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The role of radioactive iodine in the management of patients with differentiated thyroid cancer – An oncologic surgical perspective☆

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ABSTRACT

With improved understanding of the biology of differentiated thyroid carcinoma its management is evolving. The approach to surgery for the primary tumour and elective nodal surgery is moving from a “one-size-fits-all” recommendation to a more personalised approach based on risk group stratification. With this selective approach to initial surgery, the indications for adjuvant radioactive iodine (RAI) therapy are also changing. This selective approach to adjuvant therapy requires understanding by the entire treatment team of the rationale for RAI, the potential for benefit, the limitations of the evidence, and the potential for side-effects.

This review considers the evidence base for the benefits of using RAI in the primary and recurrent setting as well as the side-effects and risks from RAI treatment. By considering the pros and cons of adjuvant therapy we present an oncologic surgical perspective on selection of treatment for patients, both following pre-operative diagnostic biopsy and in the setting of a post-operative diagnosis of malignancy.

☆ This article was written by members of the International Head and Neck Scientific Group (www.IHNSG.com).

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Introduction

Follicular cell-derived thyroid carcinoma (FCTC), when it is well differentiated, is generally an indolent disease which can be managed by surgery alone in most patients; papillary thyroid carcinoma (PTC) represents 80–85% of cases of FCTC and follicular thyroid carcinoma (FTC) typically 10–15% [1]. Poorly differentiated and undifferentiated (anaplastic) thyroid cancer will not be discussed in this review. The need for additional postoperative therapy increases with the aggressiveness of disease. Radioactive iodine (RAI) has long been known to have a role in the management of both PTC and FTC and the goals of RAI therapy have recently been defined as ablation of normal thyroid tissue (remnant ablation), adjuvant treatment, or treatment of known disease (gross residual, locoregional or distant spread) [2].

Options for disease management teams to consider when managing PTC or FTC range from active surveillance, through conservative surgical resection or aggressive initial surgery with adjuvant RAI to the extreme end of the spectrum, i.e. therapeutic RAI, external beam radiation and targeted therapies for the most advanced cases [1]. For the majority of cases, who present with localized disease confined to the neck, controversy surrounds deciding whether the patient is a candidate for adjuvant RAI. As a bilobar resection approach (whether near-total or total thyroidectomy) is necessary to optimise RAI uptake, the decision to perform more extensive surgery is critical for the surgeon, and guides primary surgical management, with potentially significant consequences for the patient. International guidelines now outline an approach to selection of patients for RAI based on potential for oncological benefit [1–3]. However, a decision regarding the extent of surgical intervention relies not only on such treatment-related indications, but also complex aspects of the patient and their tumour which affect decision making throughout. The aim of this review is to consider the optimal approach to surgical management and will initially consider the evidence base supporting or opposing the use of adjuvant RAI.

Initial experience with radioactive iodine

RAI was first employed in the management of thyroid cancer in the 1940s when it was demonstrated that metastatic thyroid cancer concentrated iodine and in 1942 Keston et al. reported RAI use in treatment of a femoral metastasis [4]. For the next 25 years, reports of the use of RAI in the treatment of thyroid cancer were published in small series [5,6]. In 1967 Pochin [6] described RAI use in 200 patients with FCTC, “mainly with histologically differentiated and inoperable tumours” which they treated over 18 years in London. He demonstrated that RAI uptake developed in over 80% of differentiated tumours after thyroid hormone withdrawal and reported that an average of 6 RAI doses of 5550 MBq each was required over 3 years to abolish all evidence of remaining tumour activity. Clearly all of these patients treated by Pochin would now be considered high-risk using contemporary risk stratification methods.

By the 1970s comparative series were being published. Varma et al. compared 263 patients treated in the era of I-131 to those treated prior, and found that in patients 40 years and older, death rates were significantly lower in patients treated with RAI than in those who did not receive RAI. This difference was not observed for younger patients [7]. Krisnamurthy and Blahd demonstrated that in 54 patients who achieved successful ablation, a lower death rate was observed with a mean delivered dose of 9065MBq [8].

