



Well-differentiated thyroid cancer — are you overtreating your patients?

Wysoko zróżnicowany rak tarczycy — czy nie leczysz swoich pacjentów zbyt intensywnie?

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Abstract

Over the last 50 years there has been a move towards more aggressive therapy for well-differentiated thyroid cancer. In recent times, however, international guidelines have shown some trend back towards a more conservative approach to treating low-risk patients. This review explores how the state of the art in well-differentiated thyroid cancer research has evolved in tandem with improvements in risk-stratification. A focus on the surgical approach to the primary thyroid tumour and the regional lymphatics in addition to the interplay between surgical decision making and the use of radioactive iodine are presented to allow the reader to determine whether they are now overtreating patients with well-differentiated thyroid cancer. (*Endokrynol Pol* 2016; 67 (1): 60–66)

Key words: thyroid cancer; papillary thyroid cancer; thyroidectomy; thyroid lobectomy

Streszczenie

W ciągu ostatnich 50 lat nastąpiła zmiana w leczeniu wysoko zróżnicowanego raka tarczycy na rzecz bardziej agresywnej terapii. Jednakże, całkiem niedawno, międzynarodowe wytyczne wskazały trend w kierunku powrotu ku bardziej konserwatywnemu podejściu w leczeniu pacjentów niskiego ryzyka. W niniejszym artykule opisano jak najnowsze badania na temat wysoko zróżnicowanego raka tarczycy ewoluują równocześnie z ulepszeniami w stratyfikacji ryzyka. Podejście chirurgiczne do raka pierwotnego tarczycy oraz regionalnych węzłów chłonnych przedstawiono wraz ze wzajemnymi zależnościami operacyjnego procesu decyzyjnego i wykorzystaniem radiojodu, aby umożliwić czytelnikowi ustalenie, czy zbyt intensywnie leczy pacjentów z wysoko zróżnicowanym rakiem tarczycy. (*Endokrynol Pol* 2016; 67 (1): 60–66)

Słowa kluczowe: rak tarczycy; rak brodawkowaty tarczycy; tyroidektomia; lobektomia tarczycy

Introduction

The approach to management of well-differentiated thyroid cancer (WDTC) has evolved over the past 100 years. Advances in our understanding of the biology of disease have come during an evolution of therapeutic opportunities for patients who are diagnosed with WDTC. Treatment approaches have become increasingly standardised with the introduction of clinical guidelines, which have come to represent the consensus opinion on best practice within the field.

Patients with WDTC generally have an excellent outcome [1, 2], but improvements in risk stratification have aided clinicians in identifying both those at high risk of recurrence or death and also those at low risk.

Unfortunately, very little high-level evidence is available to clinicians managing patients with WDTC. The majority of papers are retrospective analyses of either single institutional experiences or national database

studies of data collected by clinical coders. Despite this, a large amount of often conflicting results are available, and the aim of this article is not to provide a one-size-fits-all approach to managing patients with WDTC. Instead, the aim is to review the therapeutic options for patients presenting with WDTC, with a particular focus on those considered at low risk. In particular the paper will review the approach to surgery for the primary tumour and regional lymph nodes. The review will cover the history of managing WDTC, the key studies that led us to the position we are in today, and the findings that are directing the changes we see in the most recent revisions of national clinical guidelines.

The evolution of clinical thyroid outcomes research

For centuries clinicians have recognised that thyroid cancer can be an aggressive and rapidly fatal malignancy.



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nancy. These observations supported an aggressive approach to managing this condition with radical surgery for the primary thyroid and the regional lymphatics. However, in the early 20th century surgical pathologists were able to identify those patients who would have poor outcomes from those who would do better based on light microscopy [3–6]. The recognition that poorly differentiated or anaplastic cancer was extremely aggressive whereas differentiated thyroid cancers were much less likely to be fatal was a giant step in our understanding of the biology of this disease.

The relatively indolent nature of WDTC was a challenge to further outcomes research because, with so few recurrences and fatalities, large numbers of patients had to be followed for long periods in order to provide meaningful resources for analysis. The excellent outcomes reported by the Lahey clinic in 1976 (5% mortality at 10 years) were supported by findings from other major groups and remain pertinent to this day [7, 8].

As more groups were able to analyse outcomes of large retrospective series, our understanding of both outcomes and factors associated with outcome improved. The introduction of prognostic risk stratification systems allowed clinicians both to identify those at high risk of poor outcome but also those patients who were low risk [9–12].

