: management of thyroid carcinoma. American Association of Clinical Endocrinologists. American College of Endocrinology. *Endocrine Practice* **7** 202–220.
- 2003 EANM procedure guidelines for therapy with iodine-131. *European Journal of Nuclear Medicine and Molecular Imaging* **30** BP27–BP31.
- Acharya S, Sarafoglou K, LaQuaglia M, Lindsley S, Gerald W, Wollner N, Tan C & Sklar C 2003 Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. *Cancer* **97** 2397–2403.

- Alessandri AJ, Goddard KJ, Blair GK, Fryer CJ & Schultz KR 2000 Age is the major determinant of recurrence in pediatric differentiated thyroid carcinoma. *Medical and Pediatric Oncology* **35** 41–46.
- Antonelli A, Miccoli P, Fallahi P, Grosso M, Nesti C, Spinelli C & Ferrannini E 2003 Role of neck ultrasonography in the follow-up of children operated on for thyroid papillary cancer. *Thyroid* **13** 479–484.
- Bajen MT, Mane S, Munoz A & Garcia JR 2000 Effect of a diagnostic dose of 185 MBq ¹³¹I on postsurgical thyroid remnants. *Journal of Nuclear Medicine* **41** 2038–2042.
- Bal CS, Kumar A, Chandra P, Dwivedi SN & Mukhopadhyaya S 2004a Is chest x-ray or high-resolution computed tomography scan of the chest sufficient investigation to detect pulmonary metastasis in pediatric differentiated thyroid cancer? *Thyroid* **14** 217–225.
- Bal CS, Kumar A & Pant GS 2004b Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. *Journal of Clinical Endocrinology and Metabolism* **89** 1666–1673.
- Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P, Pasquini C, Piazza F, Caciagli M & Mariani G 2003 Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. *Journal of Clinical Endocrinology and Metabolism* **88** 4110–4115.
- Basolo F, Molinaro E, Agate L, Pinchera A, Pollina L, Chiappetta G, Monaco C, Santoro M, Fusco A, Miccoli P et al. 2001 RET protein expression has no prognostic impact on the long-term outcome of papillary thyroid carcinoma. *European Journal of Endocrinology/European Federation of Endocrine Societies* **145** 599–604.
- Beierwaltes WH 1978 The treatment of thyroid carcinoma with radioactive iodine. *Seminars in Nuclear Medicine* **8** 79–94.
- Bernstein L & Gurney J 1999 Carcinomas and other malignant epithelial neoplasms. In *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995*, pp 139–148. Cancer Statistics Branch, National Cancer Institute, Bethesda, MD.
- Berthe E, Henry-Amar M, Michels JJ, Rame JP, Berthet P, Babin E, Icard P, Samama G, Galateau-Salle F, Mahoudeau J et al. 2004 Risk of second primary cancer following differentiated thyroid cancer. *European Journal of Nuclear Medicine and Molecular Imaging* **31** 685–691.
- Bingol-Kologlu M, Tanyel FC, Senocak ME, Buyukpamukcu N & Hicsonmez A 2000 Surgical treatment of differentiated thyroid carcinoma in children. *European Journal of Pediatric Surgery* **10** 347–352.
- Biondi B, Fazio S, Carella C, Amato G, Cittadini A, Lupoli G, Sacca L, Bellastella A & Lombardi G 1993 Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. *Journal of Clinical Endocrinology and Metabolism* **77** 334–338.
- Black P, Straaten A & Gutjahr P 1998 Secondary thyroid carcinoma after treatment for childhood cancer. *Medical and Pediatric Oncology* **31** 91–95.
- Blatt J, Olshan A, Gula MJ, Dickman PS & Zaranek B 1992 Second malignancies in very-long-term survivors of childhood cancer. *American Journal of Medicine* **93** 57–60.
- Bongarzone I, Fugazzola L, Vigneri P, Mariani L, Mondellini P, Pacini F, Basolo F, Pinchera A, Pilotti S & Pierotti MA 1996 Age-related activation of the tyrosine kinase receptor protooncogenes RET and NTRK1 in papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **81** 2006–2009.
- Bongarzone I, Vigneri P, Mariani L, Collini P, Pilotti S & Pierotti MA 1998 RET/NTRK1 rearrangements in thyroid gland tumors of the papillary carcinoma family: correlation with clinicopathological features. *Clinical Cancer Research* **4** 223–228.
- Borson-Chazot F, Causeret S, Lifante JC, Augros M, Berger N & Peix JL 2004 Predictive factors for recurrence from a series of 74 children and adolescents with differentiated thyroid cancer. *World Journal of Surgery* **28** 1088–1092.
- Botella-Carretero JI, Gomez-Bueno M, Barrios V, Caballero C, Garcia-Robles R, Sancho J & Escobar-Morreale HF 2004 Chronic thyrotropin-suppressive therapy with levothyroxine and short-term overt hypothyroidism after thyroxine withdrawal are associated with undesirable cardiovascular effects in patients with differentiated thyroid carcinoma. *Endocrine Related Cancer* **11** 345–356.
- Boyd CM & Baker JR Jr 1996 The immunology of thyroid cancer. *Endocrinology and Metabolism Clinics of North America* **25** 159–179.
- Brink JS, van Heerden JA, McIver B, Salomao DR, Farley DR, Grant CS, Thompson GB, Zimmerman D & Hay ID 2000 Papillary thyroid cancer with pulmonary metastases in children: long-term prognosis. *Surgery* **128** 881–886.
- Britton KE, Foley RR & Chew SL 2003 Should high hTg levels in the absence of iodine uptake be treated? *European Journal of Nuclear Medicine and Molecular Imaging* **30** 794–795.
- Burns JA, Morgenstern KE, Cahill KV, Foster JA, Jhiang SM & Kloos RT 2004 Nasolacrimal obstruction secondary to I(131) therapy. *Ophthalmic Plastic and Reconstructive Surgery* **20** 126–129.
- Cady B 1998 Presidential address: beyond risk groups—a new look at differentiated thyroid cancer. *Surgery* **124** 947–957.
- Casara D, Rubello D, Saladini G, Masarotto G, Favero A, Girelli ME & Busnardo B 1993a Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. *Journal of Nuclear Medicine* **34** 1626–1631.
- Casara D, Rubello D, Saladini G, Piotto A, Pelizzo MR, Girelli ME & Busnardo B 1993b Pregnancy after high therapeutic doses of iodine-131 in differentiated thyroid

- cancer: potential risks and recommendations. *European Journal of Nuclear Medicine* **20** 192–194.
- Castro MR, Bergert ER, Goellner JR, Hay ID & Morris JC 2001 Immunohistochemical analysis of sodium iodide symporter expression in metastatic differentiated thyroid cancer: correlation with radioiodine uptake. *Journal of Clinical Endocrinology and Metabolism* **86** 5627–5632.
- Catelinois O, Verger P, Colonna M, Rogel A, Hemon D & Tirmarche M 2004 Projecting the time trend of thyroid cancers: its impact on assessment of radiation-induced cancer risks. *Health Physics* **87** 606–614.
- Causeret S, Lifante JC, Borson-Chazot F, Varcus F, Berger N & Peix JL 2004 Differentiated thyroid carcinoma in children and adolescents: therapeutic strategy according to clinical presentation. *Annales de Chirurgie* **129** 359–364.
