Difficult Decisions in Surgery:
An Evidence-Based Approach

Zhen Gooi · Nishant Agrawal
Editors

Difficult Decisions in Head and Neck Oncologic Surgery

Springer

Difficult Decisions in Surgery: An Evidence-Based Approach

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The complexity of decision making in any kind of surgery is growing exponentially. As new technology is introduced, physicians from nonsurgical specialties offer alternative and competing therapies for what was once the exclusive province of the surgeon. In addition, there is increasing knowledge regarding the efficacy of traditional surgical therapies. How to select among these varied and complex approaches is becoming increasingly difficult. These multi-authored books will contain brief chapters, each of which will be devoted to one or two specific questions or decisions that are difficult or controversial. They are intended as current and timely reference sources for practicing surgeons, surgeons in training, and educators that describe the recommended ideal approach, rather than customary care, in selected clinical situations.

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I dedicate this book to my beloved parents, Francis Gooi and Catherina Chin.

Zhen Gooi

I dedicate this book to my dear parents (Satesh and Rupa), amazing sister (Ruchika), and wonderful wife (Vidushi) for their eternal love. I would like to thank Ariv and Agustya for bringing endless joy to my life, putting up with my work schedule, and sharing me with my patients.

Nishant Agrawal

Foreword

I am very pleased to be asked to comment about this compilation because it is CRITICALLY IMPORTANT. Comprehensive texts are imperative to maintaining currency of the core specialty knowledge, but they sometimes fall short in presenting all sides of a clinical issue and determining the most rational and reasonable solution for the time. This book accomplishes that in a contemporary fashion, acknowledging the dynamism and ever-changing nature of modern clinical science and practice.

Much as similar topics are discussed at bedside rounds, head and neck tumor boards, lectures, conferences, and with patients, highly relevant diagnostic and therapeutic issues are presented and weighted for each topic, guiding the reader toward a rational and informed resolution to the problem. The textbook is truly an example of the power of Socratic thought!

I believe that the concepts presented herein are concise, objective, and absolutely relevant. An internationally acclaimed cohort of editors and authors share their insights in a logical way that can be easily followed by members of the multidisciplinary head and neck cancer team. Head and neck oncologists from all disciplines, fellows, residents, and students will all benefit significantly from this contribution resulting in improved patient care. Congratulations to the editors and authors!

Baltimore, MD, USA — Charles W. Cummings

Preface

We are excited to present, to the multidisciplinary head and neck oncology community, a new perspective on approaching some of the controversial clinical questions within our field. There is no doubt that the practice of head and neck surgical oncology is rewarding. We help our patients through a myriad of challenges, curing and restoring vital segments of their bodies that play an outsized role in defining their human experience. They entrust us, as their physicians, to guide them through navigating the complexity of their illness.

The questions posed in this book were deliberately chosen to reflect actual clinical scenarios that perhaps all of us have struggled with. Much of what we practice is a reflection of what our own mentors did when confronted with these scenarios. We greatly benefit from the wisdom and experience of our predecessors, but ultimately advancing our field and the care of our patients mandates us to critically examine how we can improve our outcomes with evidence-based medicine.

To this end we have asked our internationally acclaimed authors to critically assess the most current scientific literature in their areas of expertise and to present their interpretation of the evidence according to the PICO (*P* population, *I* intervention, *C* comparison, *O* outcome) format and make their recommendations based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria. This structured method of analysis aims to provide the reader a more nuanced understanding of the topic at hand and to identify areas of improvement in their own individual practices.

The selection of authors in this book was deliberately chosen to reflect the global nature of head and neck cancer. To this end we are especially honored to have the perspective of our internationally respected colleagues from Asia, South America, Africa, Australia, the Middle East, and North America. We are grateful to all our colleagues who have taken time out of their busy schedules to provide insightful analysis of their topics. We hope that this text will provide the reader inspiration to advance their own clinical practices based on available scientific evidence.

Chicago, IL — Zhen Gooi
Chicago, IL — Nishant Agrawal

Acknowledgments

We are eternally grateful to our patients and their loved ones for their trust and courage in their brave fight against head and neck cancer. You (our patients) are a constant inspiration for us to continue to do better in our pursuit to treat cancer.

We are thankful to our own teachers, residents, students, and multidisciplinary head and neck oncology colleagues for always challenging us to improve on the status quo to improve outcomes for our patients.

Contents

Part I

Oral Cavity

1 Elective Versus Therapeutic Neck Dissection for Clinically Node Negative Early Oral Cancer

Anil K. D'Cruz, Harsh Dhar, and Richa Vaish

Introduction

Nodal metastasis is one of the most important prognostic factors in oral cancers. The presence of metastatic neck nodes signals an aggressive biology and upstages the disease to stage III and beyond. Control rates are influenced by the size of the metastatic nodal deposit and the presence of Extracapsular spread. It is imperative therefore to identify and treat metastasis at an early stage.

Surgery being the primary modality of treatment for oral cancers, the neck is usually addressed by way of a selective or comprehensive neck dissection. Controversy has surrounded the appropriate management of the clinicoradiological node negative neck in early oral cancers (T1–T2) where the primary is addressed per orally. Neck dissection in such cases is an additional procedure. There are two schools of thought in this situation—one that advocates an elective neck dissection (END) and the other that recommends a wait and watch approach followed by therapeutic neck dissection (TND) amongst those that develop nodal metastasis.

Proponents of END cite better locoregional control and survival. Moreover, the primary and the neck are treated in a single setting. Those advocating the wait and watch approach argue that the neck dissection procedure is unnecessary in up to two thirds of patients who are eventually true negative and is associated with morbidity and costs. They also cite the lack of robust evidence demonstrating a detriment to control and survival with this approach.

This resulted in a state of clinical equipoise and varied practice in management of the clinicoradiologically N0 neck in early oral cancers across the globe [1, 2].

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Table 1.1 PICO table

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with clinical node negative oral cavity cancer	Elective neck dissection	Observation with therapeutic neck dissection	Locoregional control and survival

There has however been recent new data to address this issue. This chapter will review the debate considering the current best available evidence and provide recommendations based on the same.

Literature Search

A thorough literature review was performed using the PICO (Population, Intervention, Comparison and Outcomes) search strategy (Table 1.1). PICO as well as detailed PubMed and Central searches were performed from 1980 to 2017 using the following keywords:

Early oral cancer, node negative neck, elective/selective/supraomohyoid neck dissection, therapeutic neck dissection and observation.

The search was planned under two major headings that are known to influence the management of the node negative neck in oral cancers, namely (1) outcomes of elective neck dissection versus a wait and watch approach and (2) follow up and its role in effective nodal salvage.

The search was narrowed down to those with the highest level of evidence, specifically randomised controlled trials (RCT), systematic reviews and meta-analyses. As some of the meta-analyses had included the significant retrospective studies, individual studies were excluded from this report. Studies pertaining to follow up with or without imaging in patients managed with a wait and watch approach were restricted to individual published series. Reviews and consensus articles addressing the management of the node negative neck were also referenced.

Results

The results are presented under the two headings adopted in the search strategy.