The introduction of large databases that collect patient and tumour details at a national level allowed groups to analyse outcomes in huge cohorts. This opportunity led to much interest in thyroid cancer outcomes research at a time when the incidence of this disease was rapidly rising. At a similar time, in order to provide larger cohorts of clinician-collected data, large institutions now collaborate in order to provide high-quality retrospective data [13].

Prospective trials, however, remain lacking. Few have been performed, and most guideline recommendations are based on low-level retrospective case series. Nonetheless, much has been learned over the past 100 years, which can be used to inform treatment decisions for patients with WDTC.

Risk stratification in well-differentiated thyroid cancer

Although the majority of patients with WDTC do well, particularly in comparison with outcomes of other solid tumours, it is possible to predict accurately both the risk of recurrence and the risk of death.

In the mid-20th century a number of groups recognised the importance of age in predicting outcome [9–12]. Young patients tended to have excellent outcomes, with older patients at risk of disease specific

death. Tumour factors, including size, the presence of extra thyroid extension, and the presence of distant metastases, were also associated with poor outcome. These patient and tumour factors were reflected in the numerous risk stratification systems designed to stratify patients by their risk of disease-specific death published in the mid to late 1900s (Table I).

No particular approach has gained universal popularity, and the existing AJCC/UICC staging system has been criticised and is likely to be significantly changed in the near future [14]. The Memorial Sloan Kettering Cancer Centre system (GAMES) considers patients as low or high risk based upon age. It recognises tumours as low risk if they are small and confined to the thyroid, and high risk if they are large or associated with distant metastases. Low-risk patients and low-risk tumours are considered as low-risk cases. High-risk patients with high-risk tumours are considered high-risk. Low-risk patients with high-risk tumours and high-risk patients with low-risk tumours represent an intermediate-risk group (Table II).

More recently a system for predicting the risk of recurrence has been published by the American Thyroid Association (ATA) in the 2009 iteration of the ATA guidelines [15]. A potential advantage of this system is that, as most patients will not die of disease, recurrence is a more clinically meaningful outcome. However, a disadvantage of the system is that many of the features required to accurately use the system are only identified after initial surgery (Table III).

Although systems to predict outcome have been available for over 40 years, an understanding of risk stratification in WDTC is critical for clinicians. It not only allows for accurate prognostication, but also can aid in therapeutic decision-making.

Primary thyroid surgery

As thyroid surgery became safer, techniques evolved and standardised to reject the nodulectomy procedure, which was associated with high levels of disease recurrence, in favour of total thyroidectomy and thyroid lobectomy as the procedures of choice in management of WDTC. With the publication of outcomes from the US Air Force database in 1977 by Mazzaferri et al. came early evidence of guided management of the thyroid in the United States and across the world [16].

This paper, which analyses outcomes for 576 patients managed in the decades prior to 1976 in an air force medical setting, provided a cohort of patients treated in a fairly standardised manner and with a uniform approach to histological reporting. Many results were reported, but the ones that gained particular traction were those finding that outcomes were superior for

Table I. Comparison of risk stratification systems

Tabela I. Porównanie systemów stratyfikacji ryzyka

System	AGES	AM ES	DAMES	GAMES	MACIS
Institution	Mayo Clinic (1987)	Lahey Clinie	Karolinska Institute	MSKCC	Mayo Clinic (1993)
			DNA ploidy	Grade	Metastasis (distant)
	Age	Age	Age	Age	Age
	Grade	Metastases (distant)	Metastases (distant)	Metastases (distant)	Completeness of resection
Factors	Extra thyroid extension	Extra thyroid extension	Extra thyroid extension	Extra thyroid extension	Extra thyroid extension
	Size	Size	Size	Size	Size

Table II. GAMES Risk of Cause Specific Mortality Stratification (ETE = extrathyroid extension, Carcinoma)

Tabela II. GAM ES ryzyko i przyczyna działania: śmiertelność stratyfikacji (ETE = powiększenie tarczycy, rak)

Risk Level	Patient Factor	Tumor Factor			
Low Risk	Age < 45 years	Papillary Ca	M ₀	No ETE	Size < 4 cm
High Risk	Age > 45 years	Follicular Ca/ Hurthle Cell Ca	M1	ETE	Size > 4 cm
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			

Table III. American Thyroid Association risk of recurrence stratification

Tabela III. Stratyfikacja ryzyka nawrotu według American Thyroid Association

	Regional metastases	Distant metastases	Extra thyroid extension	Surgical resection	Aggressive pathology	RAI uptake outside thyroid bed
Low Risk	Absent	Absent	Absent	Complete	Absent	Absent
Intermediate Risk	Present	Absent	Microscopic	Complete	Present	Present
High Risk		Present	Macroscopic	Incomplete		

patients treated with total thyroidectomy versus less than total thyroidectomy, and for patients that received RAI versus those that did not.

