Management of Invasive Differentiated Thyroid Cancer

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Background: Invasive disease is a poor prognostic factor for patients with differentiated thyroid cancer (DTC). Uncontrolled central neck disease is a common cause of distressing death for patients presenting in this manner. Advances in assessment and management of such cases have led to significant improvements in outcome for this patient group. This article reviews the patterns of invasion and a contemporary approach to investigation and treatment of patients with invasive DTC.

Summary: Aerodigestive tract invasion is reported in around 10% of case series of DTC. Assessment should include not only clinical history and physical examination with endoscopy as indicated, but ultrasound and contrast-enhanced cross-sectional imaging. Further studies including positron emission tomography should be considered, particularly in recurrent cases that are radioactive iodine (RAI) resistant. Both the patient and the extent of disease should be carefully assessed prior to embarking on surgery. The aim of surgery is to resect all gross disease. When minimal visceral invasion is encountered early, “shave” procedures are recommended. In the setting of transmural invasion of the airway or esophagus, however, full thickness excision is required. For intermediate cases in which invasion of the viscera has penetrated the superficial layers but is not evident in the submucosa, opinion is divided. Early reports recommended an aggressive approach. More recently authors have tended to recommend less aggressive resections with postoperative adjuvant therapies. The role of external beam radiotherapy continues to evolve in DTC with support for its use in patients considered to have RAI-resistant tumors.

Conclusions: Patients with invasive DTC require a multidisciplinary approach to investigation and treatment. With detailed assessment, appropriate surgery, and adjuvant therapy when indicated, this patient group can expect durable control of central neck disease, despite the aggressive nature of their primary tumors.

Introduction

THE INCIDENCE OF DIFFERENTIATED THYROID CANCER (DTC) is increasing worldwide (1). The majority of lesions now detected present with early primary disease (2). Such patients have excellent long-term outcomes (3,4). However, an increase in the number of patients with large-volume primary tumors has also been observed (5), and locally advanced disease constitutes around 5%–15% of case series (4,6,7). Uncontrolled involvement of the viscera of the central neck is associated with high rates of mortality and a most

distressing mode of death. However, several reports have shown that complete surgical resection is associated with higher survival rates compared to incomplete resections (8–11). As such, clinicians dealing with DTC must be aware of the most appropriate ways to investigate and treat patients who present with lesions that involve the viscera of the central neck.

Extrathyroidal extension (ETE) has long been recognized as an independent predictor of poor outcome in patients with DTC (8,10,12,13). Not only does such invasive disease result in higher rates of recurrence, but survival is compromised in this patient group. Cases that present with airway invasion are more

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likely to present with adverse risk factors including advanced age and aggressive histology. As such, radioactive iodine (RAI) avidity is reduced in this patient group, leading to poor or no response to adjuvant RAI. When the airway is involved by ETE, the situation is complicated not only by the negative prognostic implications of the disease itself (14) but also by the morbidity associated with surgical procedures required to adequately resect disease. Airway invasion commonly accompanies invasion of surrounding structures in the central neck, further complicating the approach to management.

The relative rarity of locally advanced disease and the lack of prospective trials in this particular field has led to controversy over investigation and management of patients who present with DTC involving the airway.

The aim of this paper was to review the patterns of invasion seen in DTC and to consider the approach to investigation and management of patients who present with locally advanced DTC.

Clinical Presentation

Patients with locally advanced DTC may present in a relatively asymptomatic manner; however, most patients will present with hoarseness, stridor, hemoptysis, dysphagia, and pain, alone or in combination. Hoarseness and stridor can develop because of recurrent laryngeal nerve (RLN), tracheal, or laryngeal invasion. Hemoptysis is always a result of intraluminal invasion, and pharyngo-esophageal invasion or extrinsic luminal compression can lead to dysphagia (15).

In patients with advanced disease, the clinician should consider the possibility of dedifferentiated thyroid malignancy or lymphoma. In cases of anaplastic thyroid cancer, the outcome is rapidly fatal and few patients, if any, will be candidates for an aggressive surgical approach. It is therefore critical to have representative tissue prior to definitive therapy. For the majority of patients, fine-needle aspiration biopsy will be the first assessment of the tumor's histological subtype. However, heterogeneity within tumors is common. Therefore, the treatment team may recommend further biopsies in the form of core or open biopsy to minimize the chance of underestimating the aggressive nature of the disease. However, the most biologically aggressive disease is often at the point of maximal invasion, and biopsy from this area is impossible. Diagnostic uncertainty will be present until formal histology is available from the resection specimen, and the patient should be counseled appropriately.

