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PROS AND CONS IN ENDOCRINE PRACTICE

Radioiodine-remnant ablation in low-risk differentiated thyroid cancer: pros

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Abstract Differentiated thyroid carcinomas are typically treated with total thyroidectomy as initial therapy. Subsequent radioactive iodine (RAI) ablation destroys post-surgical thyroid remnants, can additionally provide adjuvant therapy of residual and metastatic thyroid cancers, and enhances the sensitivity and specificity of further diagnostic studies. There is current controversy regarding whether a large number of patients, broadly considered to have "low-risk" disease, should be provided RAI ablation. This is consequent to over-reliance on short-term studies, under-appreciation of the value of RAI remnant ablation, and inflation of the side effects of RAI therapy. A balanced assessment of all of these issues provides justification to utilize post-surgical radioiodine ablation, even in cases that are considered low risk on the basis of surgical findings.

Keywords Thyroid carcinoma · Radioactive iodine · Treatment · Mortality · Toxicity

Introduction

Thyroid carcinoma is precipitously increasing in incidence in the United States and in most countries that maintain tumor registries. Most of this increase is consequent to papillary carcinoma with other types of thyroid cancer remaining constant. Although some epidemiologists have attributed this to increased discovery of small subclinical disease, larger tumors are also increasing. In addition, if subclinical tumors were solely accounting for the increase, we would expect the mortality rates to be diminishing; however, they have been increasing [1, 2]. Typically, patients with differentiated nonmedullary thyroid carcinomas (papillary carcinomas, follicular carcinomas, and their respective variants) are first treated with a total thyroidectomy, variably with local lymph node resection, and then with radioactive iodine (RAI); used for both diagnostic scanning and for therapy, RAI is the only known effective systemic tumoricidal agent for differentiated thyroid carcinomas. The initial therapeutic administration of RAI, termed radioiodine-remnant ablation (RRA), is intended to destroy the post-surgical residual normal thyroid tissue to facilitate diagnostic RAI scanning, permit use of serum thyroglobulin as a tumor marker (with the elimination of nonmalignant sources), and may also initiate treatment of iodine-avid metastatic disease (adjuvant therapy). Recently, there has been a popular effort to omit RRA from the treatment paradigm of a large number of differentiated thyroid cancer patients who are considered to have "low-risk" disease (LRD). Although it is appropriate to avoid RRA for unifocal, intrathyroidal, usual/typical papillary carcinomas at 1 cm or less diameter, which have no evidence of metastases (considered "occult" or subclinical disease), this is not necessarily appropriate for patients with tumors having features exceeding that description (as described below), despite also being considered LRD. This effort is fueled by an exaggeration of the adverse effects of RAI, an undue confidence in the predictive power of surgical staging, inadequate assessments of disease status, reliance upon underpowered, short-term, prospective studies, and retrospective series that are

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often highly flawed [3]. It is also propelled by a simplistic reliance upon disease-specific mortality as the only purpose for therapy and reduces individualized management to an algorithm based wholly on epidemiology. Proper thyroid cancer patient care requires a rational and balanced approach to recognizable goals of therapy, particularly maintaining a realistic appreciation of risks and benefits.

Defining "low-risk" disease (LRD)

The American Thyroid Association (ATA) has defined LRD as being intrathyroidal differentiated thyroid carcinoma of any size, without local or distant metastases, without vascular invasion, and not being an aggressive histological variant (e.g., tall cell, insular, columnar cell) [4]. This definition is based on preoperative staging and the surgical findings. The additional stipulation, lack of RAI-avid sites outside of the thyroid bed, cannot be applied to this discussion if RRA is not done. The American Joint Committee on Cancer and the International Union against Cancer TNM staging system [5] typically designates LRD as including stages I and II (for patients under 45 years of age: any size primary tumor, ± distant/local metastases; and for patients ≥45 years of age: any intrathyroidal primary tumor ≤4 cm diameter with no local or distant metastases). Considering that patients with distant metastases are not properly considered to have LRD, the TNM stage II cannot be considered LRD for patients less than 45 years of age [6]. The Latin American Thyroid Society and the European Thyroid Association staging systems are similar to that of the ATA in regards to LRD, with the exception that "occult" tumors are given the designation of "very low" risk [7]. There have also been some clinicians who seek to further discriminate patients with small volume local metastases as being LRD [8]. Unfortunately, merely designating patients as having LRD based on initial surgical findings and designating risk by retrospective studies is problematic.

