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Preoperative Tracheostomy Is Associated with Poor Disease-Free Survival in Recurrent Laryngeal Cancer

Birkeland AC, Rosko AJ, Beesley L, Bellile E, Chinn SB, Shuman AG, Prince ME, Wolf GT, Bradford CR, Brenner JC, Spector ME.

from ***Otolaryngology – Head & Neck Surgery, September 2017***

Objectives. It is unknown if preoperative tracheostomy for persistent/recurrent laryngeal squamous cell carcinoma (LSCC) plays a role in unrecognized local disease spread and disease recurrence after salvage laryngectomy. The goals of this study were to determine the effect of preoperative tra- cheostomy on disease-free survival (DFS) in patients with recurrent/persistent LSCC undergoing salvage laryngectomy.
Study Design. Retrospective case series derived from prospectively maintained database.
Setting. Tertiary care academic center.

Subjects. Patients with recurrent/persistent LSCC after radiation/chemoradiation (RT/CRT) who underwent salvage laryngectomy at the University of Michigan from 1997 to 2015.
Methods. Demographic, clinical, pathologic, and survival data were collected. Kaplan-Meier survival estimates were performed.

Results. DFS was worse for patients with tracheostomy prior to laryngectomy than patients without a tracheostomy (5 year: 39% vs 67%; P \.001). Patients with tracheostomy prior to RT/CRT compared to patients with tracheostomy after RT/CRT or patients without a tracheostomy had worse DFS (5-year: 25%, 49%, and 67%, respectively; P \.001). In bivariable analyses controlling for T classification, N classifi- cation, or overall stage, preoperative tracheostomy was associated with worse DFS. In multivariable analysis, pres- ence of a preoperative tracheostomy had a worse DFS (hazard ratio, 1.63; 95% confidence interval, 1.00-2.67; P = .048).

Conclusion. Preoperative tracheostomy is associated with dis- ease recurrence in patients with persistent/recurrent LSCC undergoing salvage laryngectomy, particularly in patients who had tracheostomy prior to completion of initial RT/ CRT. Notably, preoperative tracheostomy as a causal

factor vs marker for disease recurrence is difficult to ascertain. Nevertheless, clinicians should be aware of the increased risk of locoregional recurrence in patients with preoperative tracheostomy when counseling on surgical salvage and when considering the role of additional therapy.

Summary statements

1. Preoperative tracheostomy in patients that undergo salvage laryngectomy following CRT is a poor predictor for disease free survival (5-year DFS 39% vs. 67%) and locoregional control (5-year locoregional control 47% vs. 79%)
2. In particular, patients that required a tracheostomy prior to initial definitive therapy fared the worst.
3. Patients and clinicians should be aware that a preoperative tracheostomy portends a worse outcome and it can inform the discussion around goals of care and extend of surgical margins during a salvage laryngectomy.

Strengths

1. Sizable cohort in a prospectively acquired database (retrospectively analyzed)
2. Identifies tracheostomy as a risk factor for worse outcomes in patients that require salvage laryngectomy regardless of the stage of the recurrence.
3. The multivariate analysis confirms the established impact of positive margins and extra capsular nodal spread in addition to adding tracheostomy status.

Weaknesses

1. Unclear mechanism for why a tracheostomy leads to worse outcomes (some theories are proposed)
2. Location of the tracheostomy is not described (e.g. high or low). Perhaps, if a tracheostomy is required, one should not do a "high tracheostomy" so as to preserve at much normal trachea for creation of the stoma. Also relative timing between tracheostomy after recurrence/disease persistence and salvage surgery not defined.

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Preoperative 18F-FDG-PET/CT vs Contrast-Enhanced CT to Identify Regional Nodal Metastasis among Patients with Head and Neck Squamous Cell Carcinoma

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from ***Otolaryngology – Head & Neck Surgery, September 2017***

Abstract

Objective. Our objective was to compare the accuracy of preoperative positron emission tomography (PET)/computed tomography (CT) and contrast-enhanced CT (CECT) in detecting cervical nodal metastases in patients treated with neck dissection and to scrutinize the ability of each modality to determine nodal stage.

Study Design. Case series with chart review.

Setting. Montefiore Medical Center, Bronx, New York.