Patterns of Invasion

The anatomical relationship between the thyroid gland and the larynx, trachea, esophagus, and RLN place these structures at risk from both direct involvement from the primary

lesion and also from metastatic lymph nodes in the central or lateral neck (16).

Although the infra-hyoid strap muscles are the most common site of invasion from ETE (17), in more than half of locally advanced cases, such anterior extension can be excised with relatively minimal morbidity. In contrast, posterior ETE results in visceral invasion and complicates both diagnosis and management.

The trachea is invaded in around one third of locally advanced cases (17). The trachea tends to be involved by direct extension through the tracheal perichondrium toward the submucosa of the airway. Further invasion results in ulceration of the mucosa with intraluminal tumor, which may in turn present with hemoptysis or stridor.

Classification systems have been proposed by both Czaja and McCaffrey (14) and Shin *et al.* (18) based on the extent of laryngo-tracheal invasion (Table 1, Fig. 1). Early invasion results in adherence of the gland to the airway without frank invasion. As the disease progresses, first the perichondrium, the cartilage, and eventually the submucosa are invaded prior to involvement of the mucosal surface. Such systems are useful in considering the surgical approach to managing the airway in advanced cases.

Invasion of the larynx is less common (12%) (17) and may occur via direct invasion through the cartilages or the cricothyroid membrane. In addition, disease may grow posteriorly around the dorsal border of the thyroid cartilage, entering the paraglottic space of the larynx via the constrictor muscles and pyriform fossa (Figs. 2–4). Early invasion may be asymptomatic. However, more advanced disease results in hoarseness and aspiration followed by airway compromise and hemorrhage.

In contrast to the airway structures, the mucosa of the esophagus is relatively resistant to invasion. Direct extension into the muscular layers of the pharynx or esophagus is more common, occurring in around 20% of locally advanced cases (Fig. 5) (17).

Around half of locally advanced cases will also have involvement of the RLN (17). The nerve may be invaded directly from primary thyroid disease (Fig. 6) or encased in metastatic lymph nodes (Fig. 7) in the trachesophageal groove. Disease first abuts and then encases the nerve, and function will be lost at some point during this process (Fig. 8). Work by experts in intraoperative nerve monitoring (IONM) suggests that around half of patients with a clinically invaded RLN will have normal vocal cord function, and that in 60% of cases with RLN invasion, electrophysiological function can be detected (19). Some patients with vocal cord dysfunction may develop compensation from the contralateral vocal cord, and voice changes may be very subtle.

Rarely, the great vessels in the neck are directly invaded by DTC because extracapsular involvement is very infrequent even in the presence of large-volume lateral neck nodes. Such

TABLE 1. CLASSIFICATION SYSTEMS FOR STAGING EXTENT OF AIRWAY INVOLVEMENT

Stage	Czaja and McCaffrey (14)	Shin <i>et al.</i> (18)
I	Extra thyroid extension adherent to airway with no gross invasion	Invasion of perichondrium
II	Gross invasion which can be excised without mucosal disruption	Invasion of the cartilage
III	Gross invasion which requires mucosal disruption to excise but no intraluminal invasion	Involvement of submucosa
IV	Gross intraluminal invasion	Intraluminal invasion

FIG. 1. Classification of tracheal invasion as proposed by Shin *et al.* (18) (courtesy of Memorial Sloan Kettering Cancer Center).

invasion can be due to primary or nodal disease directly invading the lumen of the internal jugular vein, mainly due to intravascular growth in follicular carcinomas. As disease progresses it may extend to encase the great vessels. Direct involvement of the carotid artery usually represents transformation of DTC to poorly differentiated or anaplastic histology.

Assessment of Invasion

Clinical history may suggest that a thyroid lesion involves the viscera of the central neck. Gaissert *et al.* (20) report hemoptysis, dyspnea, neck mass, and voice change in 28%, 26%, 37%, and 36% of cases, respectively. Only 12% of locally advanced cases were asymptomatic in this series.

