Oncological outcomes for patients with well differentiated thyroid cancer

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Chapter 10

Discussion, conclusion and future directions
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With the incidence of differentiated thyroid cancer (WDTC) increasing in the US and worldwide [1-6], it is now more important than ever to be critical of understanding disease behaviour, selection of optimal treatment and outcomes of therapy. Very few patients will die of WDTC, indeed few will develop recurrent disease during follow up, and for those reasons one must consider not only oncological outcomes, but iatrogenic morbidity when deciding on therapy. The aim of this thesis was to update our understanding of the biology of WDTC, and to critically analyse the outcomes of surgery and adjuvant (RAI) radio iodine therapy.

The introduction (Chapter 1) describes the changing trends in incidence of WDTC. We go on to describe the long term outcomes experienced by patients with WDTC, and put these results in historical context. The evolution of systems to predict risk of death or recurrence from WDTC are then described, as is the evolution that has occurred in the approach to both surgical and adjuvant therapy. This historical account both serves to describe the context in which our further work exists, but also highlights the areas of controversy in selecting therapy for patients with WDTC. The approach to management of the primary lesion, the regional lymphatics and selection of patients for adjuvant radiation therapy are all highly controversial, and remain unresolved topics for debate.

In Chapter 2 we analyzed the experience of a single institution, tertiary care cancer center over eight decades. Institutional trends have mirrored patterns reported nationally, with an increasing volume of disease managed in each decade. In addition to the change in incidence, our patient group has aged, with older women constituting a larger percentage of the cohort in recent years. Not only has the patient group changed, but the tumors now managed are smaller with over half of the cohort harbouring pT1 disease (<2cm). In addition to the change in size observed, a greater percentage are described as papillary thyroid cancer (PTC) on histology. This is due to changes in histological definitions and also to the increased incidence of PTC reported nationwide.

A change in the extent of surgery was also observed with an increase in total thyroidectomy versus thyroid lobectomy during the time period studied. This trend is in keeping with national figures, although the reasons underlying this change are complex. Undoubtedly, the introduction of high resolution ultrasound scanning has allowed clinicians to identify previously occult nodularity in the contralateral lobe, resulting in a need for total thyroidectomy. However, this is unlikely to be the sole reason for the magnitude of change observed. Interpretation of the conflicting evidence on the extent of initial surgery required for WDTC has resulted in various international guidelines [7-9] recommending total thyroidectomy for all but the smallest of primary cancers. Despite the limitations of the evidence upon which such recommendations are based, they do influence practice by impacting not only on the treating surgeon, but also the patient and the endocrinologist or nuclear medicine physician involved in the care of WDTC.

Similar complex influences were also seen to affect the use of radioactive iodine (RAI) during the study, with increasing usage as RAI became readily available during the 20th century.
Despite conflicting evidence regarding efficacy, nearly half of the group in this study received adjuvant RAI, particularly in the later years of the study period.

In contrast to the changes observed in patients, tumors, extent of primary surgery and use of adjuvant RAI, outcomes have remained relatively constant. Since the introduction of a standardized risk stratified approach to therapy, less than 5% of patients treated died of disease within 10 years of surgery. We can therefore conclude that it is the biological behaviour of WDTC, that results in excellent oncological outcomes. Few patients will die of disease and recurrence rates are low. Following adequate surgery and histological analysis, those patients who are at higher risk of recurrence and/or death can be readily identified.

For these reasons we must be critical of our therapeutic approach to this usually indolent disease. An increasingly aggressive approach to surgery and widespread use of RAI has not improved survival in this patient group, highlighting the importance of selective therapy to minimize morbidity whilst maintaining excellent outcomes.

Chapter 3 further considered the interplay of disease biology and therapeutic intervention by analysing the mode of death for those patients who were considered free of disease following initial treatment for WDTC. Improvements in surgical technique, including extracapsular total thyroidectomy, (instead of subtotal or near total thyroidectomy) as the oncological procedure of choice, has had a significant impact on outcome of these patients. A disease once associated with significant rates of death secondary to central compartment recurrence, including asphyxia and haemorrhage, has now largely been eliminated. Very few patients in this series (<2%) who present with resectable locoregional disease and without evidence of distant metastases die of thyroid cancer. However, of those patients who do die of disease, instead of dying from uncontrolled central neck disease, the majority of them now die from distant metastases. Our results are in keeping with other groups’ experience [10], and underscore the need for an oncologically sound approach to WDTC both to prevent death and avoid distressing terminal events.

