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

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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.

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**Introduction**

This review evaluates the role of $^{131}$-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 ~10% of malignant tumors and ~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](image-url)
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 (Catelinois 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 (Mazzaferrari & 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) (Mazzaferrari & 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
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 ~56% of papillary and ~56% of follicular cancers in patients <20 years of age (Patel et al. 2002). In contrast, NIS expression is found 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

### Table 1

<table>
<thead>
<tr>
<th>Differences in Juvenile vs adult DTC</th>
<th>Possible mechanism(s)</th>
<th>Clinical implication(s) in children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger tumor volume at presentation</td>
<td>More aggressive growth, i.e., faster clinical onset, DTC diagnosis at a later stage, or both</td>
<td>Makes routine intensive primary treatment desirable</td>
</tr>
<tr>
<td>Extent and pattern of metastases:</td>
<td>More aggressive tumor growth, decreased local immune response, or both</td>
<td>Makes routine intensive primary treatment desirable; radioiodine treatment is particularly likely to be effective</td>
</tr>
<tr>
<td>• More frequent cervical lymph node and distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Distant metastases almost always in lungs</td>
<td>Pathophysiological differences with focal, frequently non-functional metastases seen in older adults</td>
<td></td>
</tr>
<tr>
<td>• Lung metastases almost always miliary and functional at presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor NIS expression less reduced compared to healthy thyroid cells and less often absent</td>
<td></td>
<td>Radioiodine treatment is particularly likely to be effective</td>
</tr>
<tr>
<td>Higher recurrence rate</td>
<td>More aggressive disease, less intensive treatment, or both</td>
<td>Makes routine intensive primary treatment desirable</td>
</tr>
<tr>
<td>Longer overall survival</td>
<td>Tumors of rapid clinical onset but easily exhaustible proliferation</td>
<td>May be at least partially an artifact of limited observation time relative to life span; cited as an argument against routine intensive treatment</td>
</tr>
<tr>
<td>More frequent papillary histology</td>
<td>Belief based on frequent papillary histology in radiation-induced DTC</td>
<td>Not evident from a review of the sporadic DTC literature; even if true, has minimal if any clinical impact</td>
</tr>
</tbody>
</table>

DTC, differentiated thyroid carcinoma.
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 (Lebouleux 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), or 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

<table>
<thead>
<tr>
<th>Row No. and Reference</th>
<th>Population</th>
<th>Treatment % (no.)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Upper age limit, years (other age data)</td>
<td>Histology, % (no.)</td>
</tr>
<tr>
<td>Multicenter series:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. (Newman et al. 1998)</td>
<td>329</td>
<td>21</td>
<td>P: 90 (297) F: 10 (32)</td>
</tr>
<tr>
<td>2. (Welch Dinauer et al. 1998, Robie et al. 1998, Powers et al. 2003)</td>
<td>170</td>
<td>21 (median: 19 y, 24% &lt;16 y)</td>
<td>P: 81 (137) F: 19 (33)</td>
</tr>
<tr>
<td>3. (Storm &amp; Pesko 2001)</td>
<td>165</td>
<td>14 (13% &lt;10 y)</td>
<td>NR</td>
</tr>
<tr>
<td>4. (Farahati et al. 1997)</td>
<td>114</td>
<td>18</td>
<td>P: 78 (89) F: 22 (25)</td>
</tr>
<tr>
<td>5. (Harach &amp; Williams 1995)</td>
<td>108(^d)</td>
<td>14 (mean: P: 12.4 y, F: 11.5 y)</td>
<td>P: 77 (83) F: 23 (25)</td>
</tr>
<tr>
<td>7. (La Quaglia et al. 1988)</td>
<td>103</td>
<td>17 (mean: 13.3 y, 26% &lt;10 y)</td>
<td>P: 84 (87) F: 7 (7) Not specified: 6 (6)</td>
</tr>
<tr>
<td>8. (Harness et al. 1992)</td>
<td>89(^a)</td>
<td>17</td>
<td>P: 93 (83) F: 75 (6)</td>
</tr>
<tr>
<td>9. (Dottorini et al. 1997)</td>
<td>85</td>
<td>17 (mean: 14.7 y, 8% &lt;10 y)</td>
<td>P: 85 (72) F: 15 (13)</td>
</tr>
<tr>
<td>10. (Borson-Chazot et al. 2004, Causeret et al. 2004)</td>
<td>74</td>
<td>19 (median: 17 y, 35% &lt;15 y)</td>
<td>P: 95 (71) F: 4 (3)</td>
</tr>
<tr>
<td>12. (Segal et al. 1998)</td>
<td>61</td>
<td>19 (mean: 15.8 y)</td>
<td>P: 79 (48) F: 21 (13)</td>
</tr>
</tbody>
</table>

*\(^a\)Abbreviations: DTC = differentiated thyroid cancer; PFS = progression-free survival; TBRFS = total body radioiodine-free survival; LTT = long-term thyroid; TT = total thyroidectomy; LNRFS = long-term nodal radioiodine-free survival; FU = follow-up.