Examination is also critical. The neck should be palpated with focus on fixation of the mass to deep structures. The presence of palpable central neck disease in the setting of recurrence should alert the clinician to the possibility of invasive

FIG. 2. Schematic of disease invading posteriorly into the paraglottic space (courtesy of Memorial Sloan Kettering Cancer Center).

FIG. 3. Computed tomography (CT) scan showing recurrent papillary thyroid cancer invading into the pyriform fossa at level of cricoid cartilage.

disease. Assessment of the mucosa of the laryngopharynx and trachea as well as the function of the vocal cords is also critical. This assessment should be performed in the office setting to allow a dynamic evaluation of laryngeal function (21). Additional assessment using tracheoscopy and esophagoscopy may also be required under general anesthesia to complete the clinical examination of the viscera of the central neck. Office examination allows assessment of laryngo-pharyngeal function. However, accurate assessment of the mucosa of the subglottis, trachea, and esophagus is more accurately performed under general anesthesia. Echoendoscopy may also be used to further assess the degree of disease involvement in the trachea or esophagus.

Although ultrasound can be used to identify ETE (22), cross-sectional imaging is critical in determining the extent of invasion and for accurate presurgical planning. Such additional imaging is not required in all cases of DTC. However, if evidence of nodal disease or suspicion of extra thyroid extension exists, consideration should be given to imaging that should include the mediastinal lymph nodes.

FIG. 4. Endoscopic image of same patient under general anesthesia with disease evidence in the hypopharynx.

FIG. 5. Schematic of esophageal invasion (courtesy of Memorial Sloan Kettering Cancer Center).

Contrast-enhanced computed tomography (CT) scanning allows accurate assessment of the degree of extension while also allowing the mediastinal lymph nodes and great vessels of the neck to be assessed without the movement artifact encountered with magnetic resonance imaging (MRI). In addition, synchronous examination of the chest can be used to assess for distant disease and respiratory comorbidities. MRI may provide additionally useful information about the presence or extent of prevertebral compartment invasion in select cases.

In terms of the relationship between the disease and major blood vessels, the presence of a fat plane on imaging suggests that surgical dissection will be possible. Disease that surrounds $>180^\circ$ of the vessel circumference is suggestive of encasement, which prevents successful dissection. In exceptional cases, resection with bypass of major vessels can be

FIG. 6. Primary disease encases the left recurrent laryngeal nerve at the level of the tubercle of Zuckerkandl.

FIG. 7. Metastatic lymph nodes encasing the recurrent laryngeal nerve.

considered. However, not only does this approach represent a significant clinical risk and a great technical challenge, but it also suggests particularly aggressive disease, making the decision to offer such complex surgery questionable.

Concerns about the impact of iodine-based contrast on the ability to effectively deliver adjuvant RAI therapy are likely to have been overestimated (23). Clinicians should remember that such locally aggressive disease is likely to have lost RAI avidity, and the benefit from accurate preoperative imaging to define the extent and location of invasion to facilitate complete surgical removal far outweighs any theoretical limitations about RAI administration (24). Preoperative contrast-enhanced CT does not preclude the use of therapeutic RAI postoperatively. If concern remains about iodine avidity of residual thyroid tissue due to prior contrast uptake, a washout period of between 4 and 8 weeks is generally felt to be sufficient (23), which is not a clinically significant delay.

[^{18}F]-Fluorodeoxyglucose (FDG) positron emission tomography (PET $\pm$ CT) is a useful imaging modality in patients with advanced disease because it can provide information about the biology of the tumor and thereby aid treatment decisions. Poorly differentiated and dedifferentiating tumors become FDG avid as they lose RAI avidity because of the loss of expression of the sodium iodide symporter (25). Therefore, PET positivity is associated with more

FIG. 8. Schematic of invasion of the recurrent laryngeal nerve by primary disease (courtesy of Memorial Sloan Kettering Cancer Center).

aggressive biology and a tumor that is unlikely to respond to RAI therapy. Such an assessment of disease biology may affect therapy. For example, those patients who present with significant distant disease demonstrating high levels of FDG avidity are likely to have a more limited life expectancy. The association between this finding and dedifferentiated aggressive disease may impact on the decision to offer aggressive surgery. In contrast, for non-FDG-avid distant disease, there is a greater chance of response to RAI, which may justify a more aggressive surgical approach to the primary tumor. If PET-CT is not available, additional investigations including MRI of the spine may be considered to screen for bone metastases in advanced disease.