Subjects and Methods. Patients who underwent neck dissection at our institution for primary treatment of head and neck squamous cell carcinoma (HNSCC) and had received preoperative PET/CT and CECT were included in this study. Imaging studies were reinterpreted by 3 specialists within the field and compared for interreader agreement. Concordance between radiology and histopathology was measured using neck levels and sides, along with patient nodal stage. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and agreement coefficients were calculated.

Results. Seventy-three patients were included in the study. Sensitivity was 0.69 and 0.94 (level and side) for PET/CT vs 0.53 and 0.66 for CECT (P = .056, P = .001). Specificity was 0.86 and 0.56 for PET/CT vs 0.91 and 0.76 for CECT (P = .014, P = .024). No significant difference was found in overall accuracy (P = .33, P = .88). The overall agreement percentages between N stage called by imaging modality and pathology were 52% and 55% for PET/CT and CECT, respectively.

Conclusion. No significant difference in sensitivity was found between PET/CT and CECT. CECT was found to have superior specificity compared with PET/CT. The information gleaned from each modality in the pretreatment evaluation of HNSCC appears to be complementary

Summary
This paper adds to the limited literature on the efficacy of PET/ CT in preoperative nodal staging:

- Confirms that PET/CT stages nodal involvement more accurately than conventional imaging
- Confirms that PET/CT may be more useful than CECT for nodal staging
- Confirms that PET/CT leads to upstaging and changes in patient management.
- The results cannot confirm that PET/CT overstages cervical lymph node disease. Moreover, the data show that PET/CT offers no overall accuracy advantage over CECT in the preoperative staging of HNSCC.
- Neither modality should be used in isolation to preoperatively stage cervical lymph node involvement.

Interesting results:

- When assessing concordance between imaging and pathology by neck level:
  -PET/CT was found to correctly identify occult metastases in 57 of 83 (69%) positive neck levels
  -CECT was found to identify 44 of 83 (53%) positive neck levels (Table 3).
- Absence of occult metastasis was correctly reported in
  -424 of 496 (86%) using PETCT
  -450 of 496 (91%) using CECT
- Concordance between preoperative iN stages (imaging N stage) and pathology N stages was ~50% for both PET/CT and CECT. When stage assignments were discordant
  - 37% of calls were overstaged by PET/CT while 19% were overstaged by CECT.
  - 26% of patients were understaged by CECT compared with 11% by PET/CT.
- No significant difference was found between PET/CT and CECT in terms of sensitivity (P = .056). CECT was more specific (P = .014), there was no significant difference in overall accuracy (P = .33).
- When an independent analysis was performed evaluating neck laterality rather than nodal station,
  -PET/CT was found to correctly identify the presence of occult metastases in 50 of 53 (94%) positive neck sides
  -CECT was found to correctly identify 35 of 53 (66%) positive neck sides.
- Absence of cancer involvement was correctly reported in
  - 35 of 63 (56%) negative neck sides using PETCT

  - 48 of 63 (76%) negative neck sides using CECT
- Of the 27 N0 patients who had no evidence of cervical metastasis on pathology,
  - 16 (59%) patients were assigned a preoperative stage of iN1 or higher by PET/CT
  - 8 (30%) patients were assigned a higher preoperative stage by CECT.
- All imaging studies were evaluated by 3 independent radiologists to evaluate the accuracy and reproducibility of all PET/CT and CECT results. In comparing interreader agreement for PET/CT and CECT for the detection and staging of preoperative cervical lymph node metastasis, the findings suggest that CECT has higher interreader agreement (0.85-1) than PET/CT (0.46-0.71) for both staging as well as neck-level and neck side evaluation. These data may suggest that heuristics for identifying metastatic lymph nodes for CECT are more standardized, while standards for PET/CT require further development.