There is a significant difference between surgical staging and full clinical staging, utilizing multiple diagnostic modalities (including RAI scans) to reveal the full extent of disease. Preoperative ultrasonography can show nonpalpable local nodal metastases in 30 % of papillary thyroid cancer cases [9], and prophylactic neck dissections for primary papillary carcinomas less than 2 cm in diameter with no evidence of local nodal disease by preoperative ultrasonography reveals another 30 % to have local metastases [10]: further confounded by the lack of agreement regarding whether to do prophylactic neck dissections. Chest radiographs do not reveal pulmonary metastases in more than one third of patients who have them revealed by CT scans and RAI scans [11], and even CT scans are unable to reveal the patients with micronodular pulmonary metastases who are most amenable to effective RAI adjuvant therapy [12]. Pre-ablation RAI scans will "up-stage" patients (by the TNM system), changing staging in 4 % of patients under 45 years of age and 25 % of older patients. Local nodal metastases are revealed in 38 % of the younger patients and in 26 % of the older patients who had been initially staged as not having them based on surgical findings. Likewise, unsuspected distant metastases were found in 4 % of the younger patients and in 10 % of the older patients [13]. Therefore, in the absence of RRA, evaluation for local or distant disease is highly problematic and insensitive, making comparisons between patients treated with RAI and those who did not receive RRA extremely unreliable [14].

The studies that have been used to define LRD are highly flawed with insufficient follow-up in a disease the upward slopes of recurrence and mortality of which do not plateau after several decades. Thus clinical equipoise regarding RRA is augmented by the dependence on studies with follow-up periods as brief as 5 years [15]. Although long-term studies show lower mortality of patients presenting with smaller primary tumors [16], the majority of patients have relatively small tumors, making the absolute number of deaths from small tumors be comparable to those from large tumors. A review of 161 fatal thyroid carcinoma cases by Kitamura et al. revealed that 6.1 % of differentiated carcinoma patients had presented with TNM stage I disease and an additional 5.1 % with stage II disease [17]. Considering the overlap between ATA-defined LRD and the TNM stages, this means that 5.1–11.2 % of fatal cases were ATA-defined LRD at presentation. This is similar to an analysis of cause-specific fatal differentiated thyroid cancer cases by Eustatia-Rutten et al. showing that 19.2 % presented with primary intrathyroidal tumors without evidence of distant metastases [18].

Another problem is that merely defining LRD in terms of mortality, rather than considering disease recurrence, is insufficient. Disease recurrences requiring subsequent therapies are highly stressful to patients [19]. In addition, consideration of the biological origin and progression of aggressive thyroid cancer forces the realization that large or disseminated tumors started as small primary tumors. With all of the concern regarding widespread use of ultrasonography to "over-diagnose" small primary tumors, it is inevitable that biologically aggressive disease will be discovered at a sufficiently early stage to present as small primary tumors—likely to have already hematogenously disseminated prior to thyroidectomy. Failure to properly treat and manage such disease, by administering systemic therapeutic RAI at a stage prior to progression to macroscopic local and distant disease, is a likely irrevocably lost therapeutic opportunity. Likewise, persistent post-surgical

tumor has the opportunity to lose the expression of the sodium-iodide symporter (hNIS) through acquired epigenetic changes to its gene, rendering previously treatable differentiated tumor unresponsive to delayed therapy with RAI [20, 21].

Purpose and benefits of RRA

Properly administered RAI in a carefully prepared patient is the most effective way to deliver high dosages of ionizing radiation targeted specifically to thyroid follicular cells [22], eliminating the post-surgical thyroid remnant (RRA) and providing the opportunity for effective adjuvant therapy of local or disseminated thyroid cancer cells [23]. Considering the ineffectiveness of cytotoxic chemotherapy agents for differentiated thyroid cancer [24], with the only other systemic agents having merely transitory and problematic tumoristatic effects [25], RAI constitutes the only clinically viable systemic cytotoxic therapeutic.

There are a number of well-defined benefits of RRA: (1) by eliminating the thyroid remnant, the only benign source of thyroglobulin, this serum protein becomes a sensitive and completely specific marker for persistent or proliferating thyroid cancer [26]; (2) the post-therapy whole-body scan, performed proximate to the RRA, provides the greatest sensitivity for the detection of iodine-avid disease [27]; (3) correlation of the post-therapy scan with any radiographically or sonographically evident macroscopic tumor sites permits the discrimination of iodine non-avid disease, significantly altering prospective diagnostic and therapeutic approaches; and (4) eliminating the 10–1000-fold higher RAI uptake per gram of normal thyroid remnant tissue (compared to iodine-avid thyroid carcinoma tissue), reduces competition for RAI uptake and enhances both diagnostic scan sensitivity and therapeutic efficacy [22]. In addition, besides eliminating residual normal thyroid remnant tissue, RRA frequently provides coincident adjuvant therapy of local and distant thyroid cancer metastases. In cases of incomplete resection of the primary tumor due to invasive disease, this adjuvant effect is typically intentional with increased dosages of RAI employed for that purpose.