Further assessment should be tailored to the individual patient. Assessment of the eventual comorbidities and fitness for radical surgery is critical. If life-threatening disease is encountered on preoperative assessment, be it primary disease, distant metastases, or comorbid conditions, an attempt to compare the trajectory of primary versus systemic disease should be made. This assessment of disease biology will allow clinicians to select those patients most likely to benefit from major surgery.

Surgical Management

The aim of surgery for locally advanced DTC is to achieve an optimal oncological outcome, minimize surgical morbidity, and maximize quality of life. It is widely accepted that incomplete resection of gross disease compromises oncological outcome (11,14,26,27). However, the impact of microscopic residual disease is controversial.

Preoperative assessment of the extent of primary, regional, and distant disease as well as comorbidities is critical. Details of specific surgical procedures are beyond the scope of this article and are well reported elsewhere (28,29). However, in order to manage such cases appropriately, the treating team should have experience with advanced techniques of resection and reconstruction (30). As such, consideration should be given to referring such cases to tertiary centers that have the multidisciplinary experience to manage such complex cases (31).

Invasion of the airway

When disease abuts the perichondrium or invades the perichondrium but does not involve the cartilage of the trachea or larynx, the consensus is that procedures that shave a margin of cartilage but maintain the integrity of the airway lumen are sufficient (31). For most patients managed in this way, the role of adjuvant external beam radiotherapy (EBRT) following resection of all gross disease remains controversial (32) unless there is strong suggestion that the disease is RAI resistant.

In more advanced cases, when disease extends into the cartilage without definite evidence of disease in the submucosa, the situation is more complex. In this situation, determining the exact extent of invasion requires histopathological assessment that can only be achieved postoperatively. Therefore, some authors recommend a full-thickness excision including the mucosa of the airway (9,20,33–37). This approach ensures a histologically negative margin but results in increased surgical complexity and significant functional impairment. Other groups have experienced similar oncological outcomes with an approach that reserves full-thickness excision only for disease that grossly involves the submucosa or

mucosa itself (6,14,27,38–44). This approach accepts a higher risk of leaving microscopically positive margins but results in lower immediate surgical morbidity.

The groups advocating an aggressive approach report low mortality and morbidity from extensive procedures with favorable long-term results in those patients treated in this manner (20). Similarly, groups employing a less aggressive approach also report excellent outcomes with local control rates of up to 95% and 5-year survival of 93% (41). In addition, such groups report that significant numbers of patients (over 50% in one study) are unwilling to consent to more aggressive surgery because of the risk of functional impairment (27).

All studies in the literature are retrospective, and it is highly unlikely that prospective data will become available to confirm the most appropriate surgical approach to cartilage invasion. In their absence, it is interesting to consider the reasons that may explain the differences in approach between centers. The specifics of the presenting populations may explain some of the variation. Some centers include high rates of previously operated disease in their reported series (over 50% of those treated in the Massachusetts General Hospital experience (20)), whereas other groups report only primary surgeries. Clearly, for patients who have had prior treatment, postoperative fibrosis will make conservative surgery more challenging. In addition, tertiary referral centers are likely to attract more aggressive pathology and patients who may require a more aggressive surgical approach. Some centers have included dedifferentiated histologies (including anaplastic thyroid cancer) in their series (20), whereas others excluded less differentiated disease (6,14,16). In particular, anaplastic cases may bias results because almost all patients with such aggressive disease will not be candidates for an aggressive surgical approach. Patient age may also be a factor; for example, Kowalski *et al.* reported a mean age of 41 years in their cohort (11,14,26,27) compared with 64 years reported by Gaisert *et al.* (20). It is also likely that individual surgical experience contributes to varied international institutional approaches. Institutions with higher rates of recurrent disease in older patients are more likely to encounter RAI-resistant disease and favor a more aggressive surgical approach.

In the most advanced cases, when disease extends through cartilage to involve the submucosa or the mucosa of the airway, a full-thickness resection of airway structures is required. For small tracheal segments, window or wedge resection with reconstruction may suffice (45). For more extensive tracheal invasion, sleeve resection may be required with primary anastomosis. When the larynx is invaded, disease is often well lateralized and can be excised with a partial laryngectomy. However, extensive laryngeal invasion, particularly when comorbid respiratory disease is present, will require total laryngectomy (28).