In Chapter 4 we considered thyroid isthmusectomy for select patients with solitary small cancers confined to the isthmus. This simple procedure avoids risk to the recurrent laryngeal nerves and parathyroid glands. Despite the surgical advantages of such an approach, the technique is not even referred to by international guidelines in the field of oncological thyroid surgery [7-9]. Despite the lack of evidence reported in the literature regarding outcomes for this procedure, targeted resection of disease limited to the thyroid isthmus is oncologically sound. It allows the resection of malignancy with negative margins in properly selected patients. Approximately 1% of our patients had isthmusectomy alone, and at 10 years no patient had local, regional or distant recurrence. Such excellent outcomes provide the evidence required to recommend isthmusectomy in a very select group of patients with limited disease, confined to the isthmus, with no evidence of nodular disease in the thyroid lobes and without nodal or distant metastatic disease.

Although isthmusectomy is appropriate management for a highly select group of patients, thyroid lobectomy is usually indicated in nearly half of the patients who present with WDTC,
confined to one lobe, with no other abnormality in the other lobe, and this was the focus of Chapter 5. Over the past 20 years, there has been a trend away from lobectomy, both in our own institution and nationally. This move is supported by a number of large studies which have suggested that patients who have tumors over 1-1.5cm have better outcomes when managed by total thyroidectomy versus more limited primary surgery [11, 12]. Unfortunately, the findings of these studies have been incorporated into international management guidelines without adequate recognition of their significant limitations [7]. The absence of detailed information on histological subtype, extra thyroid extension, completeness of resection and site of recurrence renders such analyses of multi-institutional databases insufficient to conclude that total thyroidectomy should be considered the standard of care for most patients with WDTC. More recent data from similar national sources has not supported these earlier reports [4, 13-15], and experience from single institutional series, with very detailed treatment and outcome data, have long supported the use of thyroid lobectomy in patients with unifocal disease limited to a thyroid lobe [16, 17]. Our recent data again demonstrates the excellent outcomes that can be expected following lobectomy for pT1/T2N0 disease. Such patients do not die of disease, and the extent of surgery on the thyroid gland had no impact on the low risk of recurrence within this group.

Indeed, when clinical staging of T1 or T2 tumors is compared to pathological staging, an important observation has emerged. In those patients with clinically intraglandular disease (T1 or T2) who are shown to have microscopic evidence of extra thyroid extension, on pathological analysis, showed no impact on outcome, as discussed in Chapter 6. Even thyroid lobectomy in such patients was not associated with either increased incidence of recurrence or mortality. The clinical implications of this finding suggest that completion thyroidectomy is not mandatory in such patients (with microscopic extrathyroid extension) as no improvement in oncological outcome would be expected as a result of further surgery.

Why should we concern ourselves with extent of surgery in the management of WDTC? Experts have demonstrated that total thyroidectomy can be performed with complication rates commensurate with thyroid lobectomy, and most patients will require post-operative thyroid stimulating hormone suppression irrespective of the extent of surgery. However, worldwide, the vast majority of thyroid surgery is not performed by by international experts, working in centers of excellence. Even if all patients were treated in such tertiary care units, the fact that a procedure can be performed with minimal collateral damage does not mean it should be done if no benefit in outcome is obtained. In contrast to the evidence from large academic units, total thyroidectomy has been reported to have higher rates of hypocalcaemia, recurrent laryngeal nerve injury and tracheostomy than lobectomy when carried out in community hospitals [18, 19]. As stated above, it has not been proven to result in benefit for low risk patients. Guidelines must take these factors into account, as they exist for the protection of patients, not only from disease but also from therapy.