Outcomes of Elective Neck Dissection Versus a Wait and Watch Approach

The earliest attempts to address the debate of elective neck dissection versus a wait and watch approach by way of a randomised trial was initiated as early as 1966 [3]. Over the next 5 decades 1966–2009, there were three more randomised trials conducted [4–6]. The trials predominantly included clinically node negative T1/T2 oral

tongue/floor of mouth cancers. A description of the inclusion criteria, outcomes and limitations have been summarized in Table 1.2. The major limitations of these trials were their small sample size, inadequate statistical considerations, variable end points and non-uniformity in treatment of neck and follow up, which may have influenced the outcomes of these trials. Three of these four trials showed a trend towards better outcomes with END but did not reach statistical significance because of the small number of patients recruited in individual studies [3, 5, 6]. In addition the Brazilian trial [5] was seen to have a much lower salvage rate of patients who recurred in the wait and watch arm (27.27%) as compared to the other trials (78% [4], 88% [3] and 100% [6]). The authors attributed this to poor follow up which may

Table 1.2 Summary of the RCTs that assessed the outcomes of END versus TND in clinically node negative oral cancers

	Sample size	Results	Inclusion criteria	Limitations	Quality of evidence
Vandenbrouck et al. [3]	75	Similar death rates in both groups (at 5 years follow up for all selected cases): END: 16.5% TND: 15.4%	T1/T2/ T3 tongue, floor of mouth	1. Small numbers 2. Primary treated by brachytherapy 3. Allocation concealment, random sequence generation and blinding of participants was inadequate 4. Complications not alluded to	Low
Kligerman et al. [5]	67	DFS END: 72% TND: 49% (significant DFS benefit with END)	T1/T2 tongue, floor of mouth	1. Small numbers 2. Poor follow up in TND arm leading to low salvages rates-only 3 out of 11 patients salvaged (27.27%) This might have skewed results in favour of END arm 3. No mention of statistical considerations 4. Allocation concealment, random sequence generation and blinding of participants was inadequate 5. Complications not alluded to	Low

(continued)

Table 1.2 (continued)

	Sample size	Results	Inclusion criteria	Limitations	Quality of evidence
Fakih et al. [4]	70	DFS END: 63.3% TND: 52.5% (trend towards better outcome in END arm at a median follow up of 20 months; results were statistically not significant)	T1/T2 tongue	1. Small numbers 2. No mention of statistical considerations; allocation concealment, random sequence generation and blinding of participants was inadequate 3. Neck dissection was RND 4. Complications not alluded to	Low
Yuen et al. [6]	71	DSS END: 89% TND: 87% (trend towards better outcome in END arm)	T1/T2 tongue	1. Small numbers 2. Complications not alluded to	Low
D'Cruz et al. [9]	500	OS END: 80.0%; 95% CI, 74.1–85.8 vs. TND: 67.5%; 95% CI, 61.0–73.9	T1/T2 tongue/ floor of mouth, buccal mucosa	1. Benefit in lesions less than 3 mm depth doubtful 2. Complications not alluded to	High

have impacted the outcomes of the trial. Given the small sample size and divergent findings, Fasunla et al. conducted a meta-analysis of these four trials and concluded that disease-specific death was significantly lower following an elective neck dissection over the wait and watch approach (fixed-effects model RR = 0.57, 95% CI 0.36–0.89, p = 0.014; random-effects model RR = 0.59, 95% CI 0.37–0.96, p = 0.034) [7]. The results of this meta-analysis, while showing a benefit for END seem to be influenced by a single trial, thus making a compelling case for more robust evidence [8].

A well designed, large, single institution RCT (NCT00193765) to address this question was conducted by our group [9]. 596 T1–T2 node negative oral cancers were randomised to two arms—END and TND. Both arms were equally balanced for stratification factors. The data and safety monitoring committee of the trial observing a difference in outcomes between the two arms mandated analysis of the first 500 patients (245 in the END arm and 255 in the TND arm). The average DOI of the analysed patients was 6 mm. The findings showed a statistically significant

improvement in overall survival (OS) [80.0%; (95% confidence interval (CI), 74.1–85.8) against 67.5%; (95% CI, 61.0–73.9) with a hazard ratio for death of 0.64 in elective surgery group (95% CI, 0.45–0.92; p = 0.01 by the log-rank test)] and disease free survival (DFS) [69.5% (95% CI, 63.1–76.0) against 45.9% (95% CI, 39.4–52.3%), respectively (unadjusted hazard ratio, 0.45; 95% CI, 0.34–0.59; p < 0.001)] in the END group. These figures translated into "numbers to treat" imply that one recurrence was prevented for every four and one death for every eight patients who underwent an END. Subgroup analysis revealed that this benefit was not as significant in tumours with ≤3 mm of DOI. However, it must be noted that the number of patients in this group was small (71) and an adequately powered trial to answer this question given the very low incidence of metastasis would run into thousands of patients. Moreover, as mentioned earlier there is lack of validated data on assessment of DOI pre-operatively and hence neck dissection is best advocated in all.

Ren et al. in a subsequent meta-analysis of 5 RCTs with 779 patients reported DFS to be higher in the END group [(Risk Ratio [RR]: 1.33; 95% CI 1.06, 1.66); p = 0.01]. Of the 5 studies, 4 trials with 708 subjects had reported OS and results demonstrated better OS for the END group [(RR: 1.18; 95% CI 1.07, 1.29); p = 0.0009]. In addition, they also performed a trial sequential analysis (TSA) to determine if any future trials were required to address the issue. The cumulative Z score crossed the TSA boundary for both DFS as well as OS, confirming that no further trials were required to address this question [10]. Abu-Ghanem et al. in a larger systematic review that included 20 retrospective and 3 prospective RCTs with 3244 cases reconfirmed the benefit of END [11]. The authors demonstrated a lower risk of regional recurrence among those in the END group as compared to those who were in the wait and watch group [OR, 0.32; 95% CI, 0.22–0.46; p ≤ 0.001]. The END group was associated with a significant benefit in DSS (HR, 0.49; 95% CI, 0.33–0.72; p ≤ 0.001). The OS, though better in the END group, was however not statistically significant (HR, 0.71; 95% CI, 0.41–1.22; p = 0.21).

Both these studies provide level I evidence establishing END as the standard of care for early stage, node negative T1–T2 oral cancers amenable to per oral excision. These two meta-analyses along with the earlier one by Fasunla et al. have been summarised in Table 1.3.

Sentinel node biopsy is a reasonable alternative recommended in various treatment guidelines and is popular in centres in Europe. Published results in various meta analyses [12–14] across all studies have consistently revealed a high diagnostic accuracy and negative predictive value. SNB however is a cumbersome procedure involving two stages (surgery among those that are positive), is associated with a steep learning curve, requires serial step sectioning and immunohistochemistry (IHC), and therefore is unlikely to gain wide acceptance in routine practice. Moreover, unlike in breast and melanoma where nodal dissection is associated with lymphedema that can be distressing a properly conducted neck dissection has minimal or no morbidity [15].