Airway sacrifice is associated with a significant psychosocial impact on the patient. Many aspects of lifestyle from appearance, feeding, communication, and in some cases even independent living will be affected. For this reason, the decision to perform a major airway resection must be individualized. In a younger patient with a good life expectancy, who is considered able to manage a laryngeal stoma independently, laryngectomy in order to achieve good surgical margins and optimize oncological outcome is well justified. In contrast, for elderly frail patients who may require prolonged hospitalizations after such a procedure, all options

TABLE 2. MANAGEMENT OF THE RECURRENT LARYNGEAL NERVE

	<i>Vocal cord function normal</i>	<i>Ipsilateral vocal cord dysfunction</i>	<i>Contralateral vocal cord dysfunction</i>
Disease minimally adherent to the nerve	Shave	Shave	Shave
Disease encasing the nerve	Dissect nerve out unless results in gross residual disease	Resect nerve en bloc	Consider preserving the nerve to avoid tracheostomy

must be considered. If such patients have symptoms related to central neck disease and are expected to have a reasonable quality of life following surgery, palliative laryngectomy should be considered. The alternative in this situation would be to either accept death from asphyxiation, or to place a temporary tracheostomy in order to bypass the nonfunctioning larynx (which may later obstruct secondary to tumor). In contrast, patients with minimal life expectancy, irrespective of central neck disease, and in whom quality of life would be negatively impacted by radical surgery, should be managed with a palliative approach.

Clearly these decisions are difficult, and all recommendations need to be individualized. Early involvement of the patient, family, and members of the wider disease management team are critical in ensuring appropriate decision making at a stressful time for all involved.

Invasion of the RLN

Management of the involved RLN demands a thorough clinical examination preoperatively. Only when the surgeon has recorded the function of both vocal cords can appropriate decisions be made.

Invasion of the RLN is common in cases of locally advanced DTC but has not convincingly been shown to be independently predictive of poor outcome (17). In addition, resection of involved nerves has not been shown to be associated with survival benefit (46). This situation has led to controversy about the optimal management of the nerve during surgery for advanced disease.

When vocal cord function is normal preoperatively, all attempts should be made to preserve the integrity of the RLN. If disease is minimally adherent to the nerve, shaving the tumor from the nerve is recommended. If disease encases the nerve, the situation is more complex. If dissecting the nerve from the tumor without leaving gross residual disease is possible, it should be attempted. If such dissection results in gross residual disease, the nerve function remains at high risk if disease progresses. In this circumstance resection of the nerve to achieve macroscopic clearance should be performed.

When the ipsilateral vocal cord is dysfunctional and disease encases the RLN at surgery, resection is indicated. If the nerve appears to be minimally adherent to tumor but is dysfunctional, shaving the disease from the nerve is recommended. In the rare setting of contralateral cord dysfunction and ipsilateral invasion (with a normally functioning ipsilateral cord), the surgeon should consider sparing the ipsilateral RLN in an attempt to avoid tracheostomy (31). The clinical team should consider that such patients are at high risk of requiring tracheostomy, either temporarily following surgery or because of subsequent disease progression resulting in RLN invasion and bilateral cord palsy (Table 2).

The role of IONM is controversial in thyroid surgery. Support now exists for the use of IONM for complex cases, particularly in the revision setting or when the RLN is suspected to be invaded by disease (47). IONM may be used as a diagnostic adjunct, with some authors recommending sparing even grossly involved RLNs which retain a positive electromyographic positive signal (48).

Invasion of the esophagus

When disease invades the muscular layer of the esophagus, it can often be dissected from the underlying mucosa without the need for formal reconstruction (Fig. 9). Limited luminal invasion can be addressed by resection with primary closure. However, when extensive invasion is encountered, resection with appropriate reconstruction is required.