- Ceccarelli C, Battisti P, Gasperi M, Fantuzzi E, Pacini F, Gualdrini G, Pierantoni MC, Luciani A, Djokich D & Pinchera A 1999 Radiation dose to the testes after ¹³¹I therapy for ablation of postsurgical thyroid remnants in patients with differentiated thyroid cancer. *Journal of Nuclear Medicine* **40** 1716–1721.
- Ceccarelli C, Bencivelli W, Morciano D, Pinchera A & Pacini F 2001 ¹³¹I therapy for differentiated thyroid cancer leads to an earlier onset of menopause: results of a retrospective study. *Journal of Clinical Endocrinology and Metabolism* **86** 3512–3515.
- Ceccarelli C, Pacini F, Lippi F, Elisei R, Arganini M, Miccoli P & Pinchera A 1988 Thyroid cancer in children and adolescents. *Surgery* **104** 1143–1148.
- Chow SM, Law SC, Mendenhall WM, Au SK, Yau S, Mang O & Lau WH 2004a Differentiated thyroid carcinoma in childhood and adolescence-clinical course and role of radioiodine. *Pediatric Blood and Cancer* **42** 176–183.
- Chow SM, Yau S, Lee SH, Leung WM & Law SC 2004b Pregnancy outcome after diagnosis of differentiated thyroid carcinoma: no deleterious effect after radioactive iodine treatment. *International Journal of Radiation Oncology, Biology, Physics* **59** 992–1000.
- Clark OH 1982 Total thyroidectomy: the treatment of choice for patients with differentiated thyroid cancer. *Annals of Surgery* **196** 361–370.
- Cohen JB, Kalinyak JE & McDougall IR 2004a Clinical implications of the differences between diagnostic ¹²³I and post-therapy ¹³¹I scans. *Nuclear Medicine Communications* **25** 129–134.
- Cohen O, Dabhi S, Karasik A & Zila ZS 2004b Compliance with follow-up and the informative value of diagnostic whole-body scan in patients with differentiated thyroid carcinoma given recombinant human TSH. *European Journal of Endocrinology/European Federation of Endocrine Societies* **150** 285–290.
- Dam HQ, Kim SM, Lin HC & Intenzo CM 2004 ¹³¹I therapeutic efficacy is not influenced by stunning after diagnostic whole-body scanning. *Radiology* **232** 527–533.
- Danese D, Gardini A, Farsetti A, Sciacchitano S, Andreoli M & Pontecorvi A 1997 Thyroid carcinoma in children and adolescents. *European Journal of Pediatrics* **156** 190–194.
- De Vathaire F, Hardiman C, Shamsaldin A, Campbell S, Grimaud E, Hawkins M, Raquin M, Oberlin O, Diallo I, Zucker JM *et al.* 1999 Thyroid carcinomas after irradiation for a first cancer during childhood. *Archives of Internal Medicine* **159** 2713–2719.
- De Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, de la GE, Meunier F, Parmentier C, Hill C & Sancho-Garnier H 1997 Leukaemias and cancers following iodine-¹³¹ administration for thyroid cancer. *British Journal of Cancer* **75** 734–739.
- DeGroot LJ, Kaplan EL, McCormick M & Straus FH 1990 Natural history, treatment, and course of papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **71** 414–424.
- DeGroot LJ, Kaplan EL, Straus FH & Shukla MS 1994 Does the method of management of papillary thyroid carcinoma make a difference in outcome? *World Journal of Surgery* **18** 123–130.
- Dorn R, Kopp J, Vogt H, Heidenreich P, Carroll RG & Gulec SA 2003 Dosimetry-guided radioactive iodine treatment in patients with metastatic differentiated thyroid cancer: largest safe dose using a risk-adapted approach. *Journal of Nuclear Medicine* **44** 451–456.
- Dottorini ME, Vignati A, Mazzucchelli L, Lomuscio G & Colombo L 1997 Differentiated thyroid carcinoma in children and adolescents: a 37-year experience in 85 patients. *Journal of Nuclear Medicine* **38** 669–675.
- Dow KH, Ferrell BR & Anello C 1997 Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. *Thyroid* **7** 613–619.
- Dragoiescu C, Hoekstra OS, Kuik DJ, Lips P, Plazier MA, Rodrigus PT, Huijsmans DA, Ribot JG, Kuijpers J, Coebergh JW *et al.* 2003 Feasibility of a randomized trial on adjuvant radio-iodine therapy in differentiated thyroid cancer. *Clinical Endocrinology* **58** 451–455.
- Dumont JE, Maenhaut C, Lamy F, Pirson I, Clement S & Roger PP 2003 Growth and proliferation of the thyroid cell in normal physiology and in disease. *Annales d'Endocrinologie* **64** 10–11.
- Elisei R, Romei C, Vorontsova T, Cosci B, Veremeychik V, Kuchinskaya E, Basolo F, Demidchik EP, Miccoli P, Pinchera A *et al.* 2001 RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. *Journal of Clinical Endocrinology and Metabolism* **86** 3211–3216.
- Faggiano A, Coulot J, Bellon N, Talbot M, Caillou B, Ricard M, Bidart JM & Schlumberger M 2004 Age-dependent variation of follicular size and expression of iodine transporters in human thyroid tissue. *Journal of Nuclear Medicine* **45** 232–237.
- Fagin JA 2004 Challenging dogma in thyroid cancer molecular genetics – role of RET/PTC and BRAF in tumor initiation. *Journal of Clinical Endocrinology and Metabolism* **89** 4264–4266.

- Farahati J, Bucsky P, Parlowsky T, Mader U & Reiners C 1997 Characteristics of differentiated thyroid carcinoma in children and adolescents with respect to age, gender, and histology. *Cancer* **80** 2156–2162.
- Farahati J, Demidchik EP, Biko J & Reiners C 2000 Inverse association between age at the time of radiation exposure and extent of disease in cases of radiation-induced childhood thyroid carcinoma in Belarus. *Cancer* **88** 1470–1476.
- Farahati J, Geling M, Mader U, Mortl M, Luster M, Muller JG, Flentje M & Reiners C 2004 Changing trends of incidence and prognosis of thyroid carcinoma in lower Franconia, Germany, from 1981–1995. *Thyroid* **14** 141–147.
- Farahati J, Reiners C & Demidchik EP 1999 Is the UICC/AJCC Classification of primary tumor in childhood thyroid carcinoma valid? *Journal of Nuclear Medicine* **40** 2125.
- Fassina AS, Rupolo M, Pelizzo MR & Casara D 1994 Thyroid cancer in children and adolescents. *Tumori* **80** 257–262.
- Fatourechi V, Hay ID, Javedan H, Wiseman GA, Mullan BP & Gorman CA 2002 Lack of impact of radioiodine therapy in Tg-positive, diagnostic whole-body scan-negative patients with follicular cell-derived thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **87** 1521–1526.
- Fazio S, Biondi B, Carella C, Sabatini D, Cittadini A, Panza N, Lombardi G & Sacca L 1995 Diastolic dysfunction in patients on thyroid-stimulating hormone suppressive therapy with levothyroxine: beneficial effect of beta-blockade. *Journal of Clinical Endocrinology and Metabolism* **80** 2222–2226.
- Fenton C, Patel A, Dinauer C, Robie DK, Tuttle RM & Francis GL 2000a The expression of vascular endothelial growth factor and the type 1 vascular endothelial growth factor receptor correlate with the size of papillary thyroid carcinoma in children and young adults. *Thyroid* **10** 349–357.