In addition to surgery for the primary disease there is considerable controversy over the role of elective central neck dissection, which was the focus of chapter 7. Existing evidence does not suggest that elective neck surgery results in any measurable benefit. Despite this, there is a
high rate of occult nodal metastasis in patients who undergo elective central neck dissection. The lack of outcome benefit demonstrated by numerous groups led to the American Thyroid Association (ATA) changing its guidance on central neck dissection from a statement suggesting that it “should be considered in papillary carcinoma” to “may be performed, particularly for advanced primary tumors”. There remains intense controversy about the place of elective neck surgery in WDT, with strong proponents of both dissection and observation. We examined outcomes for those patients who had only total thyroidectomy. Around 40% of such patients would be expected to harbour clinically occult nodal metastases. Despite that, no patient required further salvage central neck surgery. These results highlight the fact that those patients without detectable metastases in the central or lateral neck have excellent outcomes when managed by total thyroidectomy. Rates of recurrence are so low that considering more aggressive surgery in an attempt to re-stage, and therefore be even more aggressive in terms of adjuvant RAI seems unjustified. Such an approach is very likely to leave patients with side effects including nerve paralysis, hypocalcemia, dry mouth and dysphagia, when their outcome without elective central neck dissection would have been excellent anyway. Our cohort of patients was screened using clinical and intraoperative examination in the main. All patients managed today undergo ultrasound assessment of the central neck, and so higher rates of suspicious disease will be encountered. Therefore, if a patient is considered free of metastatic nodal disease following pre-operative assessment and intraoperative examination, the central neck should be left undisturbed to avoid complications whilst maintaining excellent oncological outcome.

Although surgery is the mainstay of therapy, radioactive iodine (RAI) is increasingly used in the management of WDT [20, 21]. Again controversy exists about the correct indications for selecting this relatively low morbidity treatment modality. The evidence supporting the benefit of RAI for all but the highest risk patients is conflicting. Although some groups have shown improvements in outcomes with the use of RAI [11], this has not been universal with other groups reporting that RAI has no impact on survival or recurrence rates in the majority of patients [15, 22].

Although the side effects of RAI have long been considered negligible, recent reports have demonstrated that long term changes in salivary and lacrimal gland function can result in swallowing difficulties and related changes leading to impaired quality of life [23-29]. In addition, rates of second primary malignancy have been reported to be higher in patients who receive RAI, with salivary gland malignancies, leukaemias, soft tissue tumors, as well as breast and colon cancers [20, 30].

Given the conflicting evidence regarding improvements in outcome and the increasing recognition of adverse effects, current guidelines recommend the use of RAI routinely, only for high risk patients and selectively for low risk patients. Indications for selection of patients for RAI include older age, male gender, adverse histologies, vascular invasion and multifocal disease. As a result of the lack of clear indications, in addition to witnessing increasing rates of RAI use in the USA, significant variation in practice has also been described [21]. Selecting which patients should receive, and perhaps more importantly not receive RAI, following total
thyroidectomy therefore is complex, and the issue remains unresolved. It was against this backdrop that Chapters 8 and 9 focused on the role of patient selection in the administration of RAI. As RAI use across the world increases, identifying cohorts of patients managed without RAI is increasingly difficult. However, if physicians are to consider managing patients without RAI, such evidence is crucial in order to support clinical decisions. In these chapters, we do not compare patients treated with RAI to those treated without, but instead report on specific subgroups selected for management without RAI. The aim of this approach was to allow clinicians to understand the outcomes achieved with appropriate surgery alone, when considering whether adjuvant RAI will benefit an individual patient.

In Chapter 8 we consider all patients treated with total thyroidectomy within our cohort (n=1129). As expected, outcomes within this group are excellent with 5 year disease specific survival of 99% and recurrence free survival of 92%. We then analyze specific groups separately, in an attempt to provide the reader with information that can be translated from the field of research into clinical practice. We found that the majority of patients with pT1/T2N0 disease were managed without RAI during our study. Those selected for management without RAI tended to have pT1 disease rather than pT2 tumors and were more likely to be female. There were no deaths from disease within this group, and at 5 years, less than 2% of patients had recurred. These results strongly support the management of patients with disease confined to the thyroid gland without RAI, particularly women with low volume disease (the most prevalent group presenting today).

Those patients who had pT1/T2N1 disease and those with more advanced primary lesions (pT3/T4) were also analysed. A minority of these patients were selected for management without RAI. They tended to be younger, have smaller primary tumors and have lower volume neck disease. With this approach to risk stratification, even a select group of higher risk patients had low rates of recurrence and excellent survival. Although our aim was not to assess the efficacy of RAI, we have shown that with appropriate patient selection, a significant number of patients can safely be managed without RAI. The majority of decision making within our cohort was based upon clinical, demographic and pathological factors. However, we have also assessed the role of post-operative thyroglobulin (Tg) levels in risk stratification for patients with WDTC [31]. Of 1129 patients treated with total thyroidectomy, 424 had a recorded undetectable Tg level post operatively. The majority of these patients were considered low or intermediate risk. No such patients died, and at 5 years recurrence rates were less than 5% irrespective of the use of RAI. Again we conclude that with adequate surgical management, and selection using clinical, pathological and biochemical factors, a significant number of patients considered at low or intermediate risk following surgery can be selected for management without RAI.
Conclusions

Having completed this work, we must now interpret our findings and relate them to modern clinical practice. Some facts are indisputable; the incidence of thyroid cancer is rising; the vast majority of lesions now encountered are of papillary histology; increasing numbers of tumors under 1 cm are detected; and clinicians increasingly recommend both total thyroidectomy and RAI for all groups of patients. What remains highly contentious is how to identify patients who will benefit from total thyroidectomy rather than thyroid lobectomy, and of those patients who undergo total thyroidectomy, who will benefit from adjuvant RAI.