With the publication of this manuscript came the argument for an "aggressive" approach to patients with WDTC. Rates of total thyroidectomy rose in the USA, and a corresponding rise in the use of RAI was also reported [2].

Many papers scrutinising the impact of initial therapy followed, but an analysis of the National Cancer Database between 1985 and 1998 published by Bilmoria et al. confirmed the earlier findings of Mazzaferri [17]. This publication came at a time when the ATA were considering an update to their guideline document, which in 2009 recommended total thyroidectomy for all patients with tumours over 1 cm in size.

However, not all groups agreed. Opponents of this standardised approach pointed out that the Mazzaferri paper lacked risk stratification. It was based on the outcomes of air force surgeons, who, while providing an excellent service to their patients in the 1930s and 1940s, were likely to provide a very different surgical service to that delivered by trained endocrine surgeons of the late 20th and early 21st century. In addition, the approach to diagnostics and follow-up have changed significantly during the time that this patient group were managed.

More contemporary data was criticised for lacking basic important data such as the presence of extra thyroid extension and completeness of resection. In addition, outcomes data in terms of recurrence were lacking [18].

The observation that less aggressive surgery is associated with excellent outcomes in properly selected patients is not new. In the Mayo clinic paper, which updated their risk stratification system (MACIS) in 1987, no improvement in outcome was seen in low-risk patients [19]. Similar findings were reported by Memorial Sloan Kettering in a matched pair analysis [20]. Single institutions would provide increasingly compelling evidence that more aggressive therapy was not associated with improved outcome [21–24]. These findings were supported by updated national database studies, which also concluded that a more aggressive approach could not be supported in low-risk groups [25].

Although there is little to choose in terms of oncological outcome between total thyroidectomy and thyroid lobectomy, that is not to say patient outcomes are the same irrespective of the choice of therapy. Patients treated with total thyroidectomy are at greater risk of recurrent laryngeal nerve paralysis and hypocalcaemia [26]. Although injury rates are low in the hands of high-volume surgeons, this is not true for surgeons with less experience. However, those patients who have a lobectomy do require monitoring of the contralateral lobe, and around 10% of patients will require subsequent completion thyroidectomy if this approach is selected [23]. However, it is important to remember that this means that 90% of patients will *not* require completion thyroidectomy.

Thyroid surgery is not performed in isolation. Not only does the procedure aim to rid the patient of disease, minimise the chance of recurrence, and avoid iatrogenic injury, but also prepares the patient for adjuvant therapy when indicated. Radioactive iodine therapy (RAI) is less effective unless a total thyroidectomy has been performed.

The role of RAI in the management of WDTC has been under much scrutiny in recent years. Although still supported for high-risk cases, its routine use in the lowest-risk cases is now discouraged. Risks of RAI include dry mouth and dysphagia with the potential to impact on patients' quality of life [27, 28]. In addition, high doses have been associated with second primary malignancies [29], highlighting the need to only treat those most likely to benefit.

The recent publication of two high-quality prospective randomised controlled trials scrutinising the use of high dose RAI [30, 31] are to be followed by investigation of low-dose versus no RAI for low-risk WDTC [32]. It appears that the role of RAI is changing, and it is likely to be recommended in fewer patients in the low-risk group in the future. As such, the need for total thyroidectomy to facilitate RAI has a decreasing influence on the selection of surgical therapy for low-risk patients.

Until recently, most clinical guidelines have supported total thyroidectomy for all patients with lesions > 1 cm. However, the ATA is now recommending an individualised approach for tumours between 1 and 4 cm without evidence of disease outside the thyroid gland [33]. The British Thyroid Association has recommended a similar approach [34].