In the same year, Mazzaferri el al. [9} reported outcomes for 576 PTC patients treated at US Air Force Hospitals. His series of papers not only described superior outcomes for PTC and FTC patients treated with total thyroidectomy, in contrast to less than total thyroidectomy, but also demonstrated lower postoperative recurrence rates for those patients treated with RAI [9–11]. [9–11]. In a subsequent re-analysis of the data, no improvement in recurrence rates after RAI were seen in low-risk PTC patients with tumours <1.5 cm in diameter [11]. Although these papers had a wide reaching impact on the management of PTC, careful scrutiny of the original (1977) report showed that the actual number of patients treated with RAI following successful macroscopic excision of all disease was limited (n = 33), with the majority of patients having unresected nodal disease or distant metastases [12]. Despite its limitations, this 1977 paper influenced clinicians globally and promoted the use of RAI following surgery for the majority of patients with either PTC or FTC. The interplay between RAI and completeness of initial surgery was further demonstrated by the Michigan group in 1984 who found that successful RAI ablation was more difficult to achieve if a significant thyroid remnant was left behind. They recommended performing the “best possible total thyroidectomy” to aid successful remnant ablation [13].

However, not all endocrine oncologic groups agreed with the findings reported by Mazzaferri el al. The MD Anderson group reported outcomes for 706 patients with differentiated thyroid cancer (DTC) treated from the 1950s onwards. Although patients who received RAI had fewer recurrences, this did not translate into significant differences in either disease-free interval or survival benefit [14]. In 1983 Snyder et al. [15] from the Mayo Clinic reported outcomes for 69 patients with PTC or FTC who had radioiodine remnant ablation (RRA) after being initially treated with total or near total thyroidectomy. Their finding that successful RRA did not protect against locoregional recurrence, which occurred in 9% of their DTC patients, led them to conclude that RRA in low-risk DTC may represent a “questionable pursuit of an ill-defined goal” [15].

Risk stratification and adjuvant radioactive iodine

By the 1980s, the influence of prognostic factors on outcomes and the concept of risk stratification in DTC had been well established [16–19]. The Mayo Clinic group continued their detailed analyses of the impact of therapy on outcome, time and again demonstrating that, in low-risk PTC patients with MACIS scores [19] of <6, there was no evidence that RRA improved recurrence rates or survival after initial bilateral lobar resection with complete resection of all grossly visible disease [20–23]. In 2012, Schvartz et al. studied almost 1300 low-risk DTC patients managed over a 30 year period and found no impact on survival or disease free interval associated with RAI [24]. The lack of impact demonstrated by RAI use in low-risk cases has been supported by a number of recent systematic reviews on the subject [25–27]. However, it should be noted that much of the evidence in this field is retrospective and subject to bias. As such, not all experts agree, as highlighted in a recent joint statement from American and European Societies [28].

However, at the other end of the spectrum, for high-risk disease oncological improvements were demonstrated both retrospectively and in prospective cohort studies. In 1998, Taylor et al. in a prospective North American multicentre study reported improved recurrence and survival rates in high-risk PTC and FTC patients after RAI therapy was administered following initial total or near-total thyroidectomy [29]. Interestingly however, for PTC patients, when tall cell variants were excluded the significance was lost [29]. Similar results were demonstrated by Jonklaas et al. in a later analysis of the same National Thyroid Cancer Treatment Cooperative Study (NTCTCS) Registry cohort where improved outcomes were reported from stage II-IV patients following RAI, which were not seen for stage I patients [29,30]. In aggressive variants of DTC, such as insular and Hurthle cell carcinoma, National Cancer Data Base (NCDB) analysis has also suggested a role for RAI in reducing deaths from disease [31–33]. Similar databases have also been used to show a survival benefit in older patients with larger tumours, nodal metastases and M1 disease [34].

Therefore, for high-risk and low-risk patient groups, the positions are clear both for and against the routine use of RAI, respectively. However, a large group of patients present with disease considered to represent an intermediate risk. This group has proven difficult to study for a number of reasons. Firstly, outcomes are favourable with few deaths and a limited number of recurrences. Secondly, classification of intermediate-risk disease is variable between studies. The American Thyroid Association (ATA) classifies intermediate-risk disease as demonstrating microscopic extra thyroidal extension (ETE), significant nodal disease or adverse histological features [1]. However, recent data have suggested microscopic ETE and extension in to the strap muscles (the most common site) to be lower risk than previously considered [35–37], factors which had not been considered in historical studies.