Once the early pioneers of clinical outcomes research in thyroid cancer had shown us that the majority of patients with WDTC had excellent outcomes [32, 33], many experts refined our understanding by identifying the factors which predicted outcome [17, 34, 35]. This work led to the development of multiple risk stratification systems. Although no one system has been universally adopted, all include similar factors – histology, age, distant metastases, extra thyroid extension and size of primary tumor, in addition to completeness of resection, post-operative thyroglobulin and nodal metastases. Such systems gave clinicians the ability to reliably predict outcome for their patients and recommend therapy based on such predictions.

At a similar time, advancements in the field of imaging, and in particular the introduction of high resolution ultrasound, changed our understanding of the disease itself at presentation. High rates of contralateral thyroid nodularity and regional metastases were identified leaving clinicians with a difficult dilemma: whilst these must have been present prior to the advent of such accurate imaging, radiological abnormalities could not be ignored.

So at a time when we were able to predict excellent outcomes for the vast majority of patients, the identification of clinically occult disease required surgeons to be increasingly aggressive. This change coincided with evidence that a more aggressive approach to both surgery and adjuvant therapy may result in improved outcomes. Despite the previously highlighted flaws in such research, the end result was a further drift towards more aggressive management of this generally low risk patient group. This change manifested despite evidence from multiple sources that well selected patients had excellent outcomes with a more conservative strategy.

This leaves us in a position where over 90% of patients in the US who present with papillary thyroid cancer can expect to undergo total thyroidectomy [36]. Following surgery, administration of RAI is increasingly common with around half of all patients being treated, and over a third of even the lowest risk patients receiving RAI as part of their initial therapy [20], despite the lack of evidence to suggest that such treatment strategy will benefit patients. The logical conclusion is that a large percentage of patients with WDTC are being over treated.

Analysis of our dataset confirms that the Memorial Sloan Kettering Cancer Center risk stratification system (GAMES, Table 1) remains a valid tool for predicting mortality in well differentiated thyroid cancer. The elements of this staging system have been validated in the work of many other institutions, which have highlighted age, distant metastases, extra thyroid extension and tumor size as independent predictors of outcome.

Using the GAMES system, of 1810 patients treated over the 20 year period, 32% were low risk,
45% were intermediate risk, leaving only 23% of cases classified as being at high risk of death. Five year disease specific survivals are 100%, 99.7% and 92% for low, intermediate and high risk groups respectively (p<0.001). Indeed, the same risk stratification system can be applied to recurrence. Local recurrence at 5 years was seen in 0% of low risk cases, 0.3% of intermediate and 1% of high risk cases (p=0.033). Regional recurrence is more common, occurring in 2% of low, 3% of intermediate and 7% of high risk cases by 5 years (p<0.001). Distant recurrence at 5 years was seen in 0.5% of low risk, 3% of intermediate and 5% of high risk cases (p<0.001) using the GAMES system.

By using such an approach to risk stratification, the majority of patients presenting with WDTC can be classified as being at low or intermediate risk of recurrence or death. Almost none of these patients will die of disease, and at 5 years no more than 3% will have recurred. Such excellent outcomes highlight the need for selective therapy. Any increase in morbidity of treatment, be it more aggressive surgery or the addition of adjuvant post-operative therapy, must be weighed against the low chance of improving already excellent oncological outcomes. Although total thyroidectomy carried out by an experienced surgeon is a procedure with low morbidity, this is no excuse for unnecessary surgery. In addition, there is a demonstrable difference in complication rates between thyroid lobectomy and total thyroidectomy for patients treated in the community setting. Again, the low morbidity of RAI should not be a shield used to justify its overuse. In patients who will see no benefit, the changes in lacrimal and salivary function should not be tolerated, and even though small, the association with second primary malignancies demands clinicians be selective in their approach to prescribing RAI. The costs of such potentially excessive therapies can be counted in time, morbidity, occasional mortality and health care expense.