Strengths

- PETCT read by 3 board-certified nuclear medicine physicians & CECT read by 3 neuroradiologists
- Rigorous statistical analysis evaluating interreader agreement

Weaknesses

- Various primary tumor sites
- Small sample size
- No standardized protocol for intraoperative labeling of nodes
- If only one imaging modality was used, that patient was excluded. His potentially introduces selection bias
- Included imaging from up to 27 weeks prior to surgery

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Management of Recurrent and Metastatic HPV-Positive Oropharyngeal Squamous Cell Carcinoma after Transoral Robotic Surgery

John R. Sims, MD , Kathryn Van Abel, MD , Eliot J. Martin, PA-C , Christine M. Lohse, MS , Daniel L. Price, MD , Kerry D. Olsen, MD , and Eric J. Moore, MD

from ***Otolaryngology – Head & Neck Surgery, July 2017***

Objective. To describe management and oncologic outcomes for patients who develop locoregional recurrence (LRR) or distant metastasis (DM) following transoral robotic surgery for human papilloma virus (HPV)–positive oropharyngeal squamous cell carcinoma (OPSCC).

Study Design. Case series with chart review.

Setting. Tertiary care referral center.

Subjects and Methods. A total of 286 patients with HPV-positive OPSCC who underwent transoral robotic surgery– based treatment from May 2007 to May 2015.

Results. Of 286 patients (12.2%), 35 met inclusion criteria. Of these, 19 experienced an LRR and 16 developed a DM; 2 patients with LRR subsequently developed DM. In those patients with an LRR, 79% had T1/T2 tumors, and 47% had N0/N1 nodal disease, compared with 75% and 6% in the DM group,

respectively. The median time to LRR or DM was 0.6 years (interquartile range [IQR], 0.4-1.0) and 1.8 years (IQR, 1.0-2.1), respectively. Salvage treatment with intent to cure was attempted in 23 patients (16 LRR, 7 DM). The median time from LRR or DM to last follow-up for the 18 patients who were still alive after salvage was 1.9 years (IQR, 0.4-3.8; range, 7 days–6.2 years). Estimated cancer-specific survival rates at 3 years following intent-to cure treatment were 63% (95% CI, 39-100; number still at risk, 5) in the LRR group and 100% (95% CI, 100-100; number still at risk, 2) in the DM group.

Conclusion. Overall, LRR and DM for HPV-positive OPSCC following transoral robotic surgery–based therapy are infrequent. In our subset of patients who underwent intent-to cure treatment, cancer-specific survival rates were favorable. Therefore, aggressive salvage treatment for LRR and DM for HPV-positive OPSCC should be recommended for appropriate candidates.

Summary

This paper aims to study outcomes following locoregional recurrence or distant metastasis in HPV+ oropharyngeal tumors after TORS. Their overall CSS for those undergoing salvage surgery for LRR or DM were 63% and 100% respectively.

In the discussion, the authors review papers from 1974 and 2000 that demonstrate low rates of salvage for OPSCC (3.5-18.9% and 24-28% respectively). A 2016 meta-analysis of 22 studies also demonstrated a pooled 3 year OS at 26% but when the data was stratified by studies performed before or after 2000, the pooled data of studies after 2000 demonstrated 5 yr OS of 50%. This current paper further confirms the latter finding by demonstrating a 3 yr cancer specific survival rate of 71% in those that underwent salvage therapy.

In this paper, they studied 286 patients and 35pt (12.1%) had LRR (n=19) or DM (n=16). Median time to LRR (7.2mo) and DM (20 months). 23 pt underwent intent to cure salvage treatment (16 LRR, 7DM). All 7 DM had lung or mediastinal disease. See Table I

This paper is unique in that most of their LRR with high T-stage underwent surgery alone as initial management and were therefore chemo and radiation naïve. They all did relatively well with salvage of CRT or re-operation + adjuvant radiation. Authors were very selective in salvage modalities dependent on patient's previous treatment, resectability of recurrence and morbidity of treatment regimen. For example, patients with regional recurrences in contralateral untreated necks did very well with surgical salvage. Patients who were chemo and radiation naïve also fared well.

Regarding DM, previous reports have demonstrated CSS as low as 11-16%. In this study the 3 year CSS was 57%. Again the authors were rigid in candidate selection. All 4 patients from their DM cohort with good functional status and a solitary lung met underwent wedge resection and have no disease at varied lengths of followup from 0.4to 5.4 years, (see Figure 2)

Table 1. Patient and Tumor Characteristics for 35 Patients Who Developed LRR or DM Following TORS-Based Primary Therapy for HPV-Positive OPSCC.