Analysis of the Surveillance, Epidemiology, and End Results Program (SEER) database has shown that with huge cohorts of patients, statistically significant differences in survival for intermediate-risk patients can be demonstrated. However, with survival differences of as little as 1% in some groups and the methodological limitations of such datasets, the clinical significance of these findings has been questioned [38]. Chow et al. retrospectively demonstrated a recurrence advantage when intermediate risk patients were managed with RAI, with the greatest advantage reported in those with the most advanced nodal disease [39]. Similar findings have been shown prospectively by Jonklaas et al. [29] reporting on behalf of the NTCTCS Group. The results of this analysis are complex, however, as some patients who would now be considered as intermediate risk of recurrence (younger patients with N1 disease) were categorised as low-risk in this study, and no benefit was demonstrated in this stage I disease. In keeping with these findings, the Mayo Clinic also reported no benefit in patients with nodal disease who were categorised as low risk [40]. These inconsistent findings are recognised in systematic reviews of the subject reporting a similar number of studies which demonstrate the benefit of RAI in intermediate risk disease to those that do not [27]. It is hoped that over the coming years, the “Iodine or Not” trial from the United Kingdom, which is randomising intermediate risk patients to RAI or not following total thyroidectomy, will help clarify the position in this challenging group of patients [41].

It is important however to understand that simply the discovery of a well differentiated FCDC in a lobectomy specimen is not of necessity an indication for completion thyroidectomy. Most patients with unifocal, intrathyroidal (low-risk) tumours may be cured with unilateral lobectomy alone. The need for completion total thyroidectomy should be carefully studied, as few patients with such minimal disease will benefit from adjuvant RAI, and therefore do not require a completion thyroidectomy.

The use of RAI as an alternative to completion thyroidectomy has been reported in small case series. The concept is particularly attractive in those patients who have had a diagnostic lobectomy and are found to have high-risk malignancy on final pathology, or have positive margins or gross extra-thyroidal extension of disease which may make it unresectable [42]. Due to potential risks of completion surgery, some groups have used RAI “lobectomy” in this setting. This may be considered suitable for patients who are at extremely high risk from further surgery, following initial recurrent laryngeal nerve injury [43–46]. However, experience is limited and this is not a widely accepted practice at present. There are potential drawbacks to this approach, as the residual normal thyroid tissue will absorb much of the activity, limiting the activity absorbed by residual thyroid cancer cells.

Therefore, at present, the results of progress in addressing the question of whether RAI should be used in the management of DTC have been clarified for the most advanced cases, where its use is widely supported [47]. To some degree in the lowest-risk cases clinicians agree that there is no impact on outcome. For a large group of intermediate-risk cases however, the evidence remains conflicted (Tables 1 and 2). Given the low rates of recurrence in this group (5–20% [1]) and the large cohort size therefore required, coupled with the prolonged follow-up necessary, it is unlikely that any oncological advantage of adjuvant RAI will ever be proven for intermediate-risk patients.

What dose of adjuvant radioactive iodine?

In addition to the debate over the need for RAI, there has also been controversy over the doses required for treatment. In 1987, Creutzig et al. reported similar rates of successful ablation using low (1100MBq) versus high dose (3700MBq) treatment [48]. Similar results were reported in a prospective randomised trial of 63 patients assigned low versus high dose treatment without any demonstrable difference in post ablation outcomes on the 6 week post-treatment scan [49]. Bal et al. also found no improved efficacy with higher doses of RAI, recommending no more than 1850MBq as the target dose following total thyroidectomy [50]. The same group went on, in larger prospective trials to recommend a dose between 925 and 1850MBq [51] and ultimately to conclude in 2012 that similar outcomes were seen with low, intermediate or high doses of RAI and that they were probably administering too much iodine in remnant ablation [52]. Rosario et al. found similar results in 2004 [53], as have many subsequent groups over the past 2 decades [54–60].