Table 1.3 Summary of the meta-analyses on the randomised trials addressing END versus TND

	Sample size	Relative risk	95% confidence interval, p value, I^2	Limitations	Quality of evidence
Fasunla et al. [7]	4 RCTs n = 283	END reduced the risk of disease specific death	HR = 0.57 (95% CI 0.36–0.89, p = 0.014) Test for heterogeneity—not significant i^2 = 8.5%, p = 0.35	Wide CI of the studies included, significant heterogeneity amongst studies, inadequate sample sizes, results likely skewed due to a single study	Moderate
Ren et al. [10]	5 RCTs n = 779	Significantly improved DFS and OS for END compared to observation	For DFS: RR of 1.33 (95% CI 1.06–1.66, p = 0.01) favouring better DFS in the END group, significant heterogeneity between studies—i^2 = 56%, p = 0.01 For OS: RR: 1.18; (95% CI 1.07, 1.29); p = 0.0009, favouring better OS in the END group Heterogeneity not significant between studies, i^2 = 14%, p = 0.32	Did not use individual patient database	High (trial sequential analysis showed no further trials need to be conducted to answer the question)
Abu-Ghanem et al. [11]	20 retrospective and 3 RCTs n = 3244 patients	END improved DSS significantly, but not OS	HR for DSS, 0.49; (95% CI, 0.33–0.72; p < 0.001) Non-significant heterogeneity for DSS i^2 = 57.1%; p < 0.001	Did not use individual patient database	High

Follow Up and Its Role in Effective Nodal Salvage

Meticulous follow up has been advocated by some in an attempt to pick up nodal metastasis at an early stage and effectively salvage patients without detriment to outcome. While conceptually attractive, cervical metastasis unfortunately do not occur in an orderly and predictive fashion. In a study by Andersen et al. where patients underwent a meticulous 3 monthly clinical follow up at a leading head and neck tertiary cancer centre, 77% of patients presented with adverse nodal factors (N2, N3, Extra Capsular Spread) [16]. Given the limitations of clinical examination others have attempted to use imaging in addition to help picking early nodal disease. A guided FNAC is often added to increase diagnostic accuracy and specificity. Being less invasive and the fact that it can be repeated, sonography in addition to clinical examination and follow up has been advocated as an alternative to the END. In a second randomisation of our trial alluded to earlier, patients were randomised on follow up to Physical Examination (PE) alone (n = 244) and PE + USG (n = 252). The two arms were well balanced. The compliance of patients to follow up was calculated as a quotient of duration to number of visits and the median value was reported. The median duration between visits in the PE + US arm was 2.27 months (interquartile range 1.89–2.94) while that in the PE alone arm was 2.36 months (interquartile range 1.85–2.97). It is to be noted that the ultrasounds were performed by experienced head and neck radiologists. Ours being a high volume centre, the number of neck sonographies being performed by our team of radiologists is 250–300 per month. The addition of USG did not result in any OS difference between PE + USG and PE in unadjusted analysis (3-year OS 73.3% and 73.8%, respectively, HR = 1.02, 95% CI 0.73–1.45, p = 0.89) and after adjustment (HR = 0.81, 95% CI 0.51–1.29, p = 0.37) for stratification factors, prognostic factors, surgical treatment (END vs. TND). Multivariate analysis revealed a continued benefit of END and meticulous follow up could not supplant the need for a neck dissection [17].

Yuen et al. [6] in their prospective randomised trial, using a similar approach, reported that of the 35 patients who were intensely followed up with serial ultrasound (every 3 months for the first 3 years) in the wait and watch arm, 11 failed in the neck alone (31%) and all of them required extensive surgery for the neck. Similarly, the Dutch group, strong advocates of US based follow up in a retrospective study of 77 patients with node negative oral cancers whose neck was observed with serial USg-FNAC, reported 14 (18%) patients with regional recurrences in spite of being imaged at every 2–5 visits [18]. Only 71% of these recurrences could be salvaged, demonstrating the limitations of the wait and scan approach. Of the 14 patients with regional recurrences 4 patients died due to disease. Survival detriment due to regional recurrence was not obvious given the small number of patients in this series. While this approach seemed feasible from the above, it should be noted that patients require more extensive surgery as well as greater need for adjuvant therapy.

Elective Neck Dissection should be the standard of care for all early, clinically node negative—c T1–T2-N0 oral cancers (most studies had a predominance of oral tongue cases) amenable to per oral excision, given Level I evidence to show its association with superior overall and disease-free survival. This benefit is seen in tumours with depth of invasion ≥ 3 mm, however given the lack of validated methods of preoperative assessment of DOI the management of neck in cases with thinner tumours must be with caution (quality of evidence high; strong recommendation).

Personal View of the Data

It is pertinent to note that the age-old philosophy was to advocate END when the probability of metastasis was greater than 20% [19], based on a decision tree model by Weiss et al. The limitation of this approach however, was to accurately identify those with an increased risk of metastasis. Biological factors which influence the risk of regional metastasis such as perineural invasion, lymphovascular embolism, grade and DOI are unavailable to the clinician at the time of initial treatment. Imaging, as well, has its limitations in identifying occult nodal metastasis. This fact is best illustrated by the results of the Sentinel European Node Trial (SENT), a large multicentric study which included 415 patients across 14 European centres. All patients underwent pre-operative work up that included CT and/or MRI ± guided FNAC and were confirmed to be clinicoradiologically node negative. In spite of this intensive work up in a trial setting, 94/415 (23%) patients were still SNB positive, 16 (17%) of whom had ECS as well. In addition, of the 321 patients who had negative SNB, 15 developed nodal metastasis when followed up for 3 years. This demonstrated the inadequacy of pre-operative imaging [20]. In light of these limitations, it seems reasonable to conclude that END is a safer option, given the recently published level I evidence in favour of END. This benefit is seen amongst the majority of subgroups. The benefit seems less apparent for thin tumours ≤3 mm. This is due to the low incidence of nodal metastasis in this subgroup and the lack of adequate numbers to attain statistical significance. An RCT to assess the benefit of END will entail an exceedingly large sample size and is thus not practically feasible. Moreover, there is no validated method to assess DOI accurately at the time of initial decision making, further establishing END as the standard of care in all early oral cancers.

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Management of Moderate Dysplasia of the Oral Cavity

2

Marietta Tan

Introduction

Oral squamous cell carcinoma (OSCC) is believed to be the final in a series of clinical and histopathologic stages, resulting from the stepwise accumulation of genetic mutations over time [1]. Premalignant lesions contain a number of tissue and cellular changes, termed oral epithelial dysplasia [2]. Dysplasia is a histopathologic diagnosis made on the basis of cellular atypia and architectural changes; it may be graded as mild, moderate, or severe dysplasia or as carcinoma in situ (CIS), based on the extent of cytologic abnormalities [3, 4]. Severe dysplasia and CIS carry the highest risk of malignant transformation and are typically surgically excised in order to reduce or eliminate the risk of malignancy. In contrast, the likelihood of mild dysplasia progressing to invasive cancer is considered low, so conservative management with active surveillance is often advised [4].

The management of moderate dysplasia remains controversial, given its intermediate propensity to progress to malignancy. Without early intervention, some patients may develop invasive carcinoma, whereas others may be over-treated and are at risk for unnecessary morbidity, particularly with respect to speech and swallow [4]. No definitive biomarkers currently exist that accurately predict whether a lesion will progress to cancer in an individual patient [3, 5]. Furthermore, no

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prospective randomized controlled trials have been conducted to determine optimal management of oral premalignant lesions [6, 7].

This chapter reviews the existing data regarding observation versus surgical excision for the management of moderate dysplastic lesions of the oral cavity. For the sake of brevity, chemoprevention and treatments such as photodynamic therapy are not included in this review, despite a growing body of evidence supporting the use of these modalities.

Literature Search Strategy

Review of the literature was performed in the Pubmed and Web of Science databases based on the terms detailed in the PICO table (Table 2.1). Briefly, the terms "oral cavity" AND ["dysplasia" OR "premalignant"] AND ["surgery" OR "observation" OR "management"] were used to query Pubmed, whereas the terms "oral dysplasia" and "management" were used to query Web of Science. The bibliographies of relevant articles were also manually reviewed for additional references. Titles and abstracts of retrieved articles were reviewed for applicability; full text articles were reviewed when necessary if article applicability was not clear from the abstract. Articles in the Cochrane Database of Systematic Reviews under the topic headings of "oral cancer," "head and neck cancer," and "dentistry and oral health" were also screened for applicability. Only articles in the English language published in the past 20 years were included.