- Fenton CL, Lukes Y, Nicholson D, Dinauer CA, Francis GL & Tuttle RM 2000b The ret/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. *Journal of Clinical Endocrinology and Metabolism* **85** 1170–1175.
- Finley DJ, Arora N, Zhu B, Gallagher L & Fahey TJ III 2004 Molecular profiling distinguishes papillary carcinoma from benign thyroid nodules. *Journal of Clinical Endocrinology and Metabolism* **89** 3214–3223.
- Gerard AC, Daumerie C, Mestdagh C, Gohy S, De Burbure C, Costagliola S, Miot F, Nollevaux MC, Denef JF, Rahier J et al. 2003 Correlation between the loss of thyroglobulin iodination and the expression of thyroid-specific proteins involved in iodine metabolism in thyroid carcinomas. *Journal of Clinical Endocrinology and Metabolism* **88** 4977–4983.
- Gerard SK & Cavalieri RR 2002 I-123 diagnostic thyroid tumor whole-body scanning with imaging at 6, 24, and 48 hours. *Clinical Nuclear Medicine* **27** 1–8.
- Geus-Oei LF, Oei HY, Hennemann G & Krenning EP 2002 Sensitivity of 123I whole-body scan and thyroglobulin in the detection of metastases or recurrent differentiated thyroid cancer. *European Journal of Nuclear Medicine and Molecular Imaging* **29** 768–774.
- Giuffrida D, Scollo C, Pellegriti G, Lavenia G, Iurato MP, Pezzin V & Belfiore A 2002 Differentiated thyroid cancer in children and adolescents. *Journal of Endocrinological Investigation* **25** 18–24.
- Goffman T, Ioffe V, Tuttle M, Bowers JT & Mason ME 2003 Near-lethal respiratory failure after recombinant human thyroid-stimulating hormone use in a patient with metastatic thyroid carcinoma. *Thyroid* **13** 827–830.
- Gow KW, Lensing S, Hill DA, Krasin MJ, McCarville MB, Rai SN, Zacher M, Spunt SL, Strickland DK & Hudson MM 2003 Thyroid carcinoma presenting in childhood or after treatment of childhood malignancies: An institutional experience and review of the literature. *Journal of Pediatric Surgery* **38** 1574–1580.
- Grigsby PW, Galon A, Michalski JM & Doherty GM 2002 Childhood and adolescent thyroid carcinoma. *Cancer* **95** 724–729.
- Gupta S, Patel A, Folstad A, Fenton C, Dinauer CA, Tuttle RM, Conran R & Francis GL 2001 Infiltration of differentiated thyroid carcinoma by proliferating lymphocytes is associated with improved disease-free survival for children and young adults. *Journal of Clinical Endocrinology and Metabolism* **86** 1346–1354.
- Hallwirth U, Flores J, Kaserer K & Niederle B 1999 Differentiated thyroid cancer in children and adolescents: the importance of adequate surgery and review of literature. *European Journal of Pediatric Surgery* **9** 359–363.
- Handkiewicz-Junak D, Kalembe B, Roskosz J, Wloch J, Lange D, Kukulska A, Puch Z & Jarzab B 2001 Prognostic factors for differentiated thyroid carcinoma in young patients. *Nowotwory* **51** 365–371.
- Harach HR & Williams ED 1995 Childhood thyroid cancer in England and Wales. *British Journal of Cancer* **72** 777–783.
- Harness JK, Thompson NW, McLeod MK, Pasiaka JL & Fukuuchi A 1992 Differentiated thyroid carcinoma in children and adolescents. *World Journal of Surgery* **16** 547–553.
- Harris PE 2002 The management of thyroid cancer in adults: a review of new guidelines. *Clinical Medicine* **2** 144–146.
- Hassoun AA, Hay ID, Goellner JR & Zimmerman D 1997 Insular thyroid carcinoma in adolescents: a potentially lethal endocrine malignancy. *Cancer* **79** 1044–1048.
- Haugen BR 2004 Patients with differentiated thyroid carcinoma benefit from radioiodine remnant ablation. *Journal of Clinical Endocrinology and Metabolism* **89** 3665–3667.
- Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman

- LE, Skarulis MC *et al.* 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *Journal of Clinical Endocrinology and Metabolism* **84** 3877–3885.
- Haugen BR, Ridgway EC, McLaughlin BA & McDermott MT 2002 Clinical comparison of whole-body radioiodine scan and serum thyroglobulin after stimulation with recombinant human thyrotropin. *Thyroid* **12** 37–43.
- Haveman JW, van Tol KM, Rouwe CW, Piers D A & Plukker JT 2003 Surgical experience in children with differentiated thyroid carcinoma. *Annals of Surgical Oncology* **10** 15–20.
- Hay ID 1987 Brain metastases from papillary thyroid carcinoma. *Archives of Internal Medicine* **147** 607, 611.
- Hindie E, Melliére D, Lange J, Hallaj I, Labriolle-Vaylet C, Jeanguillaume C, Lange J, Perlemuter L & Askienazy S 2003 Functioning pulmonary metastases of thyroid cancer: does radioiodine influence the prognosis? *European Journal of Nuclear Medicine and Molecular Imaging* **30** 974–981.
- Horne MK III, Singh KK, Rosenfeld KG, Wesley R, Skarulis MC, Merryman PK, Cullinane A, Costello R, Patterson A, Eggerman T *et al.* 2004 Is thyroid hormone suppression therapy prothrombotic? *Journal of Clinical Endocrinology and Metabolism* **89** 4469–4473.
- Huang Y, Prasad M, Lemon WJ, Hampel H, Wright FA, Kornacker K, LiVolsi V, Frankel W, Kloos RT, Eng C *et al.* 2001 Gene expression in papillary thyroid carcinoma reveals highly consistent profiles. *PNAS* **98** 15044–15049.
- Hung W & Sarlis NJ 2002 Current controversies in the management of pediatric patients with well-differentiated nonmedullary thyroid cancer: a review. *Thyroid* **12** 683–702.
- Jarzbab B, Handkiewicz-Junak D, Roskosz J, Puch Z, Wygoda Z, Kukulska A, Jurecka-Lubieniecka B, Hasse-Lazar K, Turska M & Zajusz A 2003 Recombinant human TSH-aided radioiodine treatment of advanced differentiated thyroid carcinoma: a single-centre study of 54 patients. *European Journal of Nuclear Medicine and Molecular Imaging* **30** 1077–1086.
- Jarzbab B, Handkiewicz JD, Wloch J, Kalembe B, Roskosz J, Kukulska A & Puch Z 2000 Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. *European Journal of Nuclear Medicine* **27** 833–841.
- Jarzbab B, Wiench M, Fujarewicz K, Simek K, Jarzbab M, Oczko-Wojciechowska M, Wloch J, Czarniecka A, Chmielik E, Lange D *et al.* 2005 Gene expression profile of papillary thyroid cancer: sources of variability and diagnostic implications. *Cancer Research* **65** 1587–1597.
- Karam M, Gianoukakis A, Feustel PJ, Cheema A, Postal ES & Cooper JA 2003 Influence of diagnostic and therapeutic doses on thyroid remnant ablation rates. *Nuclear Medicine Communications* **24** 489–495.