Management of the regional lymph nodes

During preoperative investigation, lymph nodes should be assessed from the base of the skull to the mediastinum. More than 20% of advanced DTC cases will have clinical evidence of nodal metastases (49). Indeed, some series suggest that over 95% of patients with ETE will have evidence of nodal metastases on histological examination of elective neck dissection specimens (50). In the setting of clinically evident nodal metastases, a compartment-oriented neck dissection should be performed with the aim of resecting all gross disease. Those patients considered free of nodal disease (cN0) are at high risk of harboring occult nodal metastases, particularly in the central compartment. However the clinical impact of such occult metastases is uncertain. An individualized approach seems most appropriate. If the patient is encountered in the salvage setting following prior central

FIG. 9. Disease involving the muscular layer of the esophagus. The muscularis layer of the esophagus is usually very resistant to invasion.

neck dissection, further nodal surgery may carry significant risk. However, in the primary setting most groups now recommend considering elective nodal clearance in the presence of gross ETE (16,51,52).

Patients with distant metastases at presentation

Patients with distant metastases account for up to one third of reported series of invasive thyroid cancers (27). In a series of 1038 previously untreated patients with differentiated carcinoma of the thyroid, most of them papillary carcinomas, the risk of distant metastasis for papillary, follicular, and Hürthle cell carcinomas was 10%, 22%, and 33%, respectively (53). Distant metastasis are frequent in childhood, especially in the lungs. La Quaglia *et al.* (54) showed that the survival rate of children with distant metastases is excellent, but very few such patients present with locally advanced primary tumors.

Patients with invasive thyroid cancer and distant metastasis will require RAI therapy, which should be considered when planning the surgical approach because resection of all gross disease facilitates ^{131}I imaging and treatment. Analysis of data of 1516 patients of all ages with papillary carcinoma depicted 102 patients with lung metastases only or with other organ involvement (55). The 10- and 20-year survival rates in patients with papillary thyroid carcinoma without distant metastasis and in the lung metastasis groups were 98.5%, 98.0%, and 75.0%, 51.2%, respectively. The prognosis of patients with papillary thyroid carcinoma and lung metastasis at time of diagnosis is the same as for those whose lung metastases are discovered later. Survival analysis suggests that patients with multi-organ metastases have poorer survival than those with metastases limited to the lung (56). Furthermore, Shoup *et al.* (57) identified 336 patients with distant metastasis from differentiated thyroid carcinomas, in whom distant disease was either detected at the time of diagnosis or represented the first site of recurrence. Ten-year disease-specific survival from identification of distant metastasis was 26%, and multivariate analysis identified age 45 years or more, symptoms, site other than lung only or bone only, and no RAI treatment for the metastasis as predictors of poor outcomes.

Although cure cannot be achieved for many patients with distant metastases, the aim of therapy is to palliate symptoms and alter the mode of death. Controlling invasive disease in the central neck prevents the distress of death from asphyxiation or upper airway hemorrhage. However, as stated above, decision making in such complex cases must be individualized. For patients with rapidly progressing distant disease and well-controlled central neck disease, surgical resection would not be appropriate. In contrast, patients who present with resectable central neck disease and small-volume distant metastases remain candidates for aggressive airway resection as supported by the promising oncological outcomes reported above.

Adjuvant Therapies

The majority of patients with high-risk DTC will be considered for adjuvant RAI as part of initial therapy (51,52). However, patients with invasive DTC are at high risk of harboring RAI-resistant disease, which is often associated with aggressive histological subtypes (areas of poorly dif-

ferentiated disease, tall cell or insular carcinoma) and advanced age. For that reason, RAI is likely to be less effective in this subgroup of patients (58). Nonetheless, the relatively low side effect profile of treatment and some limited evidence of effectiveness in this high-risk group (59) means that most patients will be considered for adjuvant RAI.

More controversial is the role of EBRT for invasive DTC. No prospective trials have been performed, and a recent German study designed to address this issue was closed because only 45 of 311 patients recruited agreed to randomization (60).

In the absence of prospective evidence, the role of EBRT remains controversial. Treatment decisions should be made following multidisciplinary discussion and should be based upon patient, tumor, and surgical factors.

In patients whose disease is considered unresectable or in those who have gross residual disease following surgery, EBRT may be considered. The term "very advanced disease" is now preferred to the term unresectable, but either way some patients will present with disease that the surgical team feels is not amenable to a surgical approach. This definition will depend not only on the tumor, but also on the patient. Classically, disease encircling the carotid artery or invading the prevertebral fascia was considered unresectable. However, some patients will tolerate sacrifice of the carotid artery without major cerebrovascular effects. In contrast, if disease extends into the mediastinum and surgical resection would require sternotomy, there are patients who are considered insufficiently physiologically fit to justify such an approach to resect disease even if major arteries are not grossly involved. In such patients, although treatment intent is palliative, disease control can be achieved in a high percentage of patients (61–64).