The search was narrowed to studies on observation (also referred to as "monitoring" or "active surveillance") and surgical excision (including excision with cold steel or laser). Studies investigating chemoprevention or other medical therapies were not included. In addition, treatments such as photodynamic therapy or cryotherapy were not included in this review. Studies that included patients with a clinical diagnosis of oral leukoplakia without histologic confirmation of dysplasia of at least a portion of the study cohort were excluded. Studies that did not specify degree of dysplasia were excluded. Preference was given to studies that specifically included moderate dysplasia. Given the limited number of systematic reviews and meta-analyses, review articles and retrospective and prospective studies were included for completeness.

Table 2.1 Management of moderate dysplasia of the oral cavity

Population	Intervention	Comparison	Outcomes
Adults with moderate epithelial dysplasia of the oral cavity	Surgical intervention	Observation	Rate of malignant transformation Recurrence of premalignant lesion Diagnostic accuracy

Results

Observation

Several arguments can be made in support of a strategy of observation for moderate dysplasia. The natural history of any given dysplastic lesion can be unpredictable; while some lesions may progress to malignancy, others may stabilize, improve, or regress completely over time [2, 8]. Observation may minimize or avoid unnecessarily morbid procedures for lesions that ultimately do not progress (Table 2.2).

An important question, therefore, is whether moderate dysplasia carries a high enough risk of malignant transformation to necessitate surgical intervention, or if it can instead be safely observed. The answer to this remains controversial (Table 2.3). Some studies have found that the risk of malignant transformation increases with the degree of dysplasia, such that moderate dysplasia carries a higher risk of malignancy compared to mild dysplasia. One retrospective study of 1357 patients with oral premalignant disorders, including 204 patients with dysplasia, found that those with higher grades of dysplasia were at greater risk of transformation to cancer after adjustment for sex, age, anatomical site, and diagnosis. Those with mild dysplasia had a 3.5-fold increased risk of malignancy compared to those with no dysplasia (95% CI: 0.95–13.10), whereas there was an 11.1-fold increased risk with moderate dysplasia (95% CI: 3.45–35.56) and a 21.6-fold increased risk with severe dysplasia (95% CI: 5.81–80.46) [9]. Another retrospective study of 1401 patients with oral dysplasia found that 4%, 10%, and 21% of patients with mild, moderate, and severe dysplasia, respectively, developed carcinoma. Therefore, compared to patients with non-dysplastic lesions, those with mild dysplasia had a 5.3-fold increased risk of malignancy (95% CI: 1.6–16.8), moderate dysplasia a 12.8-fold increased risk (95% CI: 4.9–33.7), and severe dysplasia a 29.9-fold increased risk (95% CI: 10.8–82.5). Furthermore, patients with higher grades of dysplasia developed carcinoma significantly faster [10]. It is important to note that both of these studies, as most others in the literature, did not differentiate between lesions that had been surgically resected versus observed; therefore, the reported rates of transformation may not represent the true natural history of epithelial dysplasia. However, one study with a distinct observation cohort also found that moderate dysplasia carried a higher risk of malignant transformation than no or mild dysplasia. This retrospective study of 578 patients with leukoplakia included a subset of 40 patients with

Table 2.2 Options for management of moderate dysplasia of the oral cavity

	Observation	Surgery
Effective?	Maybe	Maybe
Benefits	Minimizes or avoids functional and cosmetic deficits	May reduce the risk of malignant transformation Provides accurate diagnosis
Drawbacks	Patients may be at higher risk of progression to malignancy	May result in functional and cosmetic deficits Risks of anesthesia

Table 2.3 Malignant transformation of oral epithelial dysplasia

Author, year	No. patients/No. lesions	Types of lesions	No. dysplastic lesions by grade		Rate of malignant transformation by grade	Risk of malignant transformation by grade, HR (95% CI)	Follow-up, years	Type of study	Quality of data
Arduino, 2009 [12]	207/207	Dysplasia	Mild	135	5.2%	N/A	4.5 (median)	Retrospective	Low
			Moderate	50	14.0%	N/A			
			Severe	22	4.5%	N/A			
Ho, 2012 [15]	91/91	Dysplasia	Mild	40	N/A	1.0	4.0 (median)	Retrospective	Low
			Moderate	31	N/A	2.2 (0.8–6.1)			
			Severe	20	N/A	3.2 (1.1–9.2)			
Kuribayashi, 2015 [11]	578/578	Leukoplakia	None	198	1.6%	N/A	3.4 (median)	Retrospective	Low
			Mild	117	6.9%	N/A			
			Moderate	79	10.0%	N/A			
			Severe	26	0%	N/A			
Mehanna, 2009 [16]	992/992	Dysplasia	N/A	N/A	Mild/moderate: 10.3%	N/A	N/A	Meta-analysis	Moderate
					Severe/CIS: 24.1	N/A			
Sperandio, 2013[a] [10]	1401/1838	OPMD	None	325	0.85%	1.00	9.3 (mean)	Retrospective	Low
			Mild	128	4%	5.3 (1.6–16.8)			
			Moderate	166	10%	12.8 (4.9–33.7)			
			Severe	110	21%	29.9 (10.8–82.5)			
Warnakulasuriya, 2011[b] [9]	1357/1357	OPMD	None	1153	1.0%	1.00	9.04 (mean)	Retrospective	Low
			Mild	104	4.8%	3.53 (0.95–13.10)			
			Moderate	70	15.7%	11.07 (3.45–35.56)			
			Severe	30	26.7%	21.62 (5.81–80.46)			

OPMD oral potentially malignant disorders, *CIS* carcinoma in situ, *HR* hazard ratio, *CI* confidence interval

[a]Data excluding patients who underwent malignant transformation within 6 months

[b]Adjusted hazard ratio provided

moderate dysplasia who underwent observation, of which 19.5% grew larger and 9.8% underwent malignant transformation. In contrast, 4.6% of lesions with no or mild dysplasia expanded, and 3.6% showed malignant transformation [11]. Taken together, these studies suggest a significantly increased risk of malignant transformation for patients with moderate dysplasia compared to those with mild or no dysplasia.

In contrast, other studies have suggested that dysplasia grade may not in fact be predictive of malignancy [12–14] or that, while severe dysplasia may be associated with malignant transformation, mild and moderate dysplasia are not. For example, one prospective longitudinal observational study included 91 patients with oral epithelial dysplasia who were managed with either observation or surgery. After a median follow-up of 48 months, 25% of patients had undergone malignant transformation. Importantly, mild and moderate dysplasia grouped closely together as low risk for malignant transformation compared to severe dysplasia. However, in this study, even severe dysplasia was of borderline significance as a predictor of transformation compared to mild and moderate dysplasia ($p = 0.06$) [15]. In addition, a systematic review with meta-analysis of 14 nonrandomized, prospective and retrospective studies with 992 patients with oral dysplasia found that the transformation rate of mild to moderate dysplasia (10.3%, 95% CI: 6.1–16.8%) differed significantly from the transformation rate of severe dysplasia and CIS (24.1%, 95% CI: 13.3–39.5%, $p < 0.008$) [16]. These studies suggest that moderate dysplasia may be relatively low-risk for malignancy and observation may therefore be an appropriate option for management. The authors of the systematic review conclude that it may be feasible to tailor the duration of surveillance, and possibly its frequency, based on clinical factors such as dysplasia grade [16].

Compared to mild or no dysplasia, moderate dysplasia may be associated with an increased risk of subsequent malignant transformation. Dysplasia grade should therefore be taken into consideration in management decisions (quality of evidence low; weak recommendation).