- Katoh R, Sasaki J, Kurihara H, Suzuki K, Iida Y & Kawaoi A 1992 Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma. A clinicopathologic study of 105 consecutive patients. *Cancer* **70** 1585–1590.
- de Keizer B, Brans B, Hoekstra A, Zelissen PM, Koppeschaar HP, Lips CJ, van Rijk PP, Dierckx RA & de Klerk JM 2003 Tumour dosimetry and response in patients with metastatic differentiated thyroid cancer using recombinant human thyrotropin before radioiodine therapy. *European Journal of Nuclear Medicine and Molecular Imaging* **30** 367–373.
- de Keizer B, Hoekstra A, Konijnenberg MW, de Vos F, Lambert B, van Rijk PP, Lips CJ & Klerk JM 2004 Bone marrow dosimetry and safety of high ¹³¹I activities given after recombinant human thyroid-stimulating hormone to treat metastatic differentiated thyroid cancer. *Journal of Nuclear Medicine* **45** 1549–1554.
- Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE & Fagin JA 2003 High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Research* **63** 1454–1457.
- Kloos RT, Duvuuri V, Jhiang SM, Cahill KV, Foster JA & Burns JA 2002 Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **87** 5817–5820.
- Kogai T, Endo T, Saito T, Miyazaki A, Kawaguchi A & Onaya T 1997 Regulation by thyroid-stimulating hormone of sodium/iodide symporter gene expression and protein levels in FRTL-5 cells. *Endocrinology* **138** 2227–2232.
- Koh JM, Kim ES, Ryu JS, Hong SJ, Kim WB & Shong YK 2003 Effects of therapeutic doses of ¹³¹I in thyroid papillary carcinoma patients with elevated thyroglobulin level and negative ¹³¹I whole-body scan: comparative study. *Clinical Endocrinology* **58** 421–427.
- Kowalski LP, Goncalves FJ, Pinto CA, Carvalho AL & de Camargo B 2003 Long-term survival rates in young patients with thyroid carcinoma. *Archives of Otolaryngology – Head and Neck Surgery* **129** 746–749.
- Kumagai A, Namba H, Saenko VA, Ashizawa K, Ohtsuru A, Ito M, Ishikawa N, Sugino K, Ito K, Jeremiah S *et al.* 2004 Low frequency of BRAF T1796A mutations in childhood thyroid carcinomas. *Journal of Clinical Endocrinology and Metabolism* **89** 4280–4284.
- La Quaglia MP, Corbally MT, Heller G, Exelby PR & Brennan MF 1988 Recurrence and morbidity in differentiated thyroid carcinoma in children. *Surgery* **104** 1149–1156.
- La Quaglia MP, Black T, Holcomb GW III, Sklar C, Azizkhan RG, Haase GM & Newman KD 2000 Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases. A report from the Surgical Discipline Committee of the Children's Cancer Group. *Journal of Pediatric Surgery* **35** 955–959.

- Lacroix L, Pourcher T, Magnon C, Bellon N, Talbot M, Intaraphairot T, Caillou B, Schlumberger M & Bidart JM 2004 Expression of the apical iodide transporter in human thyroid tissues: a comparison study with other iodide transporters. *Journal of Clinical Endocrinology and Metabolism* **89** 1423–1428.
- Ladenson P, Pacini F, Schlumberger M, Drieger A, Kloos RT, Sherman S, Corone C, Haugen B & Reiners C 2004 Thyroid remnant ablation: A randomized comparison of thyrotropin alfa and thyroid hormone withdrawal. Abstracts of the Endocrinology Society's Annual Meeting June 17 S35–1.
- Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH et al. 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *New England Journal of Medicine* **337** 888–896.
- Landau D, Vini L, A'Hern R & Harmer C 2000 Thyroid cancer in children: the Royal Marsden Hospital experience. *European Journal of Cancer* **36** 214–220.
- Landier W, Bhatia S, Eshelman DA, Forte KJ, Sweeney T, Hester AL, Darling J, Armstrong FD, Blatt J, Constine LS et al. 2004 Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *Journal of Clinical Oncology* **22** 4979–4990.
- Lassmann M, Luster M, Häscheid H & Reiners C 2004 Impact of 131I diagnostic activities on the biokinetics of thyroid remnants. *Journal of Nuclear Medicine* **45** 619–625.
- Leboulleux S, Baudin E, Hartl DW, Travagli JP & Schlumberger M 2004 Follicular-cell derived thyroid cancer in children. *European Journal of Cancer* **40** 1655–1659.
- Leenhardt L, Grosclaude P & Cherie-Challine L 2004 Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. *Thyroid* **14** 1056–1060.
- Leung SF, Law MW & Ho SK 1992 Efficacy of low-dose iodine-131 ablation of post-operative thyroid remnants: a study of 69 cases. *British Journal of Radiology* **65** 905–909.
- Lin JD, Wang HS, Weng HF & Kao PF 1998 Outcome of pregnancy after radioactive iodine treatment for well differentiated thyroid carcinomas. *Journal of Endocrinological Investigation* **21** 662–667.
- Lippi F, Capezzone M, Angelini F, Taddei D, Molinaro E, Pinchera A & Pacini F 2001 Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human TSH. *European Journal of Endocrinology/European Federation of Endocrine Societies* **144** 5–11.
- LiVolsi VA, LoGerfo P & Feind CR 1978 Coexistent parathyroid adenomas and thyroid carcinoma. Can radiation be blamed? *Archives of Surgery* **113** 285–286.
- Loh KC, Greenspan FS, Dong F, Miller TR & Yeo PP 1999 Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **84** 458–463.
- Lubin JH, Schafer DW, Ron E, Stovall M & Carroll RJ 2004 A reanalysis of thyroid neoplasms in the Israeli tinea capitis study accounting for dose uncertainties. *Radiation Research* **161** 359–368.
- Luster M, Sherman SI, Skarulis MC, Reynolds JR, Lassmann M, Häscheid H & Reiners C 2003 Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone and after thyroid hormone withdrawal in thyroid carcinoma. *European Journal of Nuclear Medicine and Molecular Imaging* **30** 1371–1377.
- Luster M, Lippi F, Jarzab B, Perros P, Lassmann M, Reiners C & Pacini F 2005 rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review. *Endocrine Related Cancer* **12** 49–64.
- Mahoney MC, Lawvere S, Falkner KL, Averkin YI, Ostapenko VA, Michalek AM, Moysich KB & McCarthy PL 2004 Thyroid cancer incidence trends in Belarus: examining the impact of Chernobyl. *International Journal of Epidemiology* **33** 1025–1033.
- Mandel SJ & Mandel L 2003 Radioactive iodine and the salivary glands. *Thyroid* **13** 265–271.
- Mandel SJ, Shankar LK, Benard F, Yamamoto A & Alavi A 2001 Superiority of iodine-123 compared with iodine-131 scanning for thyroid remnants in patients with differentiated thyroid cancer. *Clinical Nuclear Medicine* **26** 6–9.
- Massimino M, Gasparini M, Ballerini E & Del Bo R 1995 Primary thyroid carcinoma in children: a retrospective study of 20 patients. *Medical and Pediatric Oncology* **24** 13–17.
- Massin JP, Savoie JC, Garnier H, Guiraudon G, Leger FA & Bacourt F 1984 Pulmonary metastases in differentiated thyroid carcinoma. Study of 58 cases with implications for the primary tumor treatment. *Cancer* **53** 982–992.