In contrast, Gawkowska-Suwinska et al. found a marginal improvement in post ablation results in 220 patients with T1b-T3 N0M0 DTC treated with a higher dose of RAI, when comparing 2220MBq versus 1110MBq) [61]. Zaman et al. also found higher rates of successful ablation (60% versus 40%) for 40 patients treated with 3700MBq versus 1850mBq [62]. In 2012, Fallahi et al. recommended high dose (3700MBq) RAI for remnant ablation following a randomised trial of 341 patients in whom the low dose group (1110MBq) had higher rates of requiring a second dose of I-131 (64% versus 39% successful ablation for high versus low dose respectively), resulting in higher overall activity levels being delivered and more in-patient time [63].

In 2012, the New England Journal of Medicine published two landmark trials of low- versus high-dose RAI in low-risk DTC [64,65]. Mallick et al. reported similar levels of post ablation success and a lower rate of adverse events for 438 patients with T1-T3 tumours treated with 1110MBq versus 3700MBq in a multicentre randomised trial in the United Kingdom [64]. Schlumberger et al. included over 700 patients with T1-2,N0-1 DTC treated at 24 French centres with 1110MBq versus 3700MBq. Again, outcomes in both groups were comparable with excellent post-ablation outcomes (92% complete ablation) with the authors concluding that the lower dose may be sufficient for ablation of remnant thyroid tissue. In an accompanying editorial Alexander and Larsen [66] noted that both RAI doses were equally effective at reducing serum Tg to a very low level and eliminating residual thyroid tissue, as seen on ultrasonography, and that thyroid ablation occurred even in patients with pathologically confirmed regional node involvement. They felt the results from both studies should change standard practice, but also did raise the question of whether any RAI is required for low-risk patients “since 21–59% of patients in these two studies had already met the goal of a low Tg level after thyroidectomy alone” [66].

Radioiodine remnant ablation is the term used for postoperative treatment without clear evidence of ongoing malignancy which is

Table 1
Low, intermediate and high-risk stratification (adapted from the American Thyroid Association Guidelines [2]).

	Papillary Carcinoma	Follicular Carcinoma
Low Risk	• T1-2,N0,M0 • Complete resection • No aggressive histology • No vascular invasion • Clinically N0 or <5 nodes all with less than 2 mm deposits • Multifocal microcarcinoma	• <4 foci vascular invasion
Intermediate Risk	• Microscopic extra thyroidal extension • Aggressive histology • Vascular invasion • Clinically N1 (no nodes >3 cm) • RAI-avid metastatic nodes in neck on post treatment scan	• Microscopic extra thyroidal extension • Clinically N1 (no nodes >3 cm) • RAI-avid metastatic nodes in neck on post treatment scan
High Risk	• Gross extra thyroidal extension • Incomplete resection • M1 (structural of thyroglobulin suggestive) • N1 disease and node >3 cm • Follicular carcinoma with >4 foci of vascular invasion	

Table 2
Factors related to decision to offer completion thyroidectomy for RAI following initial lobectomy.

	Favour Completion for RAI	Favour Observation
Age	Older	Younger
Personality	Anxiety about recurrence	Anxiety about side effects of treatment
Occupation		Professional voice user
Ultrasound	Contralateral nodular disease	Normal contralateral lobe
Histology	Significant lymphovascular invasion, multifocality, low volume nodal disease, extra-thyroidal extension	Small volume primary, pN0 disease
Functional status	No swallowing difficulty, no contraindication to general anaesthesia	Swallowing difficulty, contraindications to general anaesthesia, challenging initial surgery

designed to eliminate thyroid bed gland remnants which may persist after total thyroidectomy and may also serve to stage other disease sites not recognised at first surgery [28]. Thyroid bed uptake is nearly universal after even expert total thyroidectomy and a classification system has been generated to describe its pattern [67].

These results suggest therefore that there is likely little benefit in increasing doses of RAI in patients treated for low or intermediate-risk disease. Whether low dose is as good as no dose is a question that remains to be answered [41]. At present one new multicentric trial (IoN) in the United Kingdom is being carried out to address this question [41].