Surgery

The underlying rationale for surgical intervention of oral epithelial dysplasia is that complete surgical excision reduces the risk of malignant transformation. No definitive data exist to support this argument, as no randomized controlled studies have compared surgery to observation in epithelial dysplasia. As noted in two review articles, rates of subsequent carcinoma range from 7% to 43% in lesions that were observed, compared to 5% to 7% in patients treated with surgical excision [17, 18]. However, these rates of malignant transformation were based on all dysplastic lesions collectively and were not differentiated by grade of dysplasia. One systematic review and meta-analysis on the treatment of oral dysplasia reported that patients whose lesions were not surgically excised had considerably higher overall transformation rates when compared to patients who underwent surgical excision (14.6% vs 5.4%), even after adjusting for dysplasia

grade ($p = 0.003$). The authors conclude that the risk of malignant transformation, regardless of dysplasia severity, is therefore decreased by surgical excision [16].

In contrast, a number of retrospective studies including patients treated with observation and with surgery have found that surgical intervention does not significantly reduce the risk of subsequent carcinoma. It is important to remember that these studies have several major limitations. The observation and surgery cohorts are not directly comparable, and studies may be hampered by selection bias. For example, one study included 269 lesions in 236 patients, of which one third were treated with surgery while the remainder were observed. The authors found that patients with mild, moderate, or severe dysplasia, when treated with surgery, subsequently developed malignancy at similar rates (9–11%), while 33% of patients with CIS later developed malignancy. Meanwhile, 4% of all surgically untreated lesions, including 14% of mildly dysplastic lesions, underwent malignant transformation [13]. In another retrospective cohort of 207 patients with oral dysplasia treated with either observation or surgical resection, no statistical differences were found between the surgically treated or untreated lesions with regard to involution, stability, new dysplastic lesions, or malignant transformation [12]. These data together suggest that dysplasia grade is not predictive of subsequent malignant transformation and that surgical intervention does not significantly reduce the risk of malignancy.

Surgical intervention also does not eliminate the risk of recurrence of dysplasia. A number of studies have examined the utility of carbon dioxide laser surgery in the management of dysplasia. These studies argue that laser treatment is effective for treatment, as they result in reasonable rates of disease control, ranging from 55% to 71% at 5 years [19]. However, even after laser surgery, the risks of recurrence of dysplasia or malignant transformation persist. Data are conflicting as to whether these risks increase with degree of dysplasia. A prospective study of 123 dysplastic lesions in 77 patients treated with carbon dioxide laser surgery reported a 19% rate of recurrence and 9.5% rate of malignant transformation after laser treatment of moderate dysplasia, compared to 0% rates of recurrence and malignant transformation in mild dysplasia. Patients with severe dysplasia were twice as likely to recur as those with moderate dysplasia [20]. Similarly, a retrospective study of 590 patients who underwent laser treatments for oral premalignant lesions reported that patients with mild dysplasia were significantly more likely to be disease-free compared to patients with moderate or severe dysplasia (odds ratio 2.25, 95% CI: 1.27–3.98, $p < 0.0001$) [21]. In contrast, a prospective study with 100 patients treated with carbon dioxide laser surgery found that moderate dysplasia was not associated with subsequent recurrence or malignancy. In this study, neither moderate nor mild dysplasia was associated with the development of recurrence or malignant transformation, whereas severe dysplasia was, with a nearly sixfold increased risk of disease for severe dysplasia (95% CI: 1.282–28.018). Disease-free survival rates at both 2 and 5 years were significantly lower for those with either severe dysplasia or CIS, compared to moderate and mild dysplasia (63%, 76%, and 85% and 14%, 59%, and 62%, respectively, $p = 0.006$). Patients with severe dysplasia or CIS developed recurrent disease or underwent malignant transformation at 40 months, compared to 78.8 and 87.8 months in those with moderate or mild dysplasia, respectively [22]. A systematic review of the literature assessing the utility of the carbon dioxide laser in the treatment of oral leukoplakia noted that several studies found that high-grade dysplasia may be associated with

recurrence and malignant transformation. However, the authors concluded that no consensus exists and further study is therefore needed [19]. Despite these conflicting data, the evidence underscores the importance of continued surveillance even after surgical intervention, due to the persistent risks of recurrence and malignant transformation.

In addition, some authors advocate for surgical management for all patients with epithelial dysplasia of any grade, as even patients with mild dysplasia are at risk for malignant transformation. In one retrospective review, the authors found that 6 of 13 patients with mild dysplasia who underwent observation alone recurred, and 5 of 13 eventually developed malignancy. In contrast, only 2 of 13 who underwent surgical excision developed malignancy. The authors therefore conclude that excision is indicated for dysplastic lesions of all grades, given high rates of recurrence and progression to malignancy [23]. A larger retrospective study of 383 oral dysplastic lesions in 368 patients found that 2.9% of lesions progressed to higher grades of dysplasia, while 4.7% underwent transformation to invasive carcinoma. Dysplasia grade was not associated with progression or malignant transformation, suggesting that dysplasia grading is a poor predictive tool and that all dysplastic lesions should be surgically managed [2].

Other authors argue that dysplastic lesions of all grades should be excised due to concerns regarding diagnostic accuracy resulting in "under-diagnosis." Discrepancies between diagnoses made based on incisional biopsy versus definitive resection specimens have been reported. This may be due in part to sampling error, though the grading system itself is inherently subjective and therefore subject to both inter- and intra-observer variability [2]. One retrospective study compared the histopathologic diagnoses from initial incisional biopsy to definitive resection in 169 patients with oral dysplastic lesions treated with laser excision. There was concordance between the two in 56% of patients. However, 9% of patients initially diagnosed with dysplasia were subsequently noted to have OSCC in the resection specimen, while an additional 28% of patients were noted to have a higher grade of dysplasia than initially diagnosed. The authors therefore argue that all dysplastic lesions should be excised, as incisional biopsies are inadequate for diagnosis [24]. Similarly, another study retrospectively reviewed 590 patients who underwent carbon dioxide laser treatment for oral premalignant lesions. In this study, 36.1% of cases were "upgraded" due to more severe dysplasia or OSCC than diagnosed on initial biopsy, with unexpected OSCC identified in 12.0% of resection specimens [21].

When compared to observation, surgical resection of moderate dysplasia of the oral cavity may be effective in reducing, but not eliminating, the risk of malignant transformation (quality of evidence low; weak recommendation). Surgical excision of moderate dysplasia may be considered in order to improve diagnostic accuracy compared to diagnostic biopsies (quality of evidence low; weak recommendation). All patients with moderate dysplasia of the oral cavity must undergo continued surveillance regardless of initial management strategy, given the persistent risks of recurrence and malignancy with or without surgical intervention (quality of evidence low; weak recommendation).

A Personal View of the Data

Though definitive data regarding the management of moderate dysplasia are lacking, I recommend surgical excision for most cases because of the risk of progression to invasive carcinoma. Complete surgical excision also offers some degree of reassurance regarding the diagnosis. This is of particular importance in patients who may be unable to maintain consistent follow-up. Those with continue to smoke or chew tobacco may be at higher risk of progression to invasive carcinoma, in which case surgery may also be preferable. All patients with modifiable risk factors should be counseled on cessation.

However, there are several cases in which surgery is relatively contraindicated. In cases involving a large area of the oral mucosa, excision may result in unacceptable functional and cosmetic morbidity and may require extensive reconstruction. I would also be less likely to recommend surgery in patients who are elderly or who have significant medical comorbidities that could increase the risks of anesthesia.