High-risk patients require total thyroidectomy in order to rid them of disease, prepare them for adjuvant RAI, and to facilitate accurate thyroglobulin follow up. However, when selecting primary thyroid surgery in low-risk WDTC cases a balance must be achieved. In young patients and particularly professional voice users lobectomy may be preferred. For larger tumours and those demonstrating high-risk features, total thyroidectomy is likely to remain the standard of care. The treating clinician must also consider the chance of iatrogenic injury. Surgeons with low complication rates are likely to have a lower threshold for recommending total thyroidectomy than surgeons with higher complication rates. A balance must be struck on a case-by-case basis (Fig. 1).

Surgery for regional lymphatics

Neck surgery can be considered therapeutic (when disease has been detected) or prophylactic (when no disease is identified pre-operatively). The role of therapeutic neck dissection is well defined and no longer controversial. The "berry-picking" procedure, where only clinically involved nodes are excised, has been abandoned in favour of a compartment-orientated approach. This involves dissection of levels II–V for involvement of the lateral neck and levels VI and VII for involvement of the central neck [35].

Prophylactic neck dissection, however, is far more controversial. When performed, high rates of occult disease are identified. However, the impact of that disease is questionable because outcomes in low-risk patients (based on pre-operative features) are excellent. Lymphadenectomy is associated with morbidity, dependent on the region of dissection, and the perceived benefit must be balanced against the morbidity endured by the patient.

Over the past century there has been an evolution in the approach to the neck. Early surgeons were aggressive, dissecting electively in the central and lateral compartments. Recognition that there was little prognostic implication led initially to a more conservative approach to the lateral neck, followed by questions being raised about the utility of routine prophylactic central neck dissection (pCND). At the same time, our ability to identify low-volume disease in the regional nodes improved with high-resolution ultrasound. As clinical intuition drove toward a more conservative

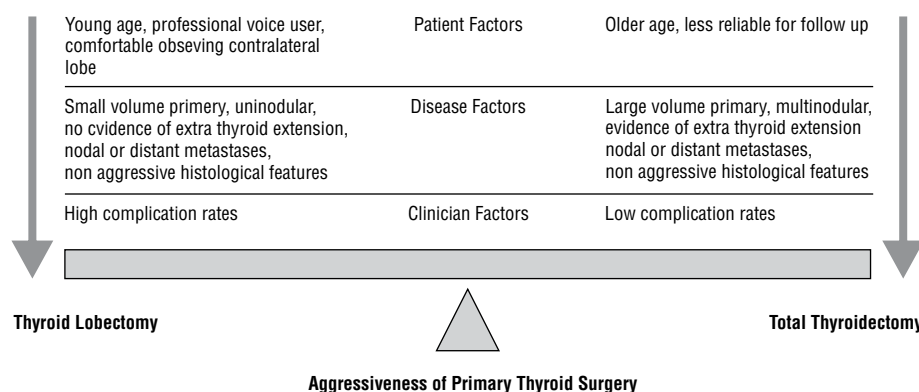


Figure 1. Patient, disease and clinician factors which influence the approach to primary thyroid surgery
Rycina 1. Czynniki pacjenta, choroby i lekarza, wpływające na podejście do pierwszej operacji tarczycy

approach, radiological evidence was pushing toward a more aggressive approach, dissecting previously occult disease with a therapeutic approach (Fig. 2).

In terms of the lateral neck, despite a significant percentage of patients harbouring occult disease, the high rates of surgical morbidity in addition to the low rate of progression to clinically meaningful disease have led most groups to abandon prophylactic lateral neck dissection.

In contrast, the role of pCND is more controversial. This argument was brought to the fore when, in 2006, the ATA guideline was published with the wording that the prophylactic central neck dissection “should be considered” for papillary thyroid cancer [36]. This statement was interpreted by many as justification for pCND for all.

Those who argue for a pCND cite the high rates of occult disease (as for the lateral neck) and highlight the fact that this additional knowledge allows patients to be more accurately risk stratified for the targeting of adjuvant RAI [37]. In addition, re-operative central neck surgery is associated with higher risks than an initial procedure. There has also been evidence to suggest that post-operative thyroglobulin levels are lower and that weak evidence that recurrence rates may be lower as a result [38].