- Matsubayashi S, Kawai K, Matsumoto Y, Mukuta T, Morita T, Hirai K, Matsuzuka F, Kakudoh K, Kuma K & Tamai H 1995 The correlation between papillary thyroid carcinoma and lymphocytic infiltration in the thyroid gland. *Journal of Clinical Endocrinology and Metabolism* **80** 3421–3424.
- Matuszewska G, Roskosz J, Włoch J, Jurecka-Tuleja B, Hasse-Lazar K, Kowalczyk P & Jarzab B 2001 Evaluation of effects of L-thyroxine therapy in differentiated thyroid carcinoma on the cardiovascular system – prospective study. *Wiadomosci Lekarskie* **54** (suppl 1) 373–377.

- Maxon HR 1999 Quantitative radioiodine therapy in the treatment of differentiated thyroid cancer. *Quarterly Journal of Nuclear Medicine* **43** 313–323.
- Mazzaferri EL 1999 NCCN thyroid carcinoma practice guidelines. *Oncology* **13** 391–442.
- Mazzaferri EL 2002 Gonadal damage from ¹³¹I therapy for thyroid cancer. *Clinical Endocrinology* **57** 313–314.
- Mazzaferri EL 2004 A randomized trial of remnant ablation – in search of an impossible dream? *Journal of Clinical Endocrinology and Metabolism* **89** 3662–3664.
- Mazzaferri EL & Jhiang SM 1994a Differentiated thyroid cancer long-term impact of initial therapy. *Transactions of the American Clinical and Climatological Association* **106** 151–168.
- Mazzaferri EL & Jhiang SM 1994b Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine* **97** 418–428.
- Mazzaferri EL & Kloos RT 2001 Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **86** 1447–1463.
- Mazzaferri EL & Kloos RT 2002 Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? *Journal of Clinical Endocrinology and Metabolism* **87** 1490–1498.
- Mazzaferri EL & Massoll N 2002 Management of papillary and follicular (differentiated) thyroid cancer: new paradigms using recombinant human thyrotropin. *Endocrine Related Cancer* **9** 227–247.
- Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD *et al.* 2003 A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **88** 1433–1441.
- McDougall IR 1997 ¹³¹I treatment of ¹³¹I negative whole body scan, and positive thyroglobulin in differentiated thyroid carcinoma: what is being treated? *Thyroid* **7** 669–672.
- Menzel C, Grünwald F, Schomburg A, Palmedo H, Bender H, Spath G & Biersack HJ 1996 ‘High-dose’ radioiodine therapy in advanced differentiated thyroid carcinoma. *Journal of Nuclear Medicine* **37** 1496–1503.
- Mian C, Lacroix L, Alzieu L, Nocera M, Talbot M, Bidart JM, Schlumberger M & Caillou B 2001 Sodium iodide symporter and pendrin expression in human thyroid tissues. *Thyroid* **11** 825–830.
- Miccoli P, Antonelli A, Spinelli C, Ferdeghini M, Fallahi P & Baschieri L 1998 Completion thyroidectomy in 131 patients with differentiated thyroid carcinoma. *Archives of Surgery* **133** 89–93.
- Michel LA & Donckier JE 2002 Thyroid cancer 15 years after Chernobyl. *Lancet* **359** 1947.
- Millman B & Pellitteri PK 1995 Thyroid carcinoma in children and adolescents. *Archives of Otolaryngology – Head and Neck Surgery* **121** 1261–1264.
- Min JJ, Chung JK, Lee YJ, Jeong JM, Lee DS, Jang JJ, Lee MC & Cho BY 2001 Relationship between expression of the sodium/iodide symporter and ¹³¹I uptake in recurrent lesions of differentiated thyroid carcinoma. *European Journal of Nuclear Medicine* **28** 639–645.
- Mitsiades N, Poulaki V, Mastorakos G, Tseleni-Balafouta ST, Kotoula V, Koutras DA & Tsokos M 1999 Fas ligand expression in thyroid carcinomas: a potential mechanism of immune evasion. *Journal of Clinical Endocrinology and Metabolism* **84** 2924–2932.
- Mizukami Y, Michigishi T, Nonomura A, Hashimoto T, Noguchi M, Matsubara F & Watanabe K 1992 Carcinoma of the thyroid at a young age – a review of 23 patients. *Histopathology* **20** 63–66.
- Modi J, Patel A, Terrell R, Tuttle RM & Francis GL 2003 Papillary thyroid carcinomas from young adults and children contain a mixture of lymphocytes. *Journal of Clinical Endocrinology and Metabolism* **88** 4418–4425.
- Morris LF, Waxman AD & Braunstein GD 2001a The nonimpact of thyroid stunning: remnant ablation rates in ¹³¹I-scanned and non-scanned individuals. *Journal of Clinical Endocrinology and Metabolism* **86** 3507–3511.
- Morris LF, Wilder MS, Waxman AD & Braunstein GD (2001b) Reevaluation of the impact of a stringent low-iodine diet on ablation rates in radioiodine treatment of thyroid carcinoma. *Thyroid* **11** 749–755.
- Morris LF, Waxman AD & Braunstein GD 2003 Thyroid stunning. *Thyroid* **13** 333–340.
- Motomura T, Nikiforov YE, Namba H, Ashizawa K, Nagataki S, Yamashita S & Fagin JA 1998 ret rearrangements in Japanese pediatric and adult papillary thyroid cancers. *Thyroid* **8** 485–489.
- Muller CG, Bayley TA, Harrison JE & Tsang R 1995 Possible limited bone loss with suppressive thyroxine therapy is unlikely to have clinical relevance. *Thyroid* **5** 81–87.
- Muratet JP, Daver A, Minier JF & Larra F 1998 Influence of scanning doses of iodine-131 on subsequent first ablative treatment outcome in patients operated on for differentiated thyroid carcinoma. *Journal of Nuclear Medicine* **39** 1546–1550.
- Murbeth S, Rousarova M, Scherb H & Lengfelder E 2004 Thyroid cancer has increased in the adult populations of countries moderately affected by Chernobyl fallout. *Medical Science Monitor* **10** CR300–CR306.
- Newman KD 1993 The current management of thyroid tumors in childhood. *Seminars in Pediatric Surgery* **2** 69–74.
- Newman KD, Black T, Heller G, Azizkhan RG, Holcomb GW, III, Sklar C, Vlamis V, Haase GM & La Quaglia MP 1998 Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline

- Committee of the Children's Cancer Group. *Annals of Surgery* **227** 533–541.
- Niedziela M, Korman E, Breborowicz D, Trejster E, Harasymczuk J, Warzywoda M, Rolski M & Breborowicz J 2004 A prospective study of thyroid nodular disease in children and adolescents in western Poland from 1996 to 2000 and the incidence of thyroid carcinoma relative to iodine deficiency and the Chernobyl disaster. *Pediatric Blood and Cancer* **42** 84–92.
- Nijhuis TF, van Weperen W & de Klerk JMH 1999 Costs associated with the withdrawal of thyroid hormone suppression therapy during the follow-up treatment of well-differentiated thyroid cancer. *Nederlands Tijdschrift voor Geneeskunde* **21** 98–100.
- Nikiforov Y & Gnepp DR 1994 Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991–1992) from the Republic of Belarus. *Cancer* **74** 748–766.
- Nikiforov YE, Rowland JM, Bove KE, Monforte-Munoz H & Fagin JA 1997 Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. *Cancer Research* **57** 1690–1694.