*\(^b\)The survival analyses in the Jarzab et al. (2000) and La Quaglia et al. (1988) series were performed on a subset of patients with PTC who were treated with radioactive iodine.

*\(^c\)The recurrence rate was not specified.

*\(^d\)The treatment was not specified.

*\(^h\)The survival analyses were performed on a subset of patients with PTC who were treated with radioactive iodine.
<table>
<thead>
<tr>
<th>Row No. and Reference</th>
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<td>No. of Patients</td>
<td>Upper age limit, years (other age data)</td>
<td>Histology, % (no.)</td>
</tr>
</tbody>
</table>
| 13. (Chow et al. 2004a) | 60<sup>b</sup> | 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% | LNRFs: 79%<sup>k</sup> 
| 14. (Zimmerman et al. 1998) | 58 | 16 | P: 100 | 28 y (1946–1975) | 36 (21) | 20 (12) | local 12% distant 7% | 97% | NR |
| 15. (Grigsby et al. 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 | 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 et al. 2000) 86% (Alessandri et al. 2000) 100% (Kowalski et al. 2003) 90% |

CI, confidence interval; DRFS, distant recurrence-free survival; F, follicular well-differentiated; FU, follow-up; LN, lymph nodes; LNRFs, 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.

<sup>a</sup>Excludes 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.

<sup>b</sup>From larger series also including adults or patients with other forms of thyroid cancer.

<sup>c</sup>Excluding deaths from medullary thyroid carcinomas, teratomas and malignant teratomas, all recorded in n=34 patients with 20-yr follow-up available.

<sup>d</sup>Shorter follow-up on 102 of these patients was reported in (Jarzab et al. 2000).

<sup>e</sup>Therapeutic radioiodine given for thyroid remnant ablation, treatment of distant metastases, or both.

<sup>f</sup>Refers to locoregional recurrence (independent of distant metastases status at presentation) and excludes patients with recurrence appearing as distant metastases only.

<sup>g</sup>Total or subtotal thyroidectomy.

<sup>h</sup>In patients with enlarged lymph nodes at diagnosis.

<sup>i</sup>In patients without enlarged lymph nodes at diagnosis.

<sup>j</sup>Ablation applied in cases of incomplete excision; therapeutic <sup>131</sup>I also given to 12 patients for distant metastases.

<sup>k</sup>In patients without distant metastases at diagnosis.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of statistical analysis</th>
<th>Key findings of statistical analysis of the influence of treatment related factors on DTC prognosis</th>
<th>Recommendations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Newman et al. 1998)</td>
<td>Univariate</td>
<td>No</td>
<td>Not recommended</td>
</tr>
<tr>
<td>(Welch Dinauer et al. 1998, Robie et al. 1998)</td>
<td>Univariate</td>
<td>No</td>
<td>Recommended</td>
</tr>
<tr>
<td>(Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wróbel A, Kukulska A, Puch Z, Wygoda Z &amp; Jarzęb B, unpublished observations)</td>
<td>Multivariate</td>
<td>Radical surgery and radioiodine ablation were significant independent predictors of local or lymph node recurrence-free survival</td>
<td>Recommended</td>
</tr>
<tr>
<td>(La Quaglia et al. 1988)</td>
<td>Multivariate</td>
<td>Thyroid surgery type was non-significant while age at diagnosis and histologic subtype were significant independent predictors of recurrence</td>
<td>Not recommended</td>
</tr>
<tr>
<td>(Borson-Chazot et al. 2004)</td>
<td>Univariate</td>
<td>Not evaluable, treatment was related to the initial staging</td>
<td>Recommended, though not performed by the authors in their low-risk patients</td>
</tr>
<tr>
<td>(Schlumberger et al. 1987)</td>
<td>Univariate</td>
<td>Significant association between less than total thyroidectomy and recurrence ($P &lt; 10^{-5}$)</td>
<td>Recommended</td>
</tr>
<tr>
<td>(Chow et al. 2004a)</td>
<td>Univariate</td>
<td>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 ($P=0.014$)</td>
<td>Not addressed</td>
</tr>
<tr>
<td>(Zimmerman et al. 1988)</td>
<td>Univariate</td>
<td>No</td>
<td>Not recommended</td>
</tr>
<tr>
<td>(Grigsby et al. 2002)</td>
<td>Multivariate</td>
<td>No</td>
<td>Recommended</td>
</tr>
<tr>
<td>(Alessandri et al. 2000)</td>
<td>Multivariate</td>
<td>Total thyroidectomy, radioiodine therapy and TSH suppression were not significant predictors of time to recurrence</td>
<td>Recommended</td>
</tr>
<tr>
<td>(Kowalski et al. 2003)</td>
<td>Univariate</td>
<td>No</td>
<td>Recommended</td>
</tr>
<tr>
<td>(Landau et al. 2000)</td>
<td>Multivariate</td>
<td>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 ($P=0.02$)</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