Observation is therefore the preferred alternative in patients with large or multiple lesions or at high anesthetic risk, whereas surgery is ideal for small, isolated lesions in healthy patients. I recommend against observation alone if there is any question as to the reliability of the biopsy that established moderate dysplasia. In these cases, repeat biopsy or surgical excision may be warranted. If, during the course of observation, any question arises as to whether the lesion may have changed or progressed, repeat biopsy should be performed to ensure there is no invasive component to the lesion. I am more comfortable with observation in patients who do not have ongoing exposures to etiologic agents (e.g. active smokers or users of chewing tobacco).

All patients should be counseled on the ongoing need for surveillance, regardless of whether they undergo surgery or not.

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Ideal Resection Margins in Oral Cavity Cancer

3

Jason Y. K. Chan

Introduction

Oral cavity cancer accounts for 2–4% of all cancer cases worldwide with an estimated 264,000 new cases and 128,000 deaths globally in 2008 [1, 2]. Evaluating margin status following the resection of OSCC is especially important, as the presence of positive surgical margins is known to significantly affect overall survival and loco-regional disease free survival in OSCC [3] and other head and neck squamous carcinomas (HNSCC) [4]. There has also been significant discussion with diverse views in the literature regarding what constitutes a clear or close margin upon pathological review. However, there has been little comment or advancement in the actual decision on surgical resection margins intraoperatively. In practice, most surgeons perform resections of 1 cm or 1.5 cm on the mucosal surface for oral cavity cancers. In this chapter we attempt to review the evidence and decision-making process on the ideal surgical margins for oral cavity squamous cell carcinoma.

Search Strategy

Based on the PICO table (Table 3.1), Pubmed searches incorporating the terms "oral cavity", "margin" and "resection margin" were used for the literature search. The search period was from the first of January 2008 to the 31st of December 2017. The bibliography of applicable articles available in English were reviewed. Articles specifically about the intraoperative resection and assessment of margins, postoperative surgical margins were reviewed. The majority of studies identified were

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Table 3.1 Margins in oral cavity squamous cell carcinoma

Population	Intervention	Comparison	Outcomes
Patients undergoing surgical resection of oral cavity squamous cell carcinoma	Resection margin ≥5 mm	Resection margin <5 mm	Final pathological margin status, local recurrence, survival

Table 3.2 Important studies in assessing margins in oral cavity squamous cell carcinoma

Paper	Number of patients	Timing of margin	Margin	Type of study	Outcomes
Maxwell et al. [5]	280	Intraoperative	Obtained from tumor or tumor bed	Retrospective	5 years LRFS worse when tumor sampled from tumor bed
Buchakjian et al. [6]	406	Intraoperative	Obtained from intraoperative tumor bed and final tumor pathology	Retrospective	Local recurrence rates 21% higher in patients with negative intraoperative frozen section from tumor bed and positive final pathology
Anderson et al. [7]	539	Postoperative	Postoperative final pathology	Meta-analysis	ARR of 21% in margins of ≥5 mm
Zanoni et al. [8]	381	Postoperative	Postoperative final pathology	Retrospective	LRFS of margins ≥2.3 mm equivalent to ≥5 mm
Dik et al. [9]	200	Postoperative	Postoperative final pathology	Retrospective	Local recurrence rate with margin ≥3 mm with ≤2 unfavourable histological margins is equivalent to margin ≥5 mm

LRFS loco-regional recurrence free survival, *ARR* absolute risk reduction

retrospective cohort studies and Table 3.2 shows the important studies in assessing margins in oral cavity squamous cell carcinoma.

Results

Intraoperative Resection Margins

The primary aim of surgical resection of any cancer is the achievement of adequate tumor free margins. Below we will further discuss what constitutes a pathologically clear margin, however here we will discuss the achievement of macroscopic clear

margins intraoperatively. Studies in the literature have focused on post resection pathological margins without a focus on macroscopic margins or intraoperative margins in approaching surgical resections. Within these studies, when evaluating the materials and methods sections, multiple different comments on the macroscopic margins attempted intraoperatively were noted, including "aim for a macroscopic surgical margin of at least 10 mm" [10], "a macroscopic safety margin of 10 mm" [9], "resected radically with curative intention (actual clinical margin more than 1 cm)" [11], "1 cm margins" [6, 12, 13] and "≥1 cm" [14]. During the macroscopic marking of resection margins, the oral cavity tissue is commonly placed under tension, compounded by the formalin fixing of tissues that inevitably leads to tissue shrinkage. Furthermore, within the tongue, the ease of tumor spread along muscle planes is an important factor in deciding on macroscopic margins. Therefore, the macroscopic margins attempted are typically 1 cm or more than 1 cm from the tumour borders based on visual inspection and palpation intraoperatively [14]. However, within this literature search there are no recent prospective or retrospective data addressing the issues if resection margins should be 1 cm or ≥1.5 cm. At our institution, for oral cavity lesions we routinely use 1.5 cm margins from the tumor border to define our mucosal resection margins where possible, the deep margin is a judgement during resection, particularly of early lesions for an adequate cuff of tissue. A review of a cohort at our own institution of 32 tongue cancer patients with T1/2 disease showed that even with a 1.5 cm resection margin the, mean margins of resection were 4.79 mm (range 0.1–10 mm) on pathological examination. Given the current limitations in accurate gross assessments of margins during resection for early lesions we do pursue 1.5 cm gross margins. However, there may not be a one size fits all answer to the macroscopic margins needed with considerations in this small confined space including tumor proximity to adjacent structures and the patient's wishes of the extent of resection, for example a total glossectomy versus a glosso-laryngectomy with tumor in the vallecula.

Gross resection margins of 1.5 cm for oral cavity squamous cell carcinoma are more likely to achieve ≥5 mm margins for early lesions in the oral cavity (evidence quality very low; weak recommendation).

Assessment of Intraoperative Margins

The assessment of intraoperative margins are to ensure the adequacy of the resection, with the goal to reduce the rates of local recurrence. The need to assess intraoperative margins is engrained in the head and neck surgeon. However, the choice of method to assess these margins is still under debate, with gross examination, microscopic examination from the tumor bed or specimen having been proposed [15, 16].

Studies have mainly focused on the retrospective analysis of intraoperative margins. A retrospective analysis of 435 patients with cancer of the oral cavity where intraoperative margin assessment using gross examination or frozen section demonstrated that there were similar rates of close and positive margins between the two

groups [16]. The gross examination entailed measurement with a sterile scale from the mucosal edge to the tumor margin, with the mucosa unstretched, using a ≥7 mm margin that was deemed as clear. The deep margin was simply assessed based on direct palpation. Conversely, the assessment with frozen section encompassed the pathologist assessing the specimen with only the closest mucosal margin followed by the deep margin with a margin ≥5 mm. Disease free survival rates were similar between both groups at 86.7% and 83.5% for frozen section and gross examination respectively at 14 months.

In further regards to the assessment of intraoperative margins according to the tumor specimen as opposed to the tumor bed a retrospective multicentre study [5] evaluating 280 patients comparing the local recurrence rates between three groups of patients that had either sampling from the tumor, tumor bed, tumor bed with revision of margins. The final pathology specimens had the lowest positive margins in the group where intraoperative sampling was taken from the specimen itself as opposed to sampling from the tumor bed. Importantly, the local recurrence free survival at 5 years was significantly worse in the group that had sampling from the tumor bed as compared to sampling from the specimen directly (80% vs 90%, $P = 0.03$), likely as a result more frequent positive final pathological margins and an overall closer margin on margin clear specimens when sampled from the tumor bed; indicating that the intraoperative choice of margin sampling technique can influence local control of patients with an oral cavity squamous cell carcinoma. Another retrospective study evaluating the association between final specimen margins and intraoperative tumor bed frozen section margins in 406 patients showed tumor bed frozen section margins were not an accurate predictor of positive margins on the main specimen [6]. Frozen section margins when correlated with final pathological margins had an accuracy of only 66% when comparing those that had positive margins on final pathology. Furthermore, there was a weaker association with local recurrence from intraoperative tumor bed frozen section positive margins as compared to final specimen positive margins.