- Nikiforova MN, Lynch RA, Biddinger PW, Alexander EK, Dorn GW, Tallini G, Kroll TG & Nikiforov YE 2003 RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. *Journal of Clinical Endocrinology and Metabolism* **88** 2318–2326.
- Orsenigo E, Beretta E, Gini P, Verrecchia F, Invernizzi L, Fiorina P & Di C V 2003 A report of six cases of familial papillary thyroid cancer. *European Journal of Surgical Oncology* **29** 185–187.
- Pacini F, Cetani F, Miccoli P, Mancusi F, Ceccarelli C, Lippi F, Martino E & Pinchera A 1994a Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. *World Journal of Surgery* **18** 600–604.
- Pacini F, Gasperi M, Fugazzola L, Ceccarelli C, Lippi F, Centoni R, Martino E & Pinchera A 1994b Testicular function in patients with differentiated thyroid carcinoma treated with radioiodine. *Journal of Nuclear Medicine* **35** 1418–1422.
- Pacini F, Ladenson P, Schlumberger M, Drieger A, Kloos RT, Sherman S, Corone C, Haugen B & Reiners C 2004 Preparation with thyrotropin alfa is equivalent to thyroid hormone withdrawal as preparation for thyroid remnant ablation in differentiated thyroid carcinoma (abstract). *Turkish Journal of Endocrinology and Metabolism* **8** 21.
- Pacini F, Molinaro E, Castagna MG, Lippi F, Ceccarelli C, Agate L, Elisei R & Pinchera A 2002 Ablation of thyroid residues with 30 mCi (131)I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. *Journal of Clinical Endocrinology and Metabolism* **87** 4063–4068.
- Parfitt T 2004 Chernobyl's legacy. 20 years after the power station exploded, new cases of thyroid cancer are still rising, say experts. *Lancet* **363** 1534.
- Park SG, Reynolds JC, Brucker-Davis F, Whatley M, McEllin K, Maxted D, Robbins J & Weintraub BD 1996 Iodine kinetics during I-131 scanning in patients with thyroid cancer: comparison of studies with recombinant human TSH (rhTSH) vs hypothyroidism (abstract). *Journal of Nuclear Medicine* **37** (Suppl) 15P.
- Pasieka JL, Thompson NW, McLeod MK, Burney RE & Macha M 1992 The incidence of bilateral well-differentiated thyroid cancer found at completion thyroidectomy. *World Journal of Surgery* **16** 711–716.
- Patel A, Fenton C, Ramirez R, Dinanuer CA, Tuttle RM, Nikiforov YE & Gary FL 2000 Tyrosine kinase expression is increased in papillary thyroid carcinoma of children and young adults. *Frontiers in Bioscience* **5** A1–A9.
- Patel A, Jhiang S, Dogra S, Terrell R, Powers PA, Fenton C, Dinanuer CA, Tuttle RM & Francis GL 2002 Differentiated thyroid carcinoma that express sodium-iodide symporter have a lower risk of recurrence for children and adolescents. *Pediatric Research* **52** 737–744.
- Phillips AW, Fenwick JD, Mallick UK & Perros P 2003 The impact of clinical guidelines on surgical management in patients with thyroid cancer. *Clinical Oncology* **15** 485–489.
- Pluijmen MJ, Eustatia-Rutten C, Goslings BM, Stokkel MP, Arias AM, Diamant M, Romijn JA & Smit JW 2003 Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma. *Clinical Endocrinology* **58** 428–435.
- Powers PA, Dinanuer CA, Tuttle RM & Francis GL 2003a Treatment of recurrent papillary thyroid carcinoma in children and adolescents. *Journal of Pediatric Endocrinology and Metabolism* **16** 1033–1040.
- Powers PA, Dinanuer CA, Tuttle RM, Robie DK, McClellan DR & Francis GL 2003b Tumor size and extent of disease at diagnosis predict the response to initial therapy for papillary thyroid carcinoma in children and adolescents. *Journal of Pediatric Endocrinology and Metabolism* **16** 693–702.
- Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J & Jaffiol C 1996 Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **81** 4318–4323.
- Ramirez R, Hsu D, Patel A, Fenton C, Dinanuer C, Tuttle RM & Francis GL 2000 Over-expression of hepatocyte growth factor/scatter factor (HGF/SF) and the HGF/SF receptor (cMET) are associated with a high risk of metastasis and recurrence for children and young adults with papillary thyroid carcinoma. *Clinical Endocrinology* **53** 635–644.
- Reiners C 2003 Radioiodine therapy in patients with pulmonary metastases of thyroid cancer: when to treat,

- when not to treat? *European Journal of Nuclear Medicine and Molecular Imaging* **30** 939–942.
- Reiners C, Biko J, Demidchik EP, Demidchik YE & Drozd VM 2002 Results of radioactive iodine treatment in children from Belarus with advanced stages of thyroid cancer after the Chernobyl accident. *Elsevier International Congress Series* **1234** 205–214.
- Reiners C, Schumm-Draeger PM, Geling M, Mastbaum C, Schönberger J, Laue-Savic A, Hackethal K, Hampel R, Heinken U, Kullak W *et al.* 2003 Thyroid gland ultrasound screening (Papillon Initiative). Report of 15 incidentally detected thyroid cancers. *Internist* **44** 412–419.
- Reynolds J 1993 Comparison of I-131 absorbed radiation doses in children and adults: a tool for estimating therapeutic I-131 doses in children. In *Treatment of thyroid cancer in children*, pp 127–135. Ed. J Robbins. Washington: US Department of Energy and US Department of Commerce, Technology, Administration, National Technical Information.
- Reynolds JC & Robbins J 1997 The changing role of radioiodine in the management of differentiated thyroid cancer. *Seminars in Nuclear Medicine* **27** 152–164.
- Ringel MD, Anderson J, Souza SL, Burch HB, Tambascia M, Shriver CD & Tuttle RM 2001 Expression of the sodium iodide symporter and thyroglobulin genes are reduced in papillary thyroid cancer. *Modern Pathology* **14** 289–296.
- Ringel MD & Levine MA 2003 Current therapy for childhood thyroid cancer: optimal surgery and the legacy of King Pyrrhus. *Annals of Surgical Oncology* **10** 4–6.
- Ringel MD & Ladenson PW 2004 Controversies in the follow-up and management of well-differentiated thyroid cancer. *Endocrine Related Cancer* **11** 97–116.
- Robie DK, Dinauer CW, Tuttle RM, Ward DT, Parry R, McClellan D, Svec R, Adair C & Francis G 1998 The impact of initial surgical management on outcome in young patients with differentiated thyroid cancer. *Journal of Pediatric Surgery* **33** 1134–1138.
- Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA & Boice JD Jr 1995 Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiation Research* **141** 259–277.
- Ronga G, Filesi M, Montesano T, Di Nicola AD, Pace C, Travascio L, Ventroni G, Antonaci A & Vestri AR 2004 Lung metastases from differentiated thyroid carcinoma. A 40 years' experience. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* **48** 12–19.
- Rubino C, De Vathaire F, Dottorini ME, Hall P, Schwartz C, Couette JE, Dondon MG, Abbas MT, Langlois C & Schlumberger M 2003 Second primary malignancies in thyroid cancer patients. *British Journal of Cancer* **89** 1638–1644.