	Patients,[a] n (%)	
	Locoregional Recurrence (n = 19)	Distant Metastasis (n = 16)
Sex		
Female	3 (16)	1 (6)
Male	16 (84)	15 (94)
Smoking history		
Never	14 (74)	9 (56)
Current	0	1 (6)
Former	5 (26)	6 (38)
Pack-years (n = 18:16)		
≤10 or never smoked	15 (83)	12 (75)
>10	3 (17)	4 (25)
Adult Comorbidity Evaluation–27 score		
0	10 (53)	6 (38)
1	5 (26)	4 (25)
2	4 (21)	5 (31)
3	0	1 (6)
Tumor grade (n = 17:15)		
1	0	0
2	0	0
3	16 (94)	12 (80)
4	1 (6)	3 (20)
Angiolymphatic invasion (n = 11:7)	2 (18)	1 (14)
Perineural invasion (n = 10:10)	1 (10)	4 (40)
No. of attempts for negative margin		
0	1 (5)	0
1	8 (42)	10 (63)
2	9 (47)	3 (19)
3	1 (5)	3 (19)
Final margin status		
Negative (R0)	19 (100)	16 (100)
Positive (R1-R2)	0	0
Pathologic T stage[b]		
T1	8 (42)	6 (38)
T2	7 (37)	6 (38)
T3	2 (11)	3 (19)
T4a	2 (11)	1 (6)
Pathologic N stage[b]		
N0	4 (21)	0
N1	5 (26)	1 (6)
N2a	3 (16)	0
N2b	5 (26)	10 (63)
N2c	2 (11)	1 (6)
N3	0	4 (25)
Total no. of positive nodes (n = 15:16)[c]		
1	8 (53)	1 (6)
≥2	7 (47)	15 (94)
Extracapsular spread (n = 14:16)[c]	8 (57)	15 (94)

Table 1. (continued)

	Patients,[a] n (%)	
	Locoregional Recurrence (n = 19)	Distant Metastasis (n = 16)
Level of largest node involved with tumor (n = 15:16)[c,d]		
I	0	1 (6)
II	12 (80)	12 (75)
III	3 (20)	5 (31)
IV	0	2 (13)
V	0	0
Matted nodes (n = 15:15)[c]	0	2 (13)
Total no. of levels containing positive nodes (n = 15:16)[c]		
1	10 (67)	5 (31)
2	1 (7)	3 (19)
3	3 (20)	5 (31)
4	0	2 (13)
5	1 (7)	1 (6)
Nodal invasion of adjacent structures (n = 15:16)[c,d]		
Carotid artery	0	0
Prevertebral fascia	0	0
Trachea	0	0
Esophagus	0	0
Sternocleidomastoid	1 (7)	4 (25)
Strap musculature	0	0
Skull base	0	0
Internal jugular vein	3 (20)	6 (38)
Spinal accessory nerve	1 (7)	2 (13)
Other cranial nerve	1 (7)	2 (13)
Other structure	0	1 (6)
Overall AJCC stage		
I	3 (16)	0
II	1 (5)	0
III	4 (21)	1 (6)
IVa	11 (58)	11 (69)
IVb	0	4 (25)
Type of locoregional recurrence		
Regional (nodal)	9 (47)	NA
Locoregional (primary and nodal)	6 (32)	
Local (primary)	4 (21)	
Location of metastases[d]		
Lungs	NA	12 (75)
Mediastinum		7 (44)
Bone		4 (25)
Liver		2 (13)
Skin		1 (6)

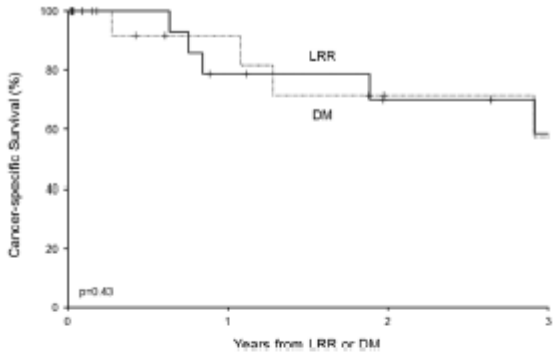

Figure 1. Cancer-specific survival from date of diagnosis of recurrent disease for all patients who developed a locoregional recurrence (LRR) or distant metastasis (DM; *P* = .43). All patient deaths were from their cancer; therefore, this figure also represents overall survival.