Those who argue against routine pCND point to evidence that the occult disease overlooked by this approach rarely manifests [39–41] and that this patient group is extremely low risk, so the concept of upstaging patients to be more aggressive in an era when the pendulum is swinging away from RAI in low-risk patients seems counterintuitive. Although re-operative neck surgery is high risk, this must be balanced against the morbidity of routine pCND with thyroidectomy, which is more morbid than thyroid surgery alone [42–44]. In

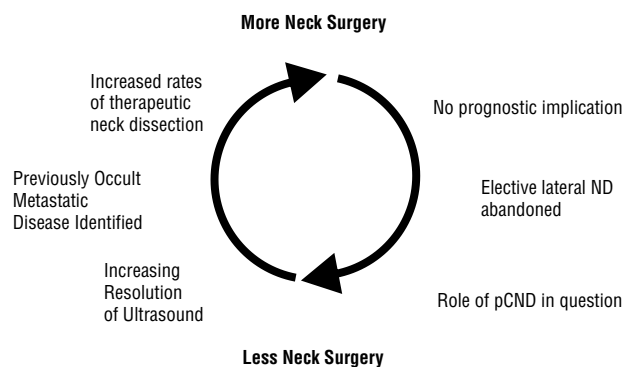


Figure 2. Factors which have resulted in the trend initially towards less then more neck surgery for well-differentiated thyroid cancer
Rycina 2. Czynniki wpływające na mniej lub bardziej inwazyjny zakres operacji w obrębie szyi z powodu wysoko zróżnicowanego raka tarczycy

terms of oncological outcomes, no group has been able to show an improvement in recurrence rates, and it is well accepted that pCND does not impact on survival.

To answer this question beyond doubt a prospective randomised trial would be required. However, when the ATA conducted a feasibility study they concluded that 5000 patients would have to be recruited and that the study design was not feasible [45]. A non-inferiority trial may be possible, but for the moment it seems unlikely that a definitive answer is going to be found.

Few groups have published the outcome of patients managed without surgery. The Memorial Sloan Kettering Cancer Centre group studied almost 1800 patients with papillary thyroid cancer, who underwent total thyroidectomy without central neck dissection. In this study only 12 patients recurred in the central neck, and all were successfully salvaged. There were no deaths during follow-up [40]. This evidence, in support of oth-

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ers' findings, suggests that observation of the central neck is safe, does not prevent later salvage in those that recur, and protects the vast majority (> 98% in this study) from the risks of central neck surgery. Another consideration is that novel surgical approaches often require high levels of surgical experience and resources. In contrast, *not* performing a central neck dissection can be practiced by any clinician equally effectively.

An improved understanding of the biology of the undissected central neck has led to a softening of the language of the ATA. The initial statement that pCND "should be considered" was changed to "may be considered" in 2009, and in the 2015 guideline it reads "management without pCND may be appropriate". While not advocating an abandoning of pCND, there does appear to be a gradual shift away from a single approach for all patients.

Challenges for the Future

There remain challenges in translating a less aggressive approach to the real world for many clinicians. Those patients who present with a malignancy in the presence of multinodular goitre are currently consigned to total thyroidectomy. Advances in imaging may allow for the risk of malignancy within the rest of the gland to be accurately quantified to allow such patients to be managed without total thyroidectomy. This is particularly an issue as the resolution of ultrasound increases and ever smaller volume nodular disease is identified.

It is also important to consider the role of no treatment in the lowest-risk patients. A number of Japanese groups have demonstrated a few patients with micro carcinoma progress during a period of active observation [46–49]. Current studies include only sub-centimetre lesions. However, the 10-mm cut-off is arbitrary and could be extended, particularly given the recent finding that adverse events during follow-up are actually higher for such low-risk patients who opt for surgery versus observation [49]. It is possible that as molecular analysis of biopsy samples improves, the lowest-risk tumour biology will be better characterised allowing an increasing number of patients who can avoid surgery altogether.

Conclusion

As our understanding of well-differentiated thyroid cancer has evolved, our ability to predict the risk of recurrence and death from disease has improved. This ability to accurately predict the risk status of an individual allows clinicians to identify those patients at the highest risk of poor outcome and focus resources on that

group. In addition, it provides the opportunity to consider the lowest-risk group for less aggressive therapy.

This approach will not suit all patients, but by being able to balance the risks of surgery against the likely clinical outcomes, disease management teams will be better able to serve their patients. The ability to identify those patients in whom the risks of prophylactic central neck dissection may outweigh the benefits, and by understanding the changing role of RAI in the management of WDTC in tandem with the likely outcome of an observed contralateral thyroid lobe, clinicians will be able to individualise therapy without compromising oncological outcomes.

Only with an insight in to these factors will you be able to determine whether you are overtreating your patients with well-differentiated thyroid cancer.

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