We cannot ignore the fact that an increasing number of patients will present for surgical management of WDTC. Although some patients will continue to present with large primary tumors, high volume neck disease and distant metastases, such patients are in the minority. An increasing percentage of our workload will consist of older patients with smaller disease. By 2007 around half of patients presenting in the US had disease limited to the thyroid gland which was less than 2cm and therefore can be considered low risk [20]. With adequate surgical management, these patients have low rates of recurrence and negligible risk of dying from their disease.

The present trend towards total thyroidectomy in this patient group must be critically addressed. In the absence of contralateral nodules or high risk features such as aggressive histologies, gross extra thyroid extension and high volume nodal metastases, the operation for WDTC should be extra capsular thyroid lobectomy. This provides equal oncological outcomes to total thyroidectomy without jeopardizing the contralateral central compartment. If an intrathyroid malignancy is encountered following diagnostic lobectomy, the notion that returning to remove an otherwise normal contralateral lobe is good medicine is unjustified. Although a percentage of patients (around 5% in our series) required completion thyroidectomy during follow up, over treating 95% of the patient group with no demonstrable benefit in terms of survival or recurrence should not be considered.
In selecting patients for adjuvant RAI, only those with high risk disease should be treated routinely. Low and intermediate risk patients have extremely low recurrence rates. The majority should have been treated with thyroid lobectomy, however for patients with multicentric disease or contralateral nodularity, following total thyroidectomy, RAI is an option. Within this group, clinicians and patients must both understand that outcome without RAI is likely to be excellent, and that any potential for improvement is small. This must be balanced against the small but real side effects of therapy. Most patients therefore will not be candidates for adjuvant RAI, but will enter post-operative follow up.

An argument is made that total thyroidectomy with adjuvant RAI facilitates post-operative follow up with serial thyroglobulin assessment. This rationale is flawed. In fact, if a true “extra capsular” total thyroidectomy is performed, the post operative Thyroglobulin, in a vast majority of patients is not measurable, thus negating the need for ‘routine RAI ablation’. In addition, low risk patients have such low rates of recurrence, that the idea of inflicting increased morbidity of RAI therapy, on all such patients simply to allow for post-operative TG surveillance to detect residual disease of questionable clinical significance, and without evidence that this improves outcome, is irrational. In contrast, for high risk patients who are subject to higher rates of recurrence, such post-operative monitoring is valuable, further highlighting the need for a selective approach to management.

It is important to highlight the limitations of the work presented in this thesis. We do not present prospective or randomized trial data. Indeed, when the ATA considered the possibility of such high quality studies, they found that over 5000 patients would have to be enrolled prospectively and followed for 7 years [37]. This calculation explains the lack of prospective evidence in the field.

Throughout our chapters we have highlighted the weaknesses of multi-institutional database studies (generated from hospital based tumor registries) which provide excellent power, but lack precision and uniformity of treatment, pathological and oncological data. Every study has strengths and weaknesses. In keeping with all retrospective studies, both physician and patient biases may have affected outcomes within our dataset. In addition, treatment approaches in terms of surgical therapy and post-operative RAI evolved during our study period. We have witnessed a trend towards total thyroidectomy and RAI within our own institution over the past 3 decades. Histological definitions also evolved between 1980 and 2005. This led to an increase in the incidence of papillary thyroid cancers, and all data presented in this thesis was based on the original interpretation of the histological material. Investigations used in both pre-operative assessment and post-operative follow up have changed, with the introduction of high definition ultrasound and serial thyroglobulin measurement.

However, despite the weaknesses, our dataset has consistency in terms of surgical, endocrine and histopathological expertise. In terms of data collection, access to detailed clinical notes allowed accuracy in coding of both recurrence and survival. Due to the high volume nature of our institution we have a large patient cohort (n=1810). In comparison to national databases our study may seem underpowered. However, if such large patient cohorts are required to prove the statistical significance of an improvement related to more aggressive therapy, one
should question the clinical significance of such an approach to treatment. It is imperative that modern day clinicians not only understand the concept of risk stratification for patients presenting with WDTC, but are able to apply such a system to their practice. Patients treated in such a manner enjoy excellent outcomes, and the vast majority will be cured without ever developing recurrence following an oncologically sound but conservative treatment regimen. This will limit the iatrogenic morbidity of excessive surgery, and limit the side effects of adjuvant RAI to those patients most likely to benefit, whilst ensuring continued excellent oncological outcomes.
Future Directions