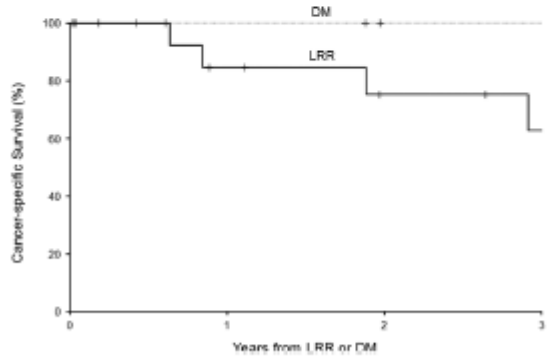

Figure 2. Cancer-specific survival from date of diagnosis of recurrent disease for all patients undergoing intent-to-cure (salvage) treatment following locoregional recurrence (LRR) or distant metastasis (DM). All patient deaths were from their cancer; therefore, this figure also represents overall survival.

Strengths

- Provides interesting data points for a “newish” population of patients with high stage OPSCC who are chemoradiation naïve.
- While a small cohort, it is a thorough evaluation of the experience of a single institution of patients treated uniformly with surgery as primary modality over an 8 year period.

Weaknesses

- -retrospective
- -selection bias
- small cohort
- -short follow-up, 20 months

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Positron emission tomography/computed tomography after primary transoral robotic surgery for oropharyngeal squamous cell carcinoma.

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from ***Laryngoscope, September 2017***

Objectives/Hypothesis: To assess the first post-treatment positron emission tomography/computed tomography (PET/CT) in prediction of disease-free survival after primary transoral robotic surgery (TORS) for oropharyngeal squamous cell carcinoma (OPSCC) with or without adjuvant chemoradiation. Study Design: Retrospective review.

Methods: Ninety-five patients with OPSCC treated with primary TORS from 2010 to 2014 at a single tertiary academic center were evaluated with PET/CT. Imaging was performed between 2 and 7 months after completing all treatment. Radiology findings were categorized as 1) negative, noting either complete resolution of foci without evidence of disease or anatomical changes likely attributed to treatment; 2) equivocal, noting equal likelihood of malignancy versus treatment-related changes; or 3) positive, noting either findings concerning for malignancy or new hyperactivity not attributed to treatment related changes. The median follow-up time was 31 months (range, 23–63 months). Recurrence was defined as biopsy proven invasive malignancy or clinical suspicion sufficient to initiate treatment occurring within 3 years of the completion of all treatment.

Results: Of 95 total patients with at least 2 years of follow-up records, 26 had positive post-treatment PET/CT results, with five experiencing actual recurrences. Of 69 patients with negative post-treatment PET/CT results, none experienced recurrences. These results indicate a sensitivity of 100%, specificity of 77%, positive predictive value of 19%, and negative predictive value of 100%.

Conclusions: A majority of TORS patients (73%) will have a negative first post-treatment PET/CT. A single negative post-treatment PET/CT is strongly correlated with 2-year disease-free survival in patients treated with primary TORS and may warrant decreased surveillance imaging.

Summary

- 95 patients with naïve oropharyngeal carcinoma (94% tonsil and base of tongue, 82% HPV +) treated with TORS with/without adjuvant radiation (27%) or chemoradiation (55%) with a PET/CT in the first 2-7 months after finishing the treatment and followed up to 3 years. 90 patients classified as T1-2and 80 N+.
- Evaluation of PET/CT as positive, equivocal or negative with specific criteria and clinical or pathologic assessment of suspicious cases. Imaging was made after a mean time of 14 weeks.
- Recurrence rate at 2 years was 5.3%
- Sensitivity was high (100%) but specificity was low (77%). Positive predictive value was low (19%)

Strengths

- Specific criteria for selection and assessment of PET/CT results
- Important number of patients with close follow-up
- Low rate of recurrent which means good selection for TORS
- A negative PET/CT currently discards the diagnosis of recurrence

Weaknesses

- There is not information about who made the evaluation of PET/CT, if original assessment was reevaluated with blind observers and the interobserver agreement rate.