Radioactive iodine for recurrent differentiated thyroid cancer

As stated above, evidence supporting the use of RAI in the primary setting is of low quality and conflicted for many patient groups. Unfortunately, there is even less evidence in the setting of recurrent disease [68]. When locoregional recurrence is structurally identified, surgery is first in the hierarchy for treatment [1]. Following surgery, in the absence of distant metastases, there is little evidence to support RAI.

Hung et al. reported no difference in outcome for 102 patients treated for recurrent PTC with or without RAI in long-term follow-up [69]. Similar findings were reported by Yim et al. who limited their analysis to PTC patients with a detectable stimulated Tg level following re-operative surgery [70].

In patients who have a rising serum thyroglobulin (Tg) level but an absence of structurally evident recurrent disease the role of "empiric" RAI is unclear. It can be used to identify sites of disease or in an attempt to reduce Tg levels. However, such an approach has not been shown to result in improved survival. Consequently, the ATA guidelines [2] do not recommend such an approach, but recommend consideration of RAI in this setting only when the Tg levels are rapidly rising. They highlight the fact that this is a weak recommendation based on low-quality evidence [1].

In the absence of strong data on which to base decisions, again treatment teams must consider a number of variables. In low-risk patients who manifest disease in the contralateral lobe following initial thyroid lobectomy, simple completion thyroidectomy may be sufficient. For those patients who develop high volume regional recurrence, surgical excision can be followed with assessment of serum Tg on throxine suppressive therapy.

Side effects of radioactive iodine

Although RAI has significantly less morbidity than external beam radiotherapy, it is not without side effects. These are dose related and expressed by the additional tissues which concentrate iodine, namely salivary and lacrimal glands [71–73].

Some patients complain of acute taste disturbance, and chronic dry eyes and a dry mouth, which contributes to difficulty in swallowing [72,74]. RAI treatment is associated with increased rates of sialadenitis [75] which in turn can have a significant impact on quality of life [76,77]. Indeed there is a reported 20% rate of dysfunctional salivary glands five years following RRA [78]. Symptoms of obstructive sialadenitis following RAI can currently be helped by sialendoscopic dilatation, rinsing and corticosteroid injection, a therapeutic option that many thyroid oncologists are unaware of [79].

In addition, there is a reported slightly increased risk of secondary haematological and salivary malignancy in patients who have received increasing doses of RAI, although this is unlikely to impact decisions at an individual level [80–82].

Therefore, the side-effects of RAI are both acute and long term. Although relatively mild in comparison with those related to external beam radiation, the chronic effects remain problematic in a group of patients who can expect long-term survival.

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The current situation

Despite conflicting evidence, guidelines on the management of DTC have attempted to provide a consensus approach. In 2009 the ATA guidelines recognised the conflicting data but recommended RAI for all high-risk patients and selected patients with 1–4 cm tumours and any high-risk feature. RAI was routinely recommended for high-risk patients with macroscopic ETE or significant regional or distant metastases. Microcarcinomas (<1 cm) were recommended not to receive RAI [83]. A similar approach was adopted in the UK with a recommendation to consider RAI in all cases other than classical micropapillary carcinoma in the British Thyroid Association (BTA) Guidelines [2]. In the 2015 updated ATA guidelines, a slight move away from an almost universal recommendation for RAI has been seen. The ATA guidelines now do not recommend RAI in low risk cases but consider its use in intermediate risk cases, particularly as risk factors such as advanced age and nodal burden increase [1]. However, mainland European groups have not endorsed such a move, pointing to the lack of prospective evidence to support it [28,84,85].

Given the conflicting evidence, combined with general support for RAI in most cases provided by powerful international guideline statements, it is hardly surprising that rates of RAI have been rising. Whereas in the 1990s around 40% of patients with tumours over 1 cm received RAI in the USA this had risen to over 60% by 2008 [86]. However, there is some suggestion that rates may now be starting to fall for lower-risk patients in the USA [87]. Within these findings there was significant heterogeneity of approach based on both patient and clinician factors suggesting continued uncertainty for many involved in this field.