- Samaan NA, Schultz PN, Hickey RC, Goepfert H, Haynie TP, Johnston DA & Ordenez NG 1992 The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. *Journal of Clinical Endocrinology and Metabolism* **75** 714–720.
- Samaan NA, Schultz PN, Ordenez NG, Hickey RC & Johnston DA 1987 A comparison of thyroid carcinoma in those who have and have not had head and neck irradiation in childhood. *Journal of Clinical Endocrinology and Metabolism* **64** 219–223.
- Samuel AM, Rajashekharrao B & Shah DH 1998 Pulmonary metastases in children and adolescents with well-differentiated thyroid cancer. *Journal of Nuclear Medicine* **39** 1531–1536.
- van Santen HM, Aronson DC, Vulsma T, Tummers RF, Geenen MM, de Vijlder JJ & van den Bos C 2004 Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. *European Journal of Cancer* **40** 1743–1751.
- Sarkar SD, Kalappambath TP & Palestro CJ 2002 Comparison of (123)I and (131)I for whole-body imaging in thyroid cancer. *Journal of Nuclear Medicine* **43** 632–634.
- Sawka AM, Thepamongkhon K, Brouwers M, Thabane L, Browman G & Gerstein HC 2004 Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **89** 3668–3676.
- Schaap J, Eustatia-Rutten CF, Stokkel M, Links TP, Diamant M, van der Velde EA, Romijn JA & Smit JW 2002 Does radioiodine therapy have disadvantageous effects in non-iodine accumulating differentiated thyroid carcinoma? *Clinical Endocrinology* **57** 117–124.
- Schlesinger T, Flower MA & McCreedy VR 1989 Radiation dose assessments in radioiodine (131I) therapy. 1. The necessity for *in vivo* quantitation and dosimetry in the treatment of carcinoma of the thyroid. *Radiotherapy and Oncology* **14** 35–41.
- Schlumberger M, De Vathaire F, Travagli JP, Vassal G, Lemerle J, Parmentier C & Tubiana M 1987 Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. *Journal of Clinical Endocrinology and Metabolism* **65** 1088–1094.
- Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, Francese C, Fontaine F, Ricard M & Parmentier C 1996a Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *Journal of Nuclear Medicine* **37** 598–605.
- Schlumberger M, De Vathaire F, Ceccarelli C, Delisle MJ, Francese C, Couette JE, Pinchera A & Parmentier C 1996b Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. *Journal of Nuclear Medicine* **37** 606–612.
- Schlumberger M, Mancusi F, Baudin E & Pacini F 1997 131I therapy for elevated thyroglobulin levels. *Thyroid* **7** 273–276.

- Schlumberger M, Berg G, Cohen O, Duntas L, Jamar F, Jarzab B, Limbert E, Lind P, Pacini F, Reiners C *et al.* 2004a Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *European Journal of Endocrinology/European Federation of Endocrine Societies* **150** 105–112.
- Schlumberger M, Pacini F, Wiersinga WM, Toft A, Smit JW, Sanchez FF, Lind P, Limbert E, Jarzab B, Jamar F *et al.* 2004b Follow-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. *European Journal of Endocrinology/European Federation of Endocrine Societies* **151** 539–548.
- Schlumberger M, Tubiana M, De Vathaire F, Hill C, Gardet P, Travagli JP, Fragu P, Lumbroso J, Caillou B & Parmentier C 1986 Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* **63** 960–967.
- Schlumberger MJ 1998 Papillary and follicular thyroid carcinoma. *New England Journal of Medicine* **338** 297–306.
- Schneider P, Biko J, Reiners C, Demidchik YE, Drozd VM, Capozza RF, Cointy GR & Ferretti JL 2004 Impact of parathyroid status and Ca and vitamin-D supplementation on bone mass and muscle-bone relationships in 208 Belarussian children after thyroidectomy because of thyroid carcinoma. *Experimental and Clinical Endocrinology and Diabetes* **112** 444–450.
- Schneider R & Reiners C 2003 The effect of levothyroxine therapy on bone mineral density: a systematic review of the literature. *Experimental and Clinical Endocrinology and Diabetes* **111** 455–470.
- Segal K, Shvero J, Stern Y, Mechlis S & Feinmesser R 1998 Surgery of thyroid cancer in children and adolescents. *Head and Neck* **20** 293–297.
- Sera N, Ashizawa K, Ando T, Ide A, Abe Y, Usa T, Tominaga T, Ejima E, Hayashi T, Shimokawa I *et al.* 2000 Anaplastic changes associated with p53 gene mutation in differentiated thyroid carcinoma after insufficient radioactive iodine (131I) therapy. *Thyroid* **10** 975–979.
- Sgouros G, Kolbert KS, Sheikh A, Pentlow KS, Mun EF, Barth A, Robbins RJ & Larson SM 2004 Patient-specific dosimetry for 131I thyroid cancer therapy using 124I PET and 3-dimensional-internal dosimetry (3D-ID) software. *Journal of Nuclear Medicine* **45** 1366–1372.
- Shah R, Banks K, Patel A, Dogra S, Terrell R, Powers PA, Fenton C, Dinanuer CA, Tuttle RM & Francis GL 2002 Intense expression of the b7-2 antigen presentation coactivator is an unfavorable prognostic indicator for differentiated thyroid carcinoma of children and adolescents. *Journal of Clinical Endocrinology and Metabolism* **87** 4391–4397.
- Shapiro LE, Sievert R, Ong L, Ocampo EL, Chance RA, Lee M, Nanna M, Ferrick K & Surks MI 1997 Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. *Journal of Clinical Endocrinology and Metabolism* **82** 2592–2595.
- Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, Haugen BR, Ho M, Klein I, Ladenson PW *et al.* 1998 Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. *Cancer* **83** 1012–1021.
- Sisson JC, Giordano TJ, Jamadar DA, Kazerooni EA, Shapiro B, Gross MD, Zempel SA & Spaulding SA 1996 131-I treatment of micronodular pulmonary metastases from papillary thyroid carcinoma. *Cancer* **78** 2184–2192.
- Sisson JC, Shulkin BL & Lawson S 2003 Increasing efficacy and safety of treatments of patients with well-differentiated thyroid carcinoma by measuring body retentions of 131I. *Journal of Nuclear Medicine* **44** 898–903.
- Spinelli C, Bertocchini A, Antonelli A & Miccoli P 2004 Surgical therapy of the thyroid papillary carcinoma in children: experience with 56 patients <or = 16 years old. *Journal of Pediatric Surgery* **39** 1500–1505.
- Stael AP, Plukker JT, Piers DA, Rouwe CW & Vermey A 1995 Total thyroidectomy in the treatment of thyroid carcinoma in childhood. *British Journal of Surgery* **82** 1083–1085.
- Storm HH & Plesko I 2001 Survival of children with thyroid cancer in Europe 1978–1989. *European Journal of Cancer* **37** 775–779.
- Straight AM, Patel A, Fenton C, Dinanuer C, Tuttle RM & Francis GL 2002 Thyroid carcinomas that express telomerase follow a more aggressive clinical course in children and adolescents. *Journal of Endocrinological Investigation* **25** 302–308.
- Sugg SL, Ezzat S, Rosen IB, Freeman JL & Asa SL 1998 Distinct multiple RET/PTC gene rearrangements in multifocal papillary thyroid neoplasia. *Journal of Clinical Endocrinology and Metabolism* **83** 4116–4122.