The rising incidence of WDTC has stimulated much interest in studying this disease. However, a number of important challenges remain. In the field of clinical research in thyroid cancer, much work remains in defining the role of selective therapy. The concept of active observation rather than surgical treatment of known thyroid cancers is being explored [38]. Such work is based on our knowledge that occult thyroid cancer is present within the normal population and has routinely been described in autopsy series without contributing to the mode of death [39-41]. Insights into the natural history of untreated disease will allow clinicians to be more accurate in the discussion of alternative strategies for the lowest risk patients parenting with incidentally discovered disease. This is currently being addressed in Japan, where Ito and colleagues are following a group of over 300 patients with PTC. Within the US, the position is more challenging, as the majority of patients will not accept such an observational policy. However, a select group of patients who agree to undergo serial ultrasound for sub centimeter primary tumors are being followed within our institution.

In terms of surgical therapy, experience has shown us that in low risk patients with uninodular disease, thyroid lobectomy can be considered safe. However, with the increasing definition of ultrasound imaging, high rates of contralateral previously occult nodules are being described, fuelling a move away from lobectomy. The excellent outcomes reported following lobectomy prior to the introduction of such high resolution imaging should still be expected, but more work is required to identify which contralateral nodules can safely be left in situ without the risk of later surgery. Predictive tools have been developed that allow clinician to individualize the risk of malignancy within a specific nodule [42, 43], and prospective application of such tools to patients with contralateral nodular disease could allow selection of patients with bilateral nodular disease for unilateral surgery.

Similar factors now influence post operative follow up. Intense monitoring of low risk patients with serial ultrasound and Tg assessment may be excessive, and lead to heightened patient anxiety and iatrogenic injury in the attempt to address potentially detectable but clinically insignificant residual disease. Future efforts in the field should focus on describing the natural history of post treatment, sonographically identified abnormalities. We know that rates of metastatic disease in the necks of patients with papillary thyroid cancer are high, so when occult subcentimeter nodes are identified on follow up, the need for biopsy and the role for, and timing of treatment are not clear. Salvage surgery of the central neck in particular presents a high risk to patients whilst the benefit of intervention in such cases remains unknown.

When considering the role of RAI, definitive evidence of benefit for the majority of patients is still lacking. Current efforts to address this deficiency should be encouraged and expanded, to provide clinicians with the evidence required to accurately select those patients most likely to benefit from RAI, whilst sparing others the side effects of therapy [44, 45]. Advances in our understanding of the molecular biology of carcinogenesis in thyroid cancer has the potential to improve our pre-operative diagnostic abilities, impact on our risk
prediction systems and provide targets for novel therapies in the future. Already such work is being translated into practice, with the introduction of targeted therapy for those few patients with advanced or unresectable disease [46-51]. It is likely that in future, molecular analysis of biopsy and surgical specimens will allow more accurate risk prediction, aiding in the process of selecting appropriate therapy and follow up regimes.

As progress is made in the field, the need for guidelines to evolve and include such a selective approach is evident. The huge volume of research relating to thyroid cancer now being reported makes it impossible for individual clinicians to keep up. The interplay of different medical specialties highlights this issue as only when all members of the disease management team work together, can inappropriate biopsies, poorly planned surgeries, unnecessary adjuvant therapies and conflicting therapeutic strategies be avoided.

In the meantime, it is beholden on clinicians to understand the concepts of risk stratification, and to be able to apply them to selection of therapy for patients with WDTC. The concept of total thyroidectomy and post operative RAI for all should be coming to an end, as we move towards the model of personalized medicine. By adopting this approach to the management of WDTC, clinicians serve the interests of their patients first and come closest to the basic medical principle :primum non nocere.
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### Table 1. GAMES Risk Stratification

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Patient Factor</th>
<th>Tumor Factor</th>
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<tbody>
<tr>
<td>Low Risk</td>
<td>Age &lt; 45y</td>
<td>Papillary Ca</td>
</tr>
<tr>
<td>High Risk</td>
<td>Age &gt; 45y</td>
<td>Follicular Ca / Hurthle Cell Ca</td>
</tr>
</tbody>
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#### Low Risk Case
- Low Risk Patient
- Low Risk Tumor

#### Intermediate Risk Case
- Low Risk Patient
- High Risk Tumor
- High Risk Patient
- Low Risk Tumor

#### High Risk Case
- High Risk Patient
- High Risk Tumor