- Retrospective assessment of results
- The low number of recurrences makes difficult to accept the high sensitivity
- A low positive predictive value indicates that a positive/equivocal result of PET/CT always have to be confirmed with clinical/pathology evaluation

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Information for Clinicians: Approach to the Patient with Progressive Radioiodine-Refractory Thyroid Cancer—When to Use Systemic Therapy

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from THYROID, June, 2017

Introduction

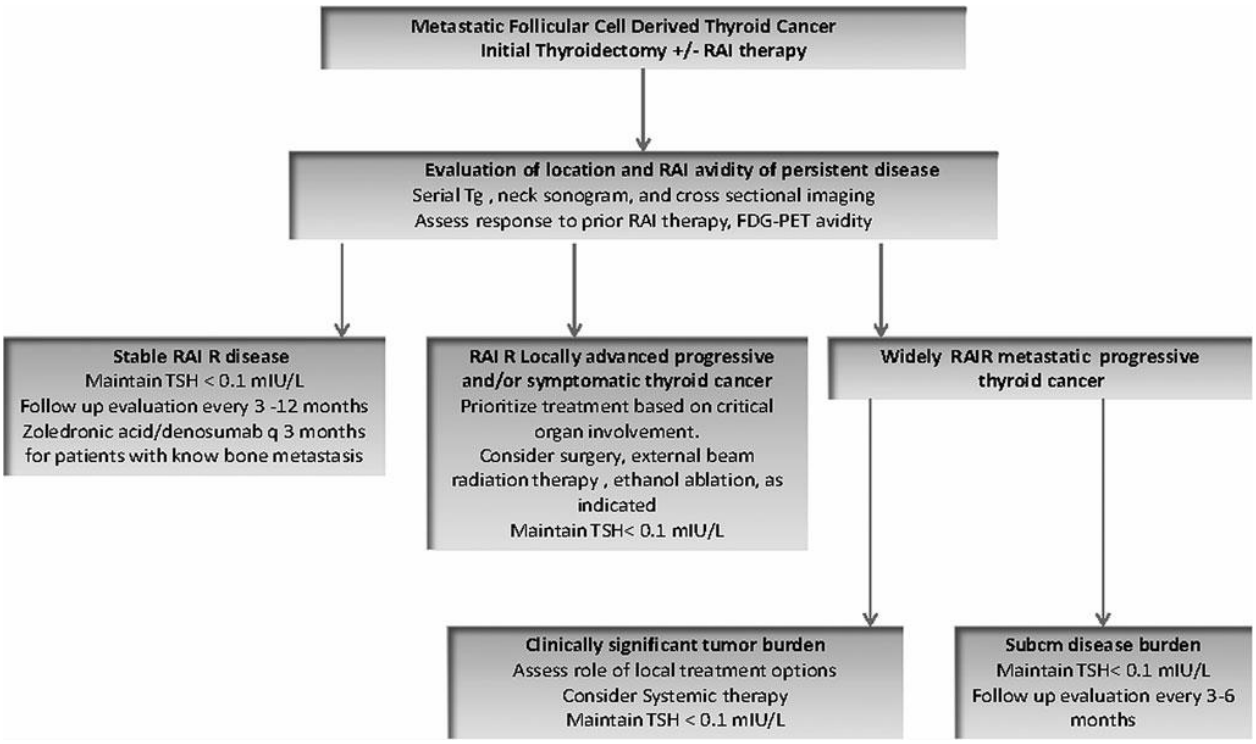
Radioiodine (RAI) therapy has been one of the primary systemic therapy options for metastatic thyroid cancer of follicular cell origin for more than 50 years. Many patients who are deemed to have responded to an initial RAI treatment eventually progress and become RAI refractory (RAI-R) (2). Large cumulative doses of RAI expose patients to potential side effects that can be clinically significant (e.g., second primary malignancies, myelodysplastic syndrome, and salivary gland dysfunction). In recent years, there has been much interest in the use of multi-kinase inhibitor (MKI) therapy for the management of metastatic thyroid cancer. These novel agents are usually prescribed as single medications when used in routine clinical care. Some of these agents are also being evaluated as combination therapies or in conjunction with RAI as part of several ongoing clinical trials. MKI therapy demonstrated promising results in clinical trials by inducing tumor shrinkage and prolonging progression-free survival (PFS) (4,5). Recent studies suggest that initiation of MKI therapy at a smaller disease burden may provide a PFS benefit when compared to starting MKI therapy after larger-volume disease develops (6). However, more data are needed with regard to the impact of MKI on overall survival and quality of life. In clinical practice, the lack of a uniform consensus regarding the indications for initiation of MKI therapy, the unproven overall survival and quality-of-life benefits, the significant costs, and the potential adverse effects of these agents often make it difficult to decide when to initiate these therapies for an individual patient.