- Sugg SL, Zheng L, Rosen IB, Freeman JL, Ezzat S & Asa SL 1996 ret/PTC-1, -2, and -3 oncogene rearrangements in human thyroid carcinomas: implications for metastatic potential? *Journal of Clinical Endocrinology and Metabolism* **81** 3360–3365.
- Suwinski R & Gawkowska-Suwinska M 2001 Radiobiologic basis for using 131I to treat patients with thyroid cancer. *Wiadomosci Lekarskie* **54** (Suppl 1) 266–277.
- Sykes AJ & Gattamaneni HR 1997 Carcinoma of the thyroid in children: a 25-year experience. *Medical and Pediatric Oncology* **29** 103–107.
- Thompson GB & Hay ID 2004 Current strategies for surgical management and adjuvant treatment of childhood papillary thyroid carcinoma. *World Journal of Surgery* **28** 1187–1198.
- van Tol KM, Jager PL, de Vries EG, Piers DA, Boezen HM, Sluiter WJ, Dullaart RP & Links TP 2003 Outcome in patients with differentiated thyroid cancer with negative diagnostic whole-body scanning and detectable stimulated

- thyroglobulin. *European Journal of Endocrinology/European Federation of Endocrine Societies* **148** 589–596.
- Tronko MD, Bogdanova TI, Komissarenko IV, Epstein OV, Oliynyk V, Kovalenko A, Likhtarev IA, Kairo I, Peters SB & LiVolsi VA 1999 Thyroid carcinoma in children and adolescents in Ukraine after the Chernobyl nuclear accident: statistical data and clinicomorphologic characteristics. *Cancer* **86** 149–156.
- Tubiana M, Schlumberger M, Rougier P, Laplanche A, Benhamou E, Gardet P, Caillou B, Travagli JP & Parmentier C 1985 Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* **55** 794–804.
- Van Nostrand D, Atkins F, Yeganeh F, Acio E, Bursaw R & Wartofsky L 2002 Dosimetrically determined doses of radioiodine for the treatment of metastatic thyroid carcinoma. *Thyroid* **12** 121–134.
- Vargas GE, UY H, Bazan C, Guise TA & Bruder JM 1999 Hemiplegia after thyrotropin alfa in a hypothyroid patient with thyroid carcinoma metastatic to the brain. *Journal of Clinical Endocrinology and Metabolism* **84** 3867–3871.
- Vassilopoulou-Sellin R 2001 Long-term outcome of children with papillary thyroid cancer. *Surgery* **129** 769.
- Vassilopoulou-Sellin R, Klein MJ, Smith TH, Samaan NA, Frankenthaler RA, Goepfert H, Cangir A & Haynie TP 1993 Pulmonary metastases in children and young adults with differentiated thyroid cancer. *Cancer* **71** 1348–1352.
- Vassilopoulou-Sellin R, Goepfert H, Raney B & Schultz PN 1998 Differentiated thyroid cancer in children and adolescents: clinical outcome and mortality after long-term follow-up. *Head and Neck* **20** 549–555.
- Vassilopoulou-Sellin R, Libshitz HI & Haynie TP 1995 Papillary thyroid cancer with pulmonary metastases beginning in childhood: clinical course over three decades. *Medical and Pediatric Oncology* **24** 119–122.
- Viglietto G, Chiappetta G, Martinez-Tello FJ, Fukunaga FH, Tallini G, Rigopoulou D, Visconti R, Mastro A, Santoro M & Fusco A 1995 RET/PTC oncogene activation is an early event in thyroid carcinogenesis. *Oncogene* **11** 1207–1210.
- Vini L & Harmer C 2002 Management of thyroid cancer. *Lancet Oncology* **3** 407–414.
- Vini L, Hyer S, Al Saadi A, Pratt B & Harmer C 2002 Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer. *Postgraduate Medical Journal* **78** 92–93.
- Viswanathan K, Gierlowski TC & Schneider AB 1994 Childhood thyroid cancer. Characteristics and long-term outcome in children irradiated for benign conditions of the head and neck. *Archives of Pediatrics and Adolescent Medicine* **148** 260–265.
- Vitale G, Lupoli GA, Ciccarelli A, Lucariello A, Fittipaldi MR, Fonderico F, Panico A & Lupoli G 2003 Influence of body surface area on serum peak thyrotropin (TSH) levels after recombinant human TSH administration. *Journal of Clinical Endocrinology and Metabolism* **88** 1319–1322.
- Voutilainen PE, Siironen P, Franssila KO, Sivula A, Haapiainen RK & Haglund CH 2003 AMES, MACIS and TNM prognostic classifications in papillary thyroid carcinoma. *Anticancer Research* **23** 4283–4288.
- Waldmann V & Rabes HM 1997 Absence of G(s)alpha gene mutations in childhood thyroid tumors after Chernobyl in contrast to sporadic adult thyroid neoplasia. *Cancer Research* **57** 2358–2361.
- Wartofsky L, Sherman SI, Gopal J, Schlumberger M & Hay ID 1998 The use of radioactive iodine in patients with papillary and follicular thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **83** 4195–4203.
- Wasenius VM, Hemmer S, Kettunen E, Knuutila S, Franssila K & Joensuu H 2003 Hepatocyte growth factor receptor, matrix metalloproteinase-11, tissue inhibitor of metalloproteinase-1, and fibronectin are up-regulated in papillary thyroid carcinoma: a cDNA and tissue microarray study. *Clinical Cancer Research* **9** 68–75.
- Watkinson JC 2004 The British Thyroid Association guidelines for the management of thyroid cancer in adults. *Nuclear Medicine Communications* **25** 897–900.
- Welch Dinauer CA, Tuttle RM, Robie DK, McClellan DR, Svec RL, Adair C & Francis GL 1998 Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. *Clinical Endocrinology* **49** 619–628.
- Wiench M, Wloch J, Oczko M, Gubala E & Jarzab B 2001 Rearrangement of the RET gene in papillary thyroid carcinoma. *Wiadomosci Lekarskie* **54** (Suppl 1) 64–71.
- Williams ED 1995 Mechanisms and pathogenesis of thyroid cancer in animals and man. *Mutation Research* **333** 123–129.
- van Wyngaarden M & McDougall IR 1996 What is the role of 1100 MBq (<30 mCi) radioiodine 131I in the treatment of patients with differentiated thyroid cancer? *Nuclear Medicine Communications* **17** 199–207.
- Yusuf K, Reyes-Mugica M & Carpenter TO 2003 Insular carcinoma of the thyroid in an adolescent: a case report and review of the literature. *Current Opinion in Pediatrics* **15** 512–515.
- Zanzonico PB 2000 Age-dependent thyroid absorbed doses for radiobiologically significant radioisotopes of iodine. *Health Physics* **78** 60–67.
- Zidan J, Hefer E, Iosilevski G, Drumea K, Stein ME, Kuten A & Israel O 2004 Efficacy of I131 ablation therapy using different doses as determined by postoperative thyroid scan uptake in patients with differentiated thyroid cancer. *International Journal of Radiation Oncology, Biology, Physics* **59** 1330–1336.
- Zimmerman D, Hay ID, Gough IR, Goellner JR, Ryan JJ, Grant CS & McConahey WM 1988 Papillary thyroid carcinoma in children and adults: long-term follow-up of 1039 patients conservatively treated at one institution during three decades. *Surgery* **104** 1157–1166.