Although exact causes for this variation in practice are unclear, they are likely to be influenced by multiple factors. The environment of clinical practice has been shown to be critical with high-volume centres more commonly recommending RAI [86]. However, approaches to imaging and pathological processing of surgical specimens have also evolved over the decades. There is an ever-increasing level of scrutiny applied to each case in order to identify evidence of higher risk features such as previously occult nodal disease on ultrasound scan, and adverse histological features on pathology. The increase in frequency of prophylactic central neck dissection has produced a stage migration, that also induces the use of more RAI. Such an approach leads to an increasing number of patients identified as having higher-risk features which further, encourage treatment intensification [88].

Radioactive iodine and the surgeon

When considering the initial approach to DTC, the surgeon must consider a number of factors. Initial investigations may clearly identify patients who should or should not receive RAI and must therefore be dealt with appropriately. Examples would include a proven intra-thyroidal carcinoma without regional or distant disease. Such patients do not benefit from RAI and do not require total thyroidectomy to facilitate adjuvant therapy. In contrast, patients with significant nodal disease, distant disease or gross posterior macroscopic extra-thyroidal extension will require RAI and should undergo total thyroidectomy [1,2,89].

For the majority of patients, however, the situation is less clear and an individualised approach is recommended by guidelines. It is now well recognised that for patients with intrathyroidal disease, in the absence of high-volume nodal disease, distant disease or posterior gross extra-thyroidal extension [37], outcomes are excellent irrespective of whether or not adjuvant RAI is used. Selecting patients for RAI based on pre-operative staging may therefore not be possible. A 2 cm cytologically proven PTC without evidence of regional disease may, on surgical pathology prove to have significant lymphovascular invasion or adverse histological features which would prompt consideration of RAI. In contrast, for a classic papillary thyroid carcinoma without such features, treatment with lobectomy alone may be sufficient.

For many patients then, the surgeon needs to consider a variety of non-cancer factors prior to intervention. For example, is there a background of multinodular disease? If there is, particularly if these are not all ultrasonically benign in appearance, consideration should be given to total thyroidectomy versus lobectomy. Is there a reason to consider the patient particularly vulnerable to recurrent laryngeal nerve injury? Professional voice users, patients with pre-existing nerve palsies or those with an unsafe swallow prior to intervention may be more suitable for lobectomy rather than total thyroidectomy. For clinicians practicing in areas of the world where ready supplies of supplements such as calcium and vitamin D are not easily obtainable, a more conservative approach may be favoured to avoid long-term complications associated with a lack of supplementation [90]. Based on these clinical factors, in addition to the initial pre-operative clinical tumour staging, the surgeon will then provide a surgical specimen of either total thyroidectomy or lobectomy. Analysis of the tumour within will then dictate further management. Of course, discussion as to the extent of thyroidectomy with a clinical endocrinologist would be important as he/she will likely contribute significantly as part of a multi-disciplinary team in the overall case management, particularly in long-term postoperative follow-up.

When a total thyroidectomy has been performed, the patient is in a position to receive an ablative dose of RAI if indicated. This is particularly important if the operation was a sub-total thyroidectomy, where RAI was historically used for thyroid remnant ablation to facilitate follow up. It is therefore crucial that, when a total thyroidectomy is contemplated, it should be a “true extra capsular total thyroidectomy”, leaving no thyroid tissue behind, thus avoiding the need for “remnant ablation”. Such an approach often renders the Tg level undetectable without the need for RAI to ablate residual normal tissue in the hope of achieving an undetectable Tg. Consideration of pathological details including tumour size, adverse histology, associated nodal metastases and clinical findings in the operating room will all contribute to the multidisciplinary decision regarding the need for RAI therapy, not just remnant ablation. Many patients with thyroid cancer have significant anxiety regarding the disease [91–93], despite the excellent outcomes and the threshold for administering adjuvant RAI is correspondingly low.

If thyroid lobectomy has been performed, a similar process of consideration of the pathology should be performed. At present, international guidelines make recommendations regarding indications for RAI based on oncological factors alone. The current ATA guideline for example recommends completion thyroidectomy when a total thyroidectomy would have been recommended if the diagnosis had been available prior to initial therapy [1]. However, this is an oversimplification of the situation at the point of considering further surgery.