Patients who undergo successful surgical excision of macroscopic disease remain at high risk of loco-regional recurrence. In this situation, careful discussion of risk factors should be undertaken within the multidisciplinary team, and EBRT can be considered for maximizing local control and organ preservation. RAI should not be discounted, although aggressive histological subtypes predict a poorer treatment response. Nonetheless, it may still be a useful adjunctive therapy. The optimal sequencing of RAI and EBRT in this situation is unknown. Some favor RAI first because EBRT may lead to reduced iodine avidity. However, concern remains about airway safety, EBRT may be administered first with RAI given subsequently.

When the approach to EBRT is considered, doses will range from 70 Gy for areas of gross disease, 60–66 Gy for postoperative high-risk sites including positive surgical margins, and 50–54 Gy for areas of lower risk including elective nodal sites (32). Treatment volumes can be restricted to areas at high risk of relapse based on preoperative radiology, intraoperative findings, and postoperative review of the pathology in order to minimize treatment toxicity. Intensity-modulated radiation techniques must be employed to achieve prescribed dose to the target volumes while remaining within critical structure tolerances (52).

If disease progresses and is refractory to RAI, palliative systemic therapies with targeted agents such as tyrosine kinase inhibitors may then be considered (65,66). The definition of RAI-refractory disease includes at least one of the following: (a) disease does not take up iodine at documented

sites of metastatic disease, (b) disease progresses despite RAI treatment and confirmed uptake, (c) distant disease grows over a 1-year period after RAI, or (d) total cumulative dose of RAI exceeds 600 mCi (67).

Although the use of tyrosine kinase inhibitors has been reported in a neo-adjuvant setting (68), experience is extremely limited and their use is not currently considered to be indicated.

Prognosis

When outcomes for patients with invasive thyroid cancer are considered, limitations of the reported studies must be kept in mind. No prospective trials exist and all experience represents retrospective surgical cohorts. Any patient deemed unfit for surgery based on tumor or patient grounds will therefore have been excluded, and the cases that are included are likely to represent the fittest patients who present with relatively limited disease.

However, despite these limitations, there are selected patients in whom prognosis may be favorable. Long-term rates of local control exceed 90% in some studies (41). Long-term survival can also be achieved in a significant group of patients, with 5-year survival approaching 90% in these selected cases (17,41).

Factors predictive of outcome have been poorly reported to date. Some investigators have demonstrated an association between the extent of airway invasion and outcome. Shin *et al.* (18) found in a study of 22 patients that 5-year survival dropped from 100% versus 29% for disease that spared or involved the luminal airway, respectively. Czaja and McCaffrey (14) also demonstrated a significant association between extent of airway invasion and survival in 286 patients with invasive disease. Univariate analysis of outcome showed survival of 60% versus 80% at 10 years for patients with and without airway invasion respectively ($p < 0.05$).

Conclusion

Visceral invasion occurs in at least 5% of patients with DTC. In patients with resectable disease, long-term outcomes are good, with up to 95% local control rates reported. Initial series reported central neck disease as the most common cause of death (69,70). However, advances in our understanding of the biology of this disease and an aggressive surgical approach to management have resulted in improved outcomes for this patient group, with death from uncontrolled central neck disease now uncommon (71–74). Even for patients who present with distant metastatic disease, not only can meaningful prolongation of life be achieved, but control of central neck disease can avoid a distressing mode of death.

Although the presence and degree of airway invasion is likely to be the strongest predictor of outcome for this patient group, controversy about the surgical approach to these cases exists. The consensus is that excision of all gross disease should be the aim of surgery. Some groups recommend full-thickness airway resections for all but the most limited of disease and report excellent outcomes with this approach. However, with careful patient selection, appropriate preoperative investigation and with a selective approach to adjuvant therapy, most groups now prefer a more conservative approach with minimal airway resection in the absence of disease extending deep to the cartilage of the trachea or larynx.

Patients with airway invasion from DTC may present in the primary or recurrent setting, with localized or systemic disease and in the presence of complex comorbidities. As such, these patients require multidisciplinary evaluation and planning to achieve optimal outcomes.

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