Summary statements:

The first step in evaluating a patient's eligibility for MKI therapy is determining whether the patient has convincing evidence of RAI-R disease. Patients are classified as having RAI-R disease if they have: (i) lack of RAI uptake on post therapy scan after RAI-administered activity >30mCi following appropriate iodine deprivation and adequate thyrotropin (TSH) elevation; (ii) lack of RAI uptake on a properly conducted diagnostic whole-body scan in the setting of known structural disease, as demonstrated by cross-sectional imaging; (iii) lack of demonstrable ability of the tumor to concentrate sufficient RAI for tumoricidal effect, based on lesional dosimetry (i.e., delivered RAI dose to metastatic foci <8000 cGy) when available; (iv) structural progression of thyroid cancer 6–12 months after RAI therapy; (v) a rising Tg level 6–12 months after RAI therapy; and (vi) continued progression of thyroid cancer, despite cumulative RAI-administered activities >500–600mCi in adult patients.

Recommendation 96 of the 2015 American Thyroid Association(ATA) guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (DTC) states that the use of MKI therapy ''should be considered in RAI-R DTC patients with metastatic, rapidly progressive, symptomatic and/or imminently threatening disease that is not otherwise amenable to suitable control via other approaches'' (9). Given the lack of evidence of improved overall survival and quality of life with the use of these MKI therapies, the

guidelines committee advocates that ‘‘patients who are candidates for kinase inhibitor therapy should be thoroughly counseled on the risks and benefits of this therapy as well as alternative therapeutic approaches including best supportive care’’ (9). It is important to note that not all patients with RAI-R thyroid cancer will be candidates for MKI therapy under these recommendations. Based on expert opinion, the ATA guidelines suggested that patients who ‘‘demonstrate at least 20% increase in sum of longest diameters of target lesions over 12–15 months follow up, the appearance of significant new metastatic lesions, or development of disease related symptoms should warrant consideration of appropriate systemic therapies beyond TSH-suppressive thyroid hormone and/or directed therapies.’’



Patients who exhibit multiple sites of progressive metastatic cancer are appropriate candidates for MKI therapy. The diagram above outlines a suggested strategy for management of RAI-R DTC. The table below summarizes the indications for systemic therapy.

TABLE 1. INDICATIONS FOR SYSTEMIC THERAPY

	Disease burden description	*Required*	*Required*	*Case-by-case basis*
Indication #1	Symptomatic disease burden	RAI-R	Cannot be managed with local therapy	
Indication #2	Clinically significant disease burden[a]	RAI-R	Progression within 6 months	Progression within 12 months
Indication #3	Disease is threatening organ or limb function	Cannot be managed with local therapy	—	

[a]Clinically significant disease burden is defined as target lesion(s) measuring at least 1.5 cm in diameter and likely to cause symptomatic disease if left untreated.
RAI-R, radioiodine refractory.

Symptomatic structural disease progression may be amenable to localized therapies or MKI therapy, depending on the location, specific symptoms involved, rate of disease progression, and extent of other

metastatic foci. In some instances, worsening pulmonary function in patients with progressive lung metastasis may be an indication for MKI therapy. In contrast, MKI therapy would not be considered for those patients with stable lung capacity and slowly progressive metastasis. The patient's age and functional status are important factors to be considered when MKI therapy is being entertained.
In asymptomatic patients, the clinically significant tumor burden, or minimal tumor size requirement, needed for eligibility for molecular targeted therapy is at least one lesion with largest diameter >1.5 cm in the shortest axis for lymph nodes and 1 cm in the longest axis for non-lymph nodes, and/ or rapid development of new lesions, as defined by RECIST (12). Here, it is important to note that in metastatic thyroid cancer of follicular cell origin, the majority of patients presenting with structural disease progression (68%) demonstrate new lesions with a corresponding increase in the volume of known foci, while only 15% of patients develop new lesions with continued stability of previously identified tumor metastasis (13). ''Rapid development'' of new metastasis is defined as the appearance of new tumor foci at 3- to 12-month intervals. Furthermore, a 20% increase in the longest tumor diameter of any given tumor foci >1–1.5 cm in size within 6–15 months is considered as the minimum requirement for consideration of MKI therapy in asymptomatic patients.