In contrast to the patient who underwent total thyroidectomy, adjuvant RAI will require a readmission for completion thyroidectomy. It has been well demonstrated that this procedure rarely, if ever, results in additional primary disease risk factors being identified other than previously occult small volume multifocal disease [94,95]. Therefore, clinicians should recognise that this procedure is only performed to facilitate RAI. The risks of completion thyroidectomy are not insignificant with long-term complications recorded in up to 10% of cases [96,97]. Such an approach should only be recommended if the management team consider the benefit of RAI to exceed the inconvenience and risk of further admission for

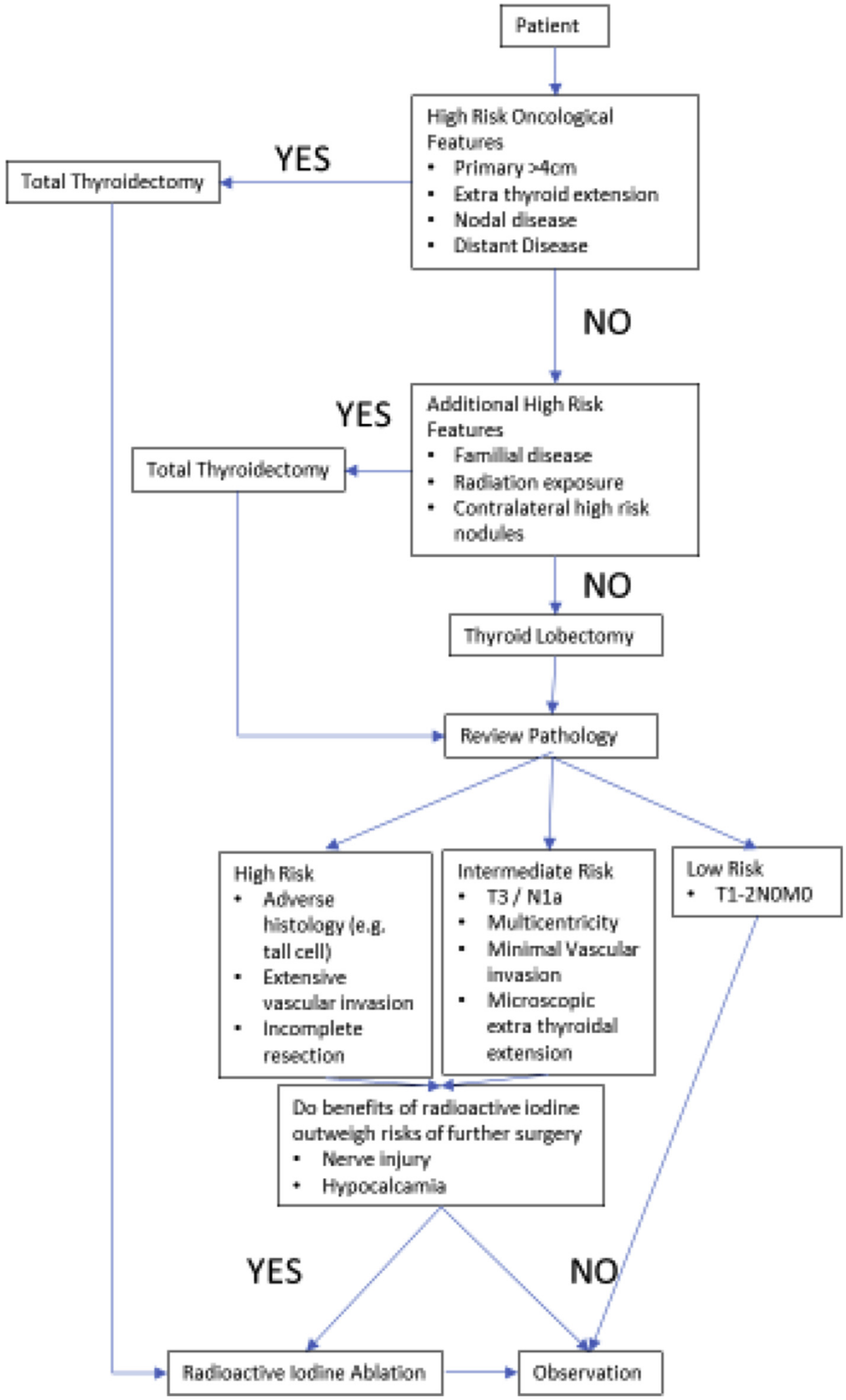

Fig. 1. Flow chart for surgical planning in differentiated thyroid cancer.

surgery and then radiation and the associated long-term side effects. In practice this can be a difficult estimate to make. For lesions which demonstrate widely accepted high risk features such as tall cell variant PTC or gross extra-thyroidal extension, RAI will be indicated. For low-risk lesions without any adverse features, no further therapy is required. A framework for considering the situation following treatment without RAI based on imaging and serum Tg levels in the post-surgical setting has been reported by Momesso et al. [98].