Failure to demonstrate beneficial effects of RRA upon mortality have been consequent to the short duration of follow-up of most studies [14], and these effects are clearly demonstrated when larger numbers of patients are followed for more extended periods of time [28]. RAI therapy clearly reduces locally recurrent disease, both in patients presenting with local metastases and those without evidence of local metastases at the time of primary resection [29]. Verburg et al. have demonstrated a RAI therapy dose-response effect on survival, even in patients considered to have LRD, providing substantive evidence of the value of RRA [30]. There is a growing understanding that radiation-induced destruction of thyroidal tissues, both normal remnant and metastatic disease, can stimulate immune surveillance consequent to release of thyroidal antigens, resulting in radiation-induced immunomodulation of tumor throughout the body [31]. It appears that RAI therapy can induce an abscopal effect [32], causing late regression of tumor despite the absence of demonstrated radioiodine uptake, as evidenced by late regression of thyroglobulin levels in patients previously treated with RAI [33, 34]. The full spectrum of therapeutic benefits of RAI therapy is only beginning to be understood.

Side effects and risks of RRA

RAI therapy for thyroid carcinoma, first started in 1946, is among the best tolerated of systemic cancer therapies. Transient, self-limited effects of typical RAI dosages used for RRA include sialoadenitis [35], nasal irritation [36], dysgeusia, transient bone marrow suppression, temporary amenorrhea, and transient gastrointestinal discomfort [23]. Longer-lasting side effects include episodic salivary duct obstruction in around 12 % of patients, xerostomia in around 5 %, and nasolacrimal duct obstruction in around 5 %.

There is no evidence that RAI causes female infertility or birth defects in subsequent offspring [37]. Likewise, except in the context of repetitive high-dose RAI therapy, its effect upon male gonadal function is minimal and temporary [38]. A key concern has been the issue of second primary malignancies. A meta-analysis by Sawka et al. [39] demonstrated that there was an increased relative risk of leukemia; however, the absolute risk increase was not clinically relevant. Some clinicians harbor a misconception that RAI therapy can contribute to subsequent loss of iodine avidity in surviving thyroid cancer cells. As a source of ionizing radiation, RAI causes DNA damage via mutations and translocations [40]; however, loss of iodine avidity has been demonstrated to be consequent to epigenetic silencing of the hNIS gene, rather than by mutation. Thus, pharmacologic agents, such as selumetinib and methylation inhibitors, can sometimes restore hNIS expression in iodine nonavid tumors [21, 41]: an effect that would not be possible if hNIS were mutated.

Patient perceptions of risk are highly dependent upon emotional factors and subjective perceptions [42] rather than strictly consequent to numerical rationality [43]. Even when significant efforts are made to provide information for decision-making, subjective influences may predominate [44]. In addition, the attitudes of caregivers and public opinions contribute to side effects [45] that are not

Table 1 Comparison of side effects and toxicities of RRA and aspirin

Agent	^{131}I remnant ablation therapy	Aspirin (acetylsalicylic acid)
Date first used	1946	1899
Acute self-limited toxicities	Sialoadenitis	Epistaxis
	Dysgeusia	Dyspepsia
	Nasal irritation/ulcers	Acute hematemesis
	Nausea/vomiting	Asthma
	Stomatitis	
	Diminished platelets and leukocytes	
Chronic persistent toxicities	Xerostomia	Anemia
	Salivary duct obstruction	Nasal polyps
	Nasolacrimal duct obstruction	Bowel mucosal lesions (2 weeks): inc RR 4.0
	Earlier menopause	Tinnitus
		Hearing loss
		General: inc RR 1.21
		Young men: inc RR 1.33
Risk of new malignancy	Any second primary malignancy	ER/PR-negative breast cancer: inc RR 1.81 (1.12–2.92)
	inc RR 1.19 (1.04–1.36)	
	AR + 1.0 % over baseline	
	Leukemia	
	inc RR 2.50 (1.13–5.53)	
	AR + 0.4 % over baseline	
Fatal effects	None	GI bleed
		Women: 0.45/1000/year AED
		Men: 0.79/1000/year AED
		Peptic ulcer: inc RR 1.2–1.6
		Hemorrhagic stroke: inc RR 1.34
		Reye's syndrome (potentially fatal)
		Anaphylaxis

inc increased, *RR* relative risk, *AR* absolute risk, *AED* annual excess deaths

otherwise attributable to RAI therapy. For example, Table 1 directly compares side effects and risks of RAI therapy to those of ordinary over-the-counter aspirin [46–54], in widespread use since 1899: a medication the public considers exemplifying safety. Objective comparison suggests RAI therapy to be far safer than therapy with aspirin.

Balancing benefits and risks

Considering that RAI is the only effective systemic tumoricidal therapy for differentiated thyroid carcinoma and a number of patients have disseminated disease at the time of primary surgery (whether recognized then or not), the only rational and valid reason to avoid RRA would be if a critical appraisal of its risks exceeded its benefits. Unfortunately, those who advocate avoiding RRA, for what is commonly presumed to be LRD, are reflecting an inappropriate magnification of RAI risks and an underappreciation of its benefits, which are not merely limited to short-term assessments of effects on mortality. Although it would be helpful to have long-term (decades) prospective randomized trials to better define the value of RRA, these are unlikely to be feasible [55]. With careful and balanced consideration of the full spectrum of RRA benefits and a frank appraisal of its risks, patients with LRD thyroid carcinoma and their physicians would likely choose RRA therapy.

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