There are two Food and Drug Administration (FDA)- approved drugs that can be used for RAI-R DTC: sorafenib and lenvatinib. Sorafenib was FDA approved based on the results of a randomized, placebo-controlled, Phase III clinical trial (DECISION trial) (4). Patients enrolled in this trial were treatment naïve, RAI-R, and had evidence of structural disease progression. The median PFS in the sorafenib-treated patients was 10.8 months versus 5.8 months in the placebo treated patients (hazard ratio [HR] = 0.59). There was no overall survival advantage. However, patients were allowed to cross over from the placebo arm. While objective responses in the sorafenib group were only 12.2% (all partial responses), most patients had tumor regression that did not meet the criteria for partial response. No complete responses were observed. The starting dose of sorafenib is 400 mg twice daily.

Lenvatinib was FDA approved based on the results of a randomized, placebo-controlled, Phase III clinical trial (SELECT trial) (5). Similar to the sorafenib trial, patients were RAI-R and had evidence of structural disease progression. However, in the SELECT trial, patients were allowed previous treatment with vascular endothelial growth factor– based therapy. This previously treated group comprised 24% of the study population. The PFS in the lenvatinib treated patients was 18.3 months versus 3.6 months in the placebo treated patients (HR = 0.21). The response rate in lenvatinib treated patients was 64.8%, mostly consisting of partial responses but also including four complete responses. The starting dose of lenvatinib is 24 mg once daily.

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TABLE 2. DRUGS AVAILABLE FOR DIFFERENTIATED THYROID CANCER

Drug	*FDA-approved for DTC*	*Clinical trial*	*Comment*	*Reference/NCT number*
Axitinib		×	Anti-angiogenic	(29)
Cabozantinib		×	Anti-angiogenic	(20,30)/NCT02041260
Dabrafenib		×	Selective *BRAF* inhibitor For *BRAF*-mutated PTC	(16,18)/*NCT01723202/*NCT01947023
Lenvatinib	×	×	Anti-angiogenic	(5,31)
Pazopanib		×	Anti-angiogenic	(32)/*NCT01438554
Sorafenib	×	×	Anti-angiogenic	(4,33)
Sunitinib		×	Anti-angiogenic	(34)
Vandetanib		×	Anti-angiogenic	(35)
Vemurafenib		×	Selective *BRAF* inhibitor For *BRAF*-mutated PTC	(15)/NCT01709292/*NCT02145143/NCT02456701

FDA, Food and Drug Administration; PTC, papillary thyroid carcinoma.

A list of all available MKI drugs is listed above.

While great strides have been made in the past decades with the discovery of the kinase inhibitors, these drugs have toxicities, some of which are tolerable while others can be life-threatening. Effective management of these toxicities is critical in order to maintain patients on treatment. Furthermore, patients should be educated regarding the potential adverse effects with these drugs, and informed consent should be obtained. There are various publications available to help clinicians to manage toxicities from kinase inhibitors (21–25). The most common adverse effects of the anti-angiogenic kinase inhibitors are hypertension, diarrhea, fatigue, weight loss, hypothyroidism, and skin changes, including hand–foot skin reaction and, in the case of sorafenib, squamous-cell carcinomas of the skin. Rare but serious adverse events of anti-angiogenic drugs include intestinal perforation, tracheoesophageal fistula formation, bleeding, thrombosis, and heart failure. Although there are no contraindications, it is our opinion that comorbid conditions such as colitis, history of diverticulitis, congestive heart failure, and tracheal invasion should be taken into account when considering which kinase inhibitor is most appropriate for a patient.

Strengths: Provides evidence based recommendations of the available drugs and the specifics to their indications and patient inclusion criteria.

Weaknesses: Could include more about what is known about the mechanisms of action and the impact use of these medications have on patient quality of life.