Many patients, however will have disease which is difficult to risk stratify. The presence of multifocality for example, uncertainty regarding lymphovascular invasion, small volume incidentally excised metastatic nodes or the presence of microscopic extra thyroidal extension are all risk factors which were not part of the original risk stratification systems but are now routinely reported. For these cases the surgeon must recognise not only the oncological uncertainty regarding the importance of these factors but also more subtle features of the patient. These will include age, the patient's personality, occupation and pre- and post-operative functional status. In addition, findings in the operating room may influence the recommendation for further surgery. In lower risk cases where surgical anatomy or physiological fitness made a case challenging, the risk of surgery is higher and may outweigh the potential benefit of adjuvant RAI (Table 2).

Brief mention of the regional lymphatics should also be made. Although the role of therapeutic neck dissection is generally accepted, that of elective surgery remains highly controversial. In the setting of selection of patients for RAI, some groups recommend elective staging of the neck in order to more accurately identify those patients who may benefit from RAI [88]. This practice identifies occult central neck disease in around one third of patients. These patients are then considered for RAI treatment based on nodal factors rather than primary disease features alone. However, such an approach has never been shown to be beneficial in terms of recurrence or survival and many groups who choose to leave such cN0 necks undissected do so without any evidence of adverse outcome for their patient groups [99]. Clinicians who choose this approach to treatment should understand that, although they may demonstrate pN0 disease in many patients and thereby reduce pressure to consider adjuvant RAI, they will also upstage a significant number of patients with small volume nodal disease for whom most teams will feel compelled to recommend further therapy without clear evidence of benefit.

The surgeon factor must also be considered. The relationship between surgical volume and complications is clear [100], but the relationship with complete thyroidectomy is poorly explored. The definition of total thyroidectomy is heterogenous, and some surgeons leave a small piece of thyroid gland near Berry's ligament or the upper poles in order to protect the recurrent laryngeal nerve or the parathyroid glands. Surgeons who perform this type of surgery will experience a higher post-operative serum Tg level in their patients. In some practices, it is assumed that RAI will compensate for this surgical approach; however, it may partially explain differences between rates of use of RAI.

Finally, the patient's wishes must be considered. Some patients press to receive RAI under the assumption that it will offer an advantage. In many practices, this pressure is hard to manage and some treatment teams may feel obliged to offer RAI even when not fully convinced of its oncological benefit.

Conclusion

In common with many aspects of the management of patients with DTC, the role of adjuvant RAI is complex and hindered by a significant amount of low-quality evidence. Early evidence demonstrated the potential that RAI had in treating the most advanced thyroid cancers. In the middle of the 20th century RAI became the standard of care for the majority of cases. However, the advent of risk stratification allowed identification of low-risk groups with little to gain from adjuvant therapy and high-risk groups who gained the most. Most recently, high-quality prospective clinical trials are demonstrating a reducing role for radioactive iodine, limiting its use to higher-risk cases. This decrease in use of routine RAI also withdraws one of the former reasons for total thyroidectomy (to facilitate RAI) and dovetails with our increasing awareness of lobectomy as an adequate initial treatment for patients with smaller tumours without extrathyroidal extension or clinically apparent nodal disease. It is critical therefore that the modern thyroid surgeon appreciates patient, tumour and background thyroid-related factors which will influence decisions regarding initial surgical therapy (Fig. 1). By carefully balancing the information available at the pre-surgical, peri-operative and post-operative stages, the surgeon can provide personalised recommendations which aim to optimise both oncological and functional outcomes for patients with DTC.

Declaration of competing interest

The authors have no conflicts of interest to declar.

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