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

* Excludes 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.

* Multivariate 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 <100μm, considered active, were prevalent in children <12 years old, while follicles >200μm, 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 Dinauer 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, Mazzaferrifound 15% of locoregional and 24% of distant recurrences more than two decades after initial therapy (Mazzaferr2004).

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, Kukulśka 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

<table>
<thead>
<tr>
<th>Goal of Ablation</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Ablate any residual cancer, including microfoci</td>
<td>Ablation decreases cause-specific death risk independently of extent of surgery (Mazzaferri &amp; Kloos 2001)</td>
</tr>
<tr>
<td></td>
<td>In large pediatric studies, ablation decreased DTC locoregional recurrence risk by a factor of 2.1 ($P&lt;0.0001$) (Newman et al. 1998), and thyroid or lymph node recurrence risk by factors of 11.0 ($P&lt;0.03$) and 3.2 ($P&lt;0.03$), respectively (Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Wrobel A, Kukulska A, Puch Z, Wygoda Z &amp; Jarza˛b B, unpublished observations)</td>
</tr>
<tr>
<td>Ablate healthy thyroid remnant</td>
<td>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 et al. 1997, Mazzaferri &amp; Kloos 2002, Haugen et al. 2002, Mazzaferri et al. 2003)</td>
</tr>
<tr>
<td>Enable sensitive post-ablation WBS</td>
<td>Ablation eliminates sources of thyroid hormone that may prevent endogenous TSH increase after thyroid hormone withdrawal, precluding withdrawal-aided Tg testing or diagnostic WBS</td>
</tr>
</tbody>
</table>

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 >pT1a (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 <2 ml 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 $^{131}$I 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. 1992).
of thyroid carcinoma. 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 (T₄). 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).

### Table 4: Potential predictors of recurrence-free survival in 274 DTC patients diagnosed at age < 28 Years²: results of multivariate analysis

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

CI, confidence interval; DTC, differentiated thyroid carcinoma.

*Statistically significant at \( P < 0.05 \).

²Includes 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.
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 et al. 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 131I is given mostly by authors agreeing that both modalities improve final outcome. There is no apparent 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
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 131I, and one each, external beam irradiation or suppressive T4 only. Excluding three recent patients, median follow-up was 27 years (range, 1–45 years). All patients remained alive, including the two without 131I therapy, who were followed for ~24 years. The individual given only T4 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 131I 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 1997, Van Nostrand & Robbins 1999). 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% loco-regional 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, Fatourechi 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 cases, stressing that foci of uptake were localized by authors supported radioiodine administration in these significantly differ between groups. Nevertheless, the advantage effects in adult patients.

Specifically addressed this question, reported no such disadvantage 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 T3 withdrawal, often with a mixed regime including 2–3 weeks of triiodothyronine (T3) 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 $\geq 3.7$ 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 $200 \pm 66$ mIU/l (range 128–289 mIU/l) then, falling to a mean $4.4 \pm 2.7$ 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. 2003). 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 131I. 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 131I 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 131I 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 131I 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 131I 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 131I treatment (Ceccarelli et al. 2001). Chow et al. (2004b) recently described more than 250 pregnancies in 104 female DTC patients and also concluded that 131I 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 131I, vs 9% in DTC patients who received only small 131I 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 (Mazaferri & Kloos 2001).

Regarding potential harmful effects of radioiodine therapy on reproduction, it should be recalled that ruling out pregnancy at each 131I administration in young women is obligatory. Additionally, females of childbearing age should be instructed to avoid conception within one year after therapeutic 131I, 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 131I activity (Rubino et al. 2003).

Leukemia risk is the reason most authors advise not administering cumulative 131I 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 131I 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 131I 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 131I activity administered, but also considerably influenced by the maximal uptake and effective half-life of 131I 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 131I 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 131I 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, Mazzaferrri & 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 (8.1–120h), 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 but 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 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 131I 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.

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