> The intraoperative assessment of resection margins should be assessed from the resected specimen for oral cavity squamous cell carcinoma (evidence quality low; weak recommendation).

Postoperative Surgical Margins

Following the surgical resection of tumors intraoperatively margin shrinkage occurs immediately by 20–40% [17, 18], this followed by formalin fixation causes further shrinkage of the tissue by 10%. These factors all influence the final specimen pathological margins that are routinely used to assess for the need of adjuvant therapy, particularly in smaller T1–2 tumors. Currently, the most widely accepted definition of a clear margin is one ≥5 mm, with any margin less than <5 mm classified as a close margin [19]. However, the evidence supporting the significance of margins

has been conflicting as evidenced with a meta-analysis by Anderson et al. [7] of oral cavity squamous cell carcinoma including studies that consisted of patients treated with primary surgery alone for squamous cell carcinoma of the oral cavity, pathological specimen reporting of margins as clear, close or involved with definitions of how these were assigned. The analysis showed that patients that received surgery alone showing a 21% absolute risk reduction in local recurrence with margins ≥5 mm. Ganly et al. [20] described a significantly worse survival outcome for patients with <5 mm margins in oral cavity SCC. Similarly, Chen et al. in Taiwan in early oral cavity SCC's described worse survival with close margins defined as between 1–5 mm [21]. Conversely, previous retrospective reviews [22, 23] suggested that <5 mm margins or close margins had no significant association with an increased local recurrence when compared to clear margins.

In searching for an optimal margin beyond the traditional 5 mm margins, there is conflicting evidence about what the actual margin should be used to define a negative margin in oral cavity SCC. Recently in a retrospective review of 432 patients showed that improved outcomes with each additional 1 mm of margin achieved, however using receiver operator characteristics the optimal cutoff was at 1 mm where there was a significant difference in local recurrence rates between <1 mm and ≥1 mm [13]. Zanoni et al. [8] in another recent retrospective review of 381 patients with oral cavity SCC a cutoff of 2.2 mm between close and clear margins was determined, with patients having a margin of 2.3–5.0 mm having a similar locoregional recurrence free survival to those with a ≥5 mm margin. This study involved predominantly T1/T2 lesions, where adjuvant therapy is on a practical basis determined by the pathological margins identified, in addition to other factors. A further retrospective review by Dik et al. [9] of 200 patients with early stage oral cavity SCC the local recurrence rate between two cohorts, one with a median of 3 mm margins and another with a 6 mm median margin was not significantly different when they had less than two other adverse factors.

Pathological margins of ≥5 mm for oral cavity squamous cell carcinoma should definitively be considered clear resection margins (evidence quality low; weak recommendation).

A Personal View of the Data

The ideal resection margin for intraoperative gross tumor resections of the oral cavity we routinely use are 1.5 cm margins where allowed, this is particular the case for small T1/2 lesions where the achievement of adequate margins can significantly improve the odds of avoiding adjuvant radiotherapy and local recurrence. Our own institutional data as mention previously support this, given the particular difficulty in assessing gross margins during resection. However, in larger T3/4 lesions given

the likely proximity of critical structures we endeavour to resect a minimum 1 cm margin in the oral cavity where permitted. Based on the current evidence and guidelines intraoperative frozen section sampling of the specimen rather than the tumor bed is the ideal choice for intraoperative margin sampling. But the logistics in performing this may not be possible in all institutions around the globe currently, given the need for the pathology lab to be in close proximity to the operating rooms and a dedicated head and neck pathologist. Therefore sampling of the tumor bed frozen section may be still a viable option while developing a system for sampling from the specimen. Finally, in the assessment of the final specimen pathology margins one must take into account the biology of the tumor particularly for early stage tumors, where for example a 3 mm margin in a small tumor with no extracapsular spread, no perineural invasion and the absence of lymph node positivity may avoid adjuvant therapy, as opposed to using a strict definition of ≥5 mm margins as negative margins.

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4 Should Margin Sampling Be Obtained from the Specimen or from the Resection Bed in Oral Cavity Cancer?

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Introduction

Whereas non-surgical treatment modalities have progressively achieved a greater role in the primary treatment of head and neck malignancies, oral cavity cancer has largely remained a surgical disease, with chemotherapy and radiation therapy reserved as adjuvant treatment for advanced stage tumors, positive surgical margins, or other high-risk features [1]. Compared to other sites of the head and neck such as the larynx or skull base, the oral cavity and its subsites (lip, floor of mouth, oral tongue, buccal mucosa, retromolar trigone, alveolus, and hard palate) represent an anatomically accessible location that can consistently be visualized with a headlight and loupe magnification. As such, the historic oncologic principle of achieving en bloc tumor resection with a cuff of normal tissue surrounding the tumor margins continues to be the gold standard of surgery, with numerous studies indicating that the best prognosis is achieved by complete surgical excision of the tumor with at least 5 mm margins [2, 3]. While achieving negative margins with a cuff of normal tissue sounds straightforward, the practice of achieving negative margins can present a complex challenge to the surgeon for numerous reasons, including the

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infiltrative nature of oral cavity tumors and difficulty in achieving the balance between resecting adequate normal tissue around the tumor while preserving sufficient tissue to maintain normal function.

Unfortunately, survival rates for oral cavity cancer have failed to significantly improve in recent years, with the reported 5-year survival rate of oral cavity squamous cell carcinoma remaining approximately 50% [4]. This is attributed to multiple factors, including the significant number of patients with advanced stage disease at the time of diagnosis, as well as the ability of surgeons to obtain negative margins in only 50–80% of patients treated even in high volume cancer centers [5–8]. The oncologic significance of complete tumor removal has long been emphasized, highlighted by American Head and Neck Society (AHNS) quality initiatives emphasizing the importance of negative margins and multiple studies reporting that microscopic positive margins are associated with increased local recurrence and decreased survival [9–11]. The imperative of obtaining negative surgical margins justified the adoption of intraoperative frozen margin analysis to increase the likelihood of obtaining negative margins.

In a AHNS survey from 2005, 97% of head and neck surgeons reported using frozen section margin assessment, with a significant majority (76%) sampling frozen specimens from the tumor resection bed rather than the main specimen, and 90% believing that initially positive margins resected to negative are ultimately negative margins [12]. In contrast, a survey of North American Society of Head and Neck Pathology members reported that most pathologists report on the status of margins from the resected specimen rather than from the margins obtained from the tumor bed [13]. While multiple controversies surrounding oral cavity cancer margins persist, including the definition of a "close" versus "negative" margin, the role of specimen shrinkage in reporting of margin outcomes, and the utility of intraoperative frozen margins, this chapter seeks to answer the question, "Should margin sampling be obtained from the specimen or from the resection bed in oral cavity cancer?"

Literature Search Strategy

Based on the PICO (Patient, Intervention, Comparator, Outcomes) table (Table 4.1), Pubmed and CENTRAL searches incorporating the terms "oral cavity" and "cancer" and "margin" were used to review the literature. The bibliography of applicable articles was then reviewed. The search was narrowed to focus on studies specifically

Table 4.1 Assessment of margin status in oral cavity cancer

Population	Intervention	Comparison	Outcomes
Adults with oral cavity squamous cell carcinoma	Tumor bed sampling for margin analysis	Gross specimen examination for margin analysis	Adequacy of tumor resection Locoregional recurrence Overall survival

investigating the application of gross examination of main specimen for margin analysis versus margins obtained from the tumor bed. Studies were included if they were published from the years 2000 to 2017. We gave preference to prospective, randomized controlled trials and meta analyses; however, the paucity of literature of prospective trials concerning the subject necessitated the inclusion of retrospective reviews for completeness.

Defect-Driven Approach

While the approach to margin sampling varies from surgeon to surgeon, there are two main approaches to obtaining margins in patients undergoing oral cavity cancer resection: defect-driven and specimen-driven. In the defect-driven approach, once the tumor specimen has been removed from the operative field, the surgeon then goes back and takes additional samples from the tumor bed from areas of concern for possible residual tumor [14]. In the AHNS survey, the majority (76%) of surgeons obtained intraoperative margins using the defect-driven approach. While it appears to be the most common margin sampling technique employed by surgeons who responded to the AHNS survey, multiple pathological shortcomings exist to this technique including: assessment of surgical margin distance from tumor cells is impossible, identification of tumor cells is more difficult because the core of the tumor is missing, electrocautery artifacts are present, and random sampling error, the sampling of inadequate margins that may be ultimately detected on final specimen histopathology, is common.

Buchakjian et al. investigated the prognostic value of margin sampling from the tumor bed in a single-institution, retrospective review of 406 patients with oral cavity cancer treated surgically at the University of Iowa from 2005–2014 [15]. In their review, a total of 3308 intraoperative frozen sections were sampled, or an average of 8.15 frozen sections per patient. Investigating the correlation of intraoperative frozen margin status as a predictor of final pathological margin status, their retrospective review showed 149 patients with initial involved margins on frozen section compared to 115 involved margins assessed on the corresponding tumor specimen, yielding a sensitivity of 55% (95% CI, 45–64%), specificity of 70% (95% CI, 65–76%), and accuracy of 66% for frozen section margin as a predictor of final specimen margin, with a false negative rate of 45% and negative predictive value of 79%. Examining disease control as an endpoint, both intraoperative frozen and final specimen margins demonstrated some prognostic information for local recurrence, though the main specimen margin assessment demonstrated a stronger correlation with local recurrence and survival than did the tumor bed margin. The authors divided the patients into four groups based on margin clearance: Group A (uninvolved frozen and specimen margins), Group B (involved frozen margins, final margins clear), Group C (uninvolved frozen margins, specimen margins involved), and Group D (involved frozen margins, final margins not clear). Local recurrence rates were 13%, 27%, 34%, and 29% for Groups A–D, respectively, while Kaplan-Meier estimates of 5-year survival was 72%, 61%, 43%, and 19%,

respectively. The authors additionally examined the effect of additional tumor bed resection upon confirmation of a positive frozen margin, identifying no significant benefit in survival for those patients who underwent further resection, ultimately affirming that concordance between tumor bed and tumor specimen margins is poor, with the intraoperative margin sampling from the tumor bed failing to detect residual disease in more than half the cases of an involved margin on the tumor specimen.

Specimen-Driven Approach

In contrast to the defect-driven approach, the specimen-driven approach involves the surgeon orienting the specimen and reviewing the specimen with the pathologist so that the margin distance from the invasive front of the tumor to the resected front can be measured, same as the final pathological assessment after formalin fixation and paraffin embedding of the tissue. In a retrospective study from the University of Pittsburgh, Chang et al. reviewed 126 patients with previously untreated T1 or T2 oral cavity squamous cell carcinoma with histologically proven N0 neck disease [16]. Intraoperative frozen margins were performed in 117 (93%) cases, with the patients divided into three groups. In group 1 (n = 60), margins were assessed from the specimen only (specimen-driven approach), in group 2 (n = 40), intraoperative evaluation of specimen margins was followed by revision of some margins obtaining additional tissue from the tumor bed, and in group 3 (n = 26), all margins were assessed from the tumor bed (defect-driven approach). The specimen-driven approach was found to have superior local control compared to both group 2 and 3, with a 3-year survival of 90%, 76%, and 73% in groups 1, 2, and 3 respectively. Like the Buchakjian review, the final tumor bed margin status did not correlate with local recurrence, as the tumor bed margin status failed to predict 4 of 6 (67%) positive specimen margins and 12 of 14 (86%) close margins. However, the final status of tumor specimen margins was significantly correlated with local recurrence. Additionally, it was demonstrated in this retrospective review that revision of tumor margins was associated with increased local recurrence. Though the exact reason is not supported by this review, it is speculated that in cases in which margins are revised by tumor bed sampling, the initial resection was narrower, and the perceived extra cuff of tissue from the tumor bed does little to offset the initial positive or narrower margins. In this study, as in previous studies, up to 78% of the revised margins did not contain residual tumor, again implying extremely high rates of sampling error and suboptimal relocalization of the area of concern in the tumor bed [17].

Specimen-Driven vs Defect-Driven Approaches

Whereas the Chang and Buchakjian studies were both retrospective reviews, Amit et al. performed a single-blinded, prospective, randomized, controlled trial directly comparing the specimen-driven approach to the defect-driven approach in 71

patients, seeking to identify the rate of positive or close surgical margins in final pathology [18]. 20 (29%) patients were allocated to the defect-driven arm and 51 (71%) to the specimen-driven arm. The initial patient allocation was 1:1; however, based on the first 37 patients, higher positive margin rates were found in the defect-driven margin arm than in the specimen-driven margin arm, prompting discontinuation of the defect-driven margin arm. At final pathological analysis, positive or close margins (<5 mm) were identified in 45% of the defect-driven patients, compared to 16% in the specimen-driven group. In this prospective, randomized control trial, specimen-driven margin assessment resulted in 84% negative margins, whereas the defect-driven margin technique revealed only 55% negative margins. Unfortunately, the Amit study failed to include local control as a study endpoint. However, Maxwell et al. conducted a multi-institutional retrospective review of 280 patients, comparing defect-driven margins to specimen-driven margins, focusing on local recurrence as the primary endpoint of the study [19]. In patients whose margins were primarily sampled from the tumor bed rather than the resected specimen, rates of local recurrence were found to be significantly higher, and the tumor bed margins were only 24% sensitive for detecting a positive glossectomy margins. As in the Chang study, an exclusive reliance on tumor bed margins to determine the margin status was associated with worse local control.

Recommendations Based on the Data

For the question of whether intraoperative margin sampling should be obtained from the resected specimen or from the tumor bed, the published data of the one randomized control trial and multiple large institutional reviews are concordant: margin sampling obtained from the tumor bed is less reliable than sampling from the tumor specimen and has low sensitivity detecting true positive margins. The studies agree that intraoperative margins obtained from the tumor specimen have a much higher correlation with the final histopathological margin and carry a greater prognostic value than margins obtained from the tumor bed. The exact reasons for this discrepancy are not completely known, but it is suspected that the inherent limitation of the defect-driven approach to sampling margins, namely the difficulty in returning to the exact site of the positive margin and re-resecting the exact portion of tissue correlating to the positive margin may be the cause, as investigators have previously demonstrated that surgeons are off target by nearly 1 cm in over 30% of relocalization attempts. In Kerawala's 2001 study of 14 patients undergoing surgical resection of oropharyngeal cancer, after the tumor was extirpated, one surgeon marked the position of 4–6 proposed frozen sections form the tumor bed with sutures; this surgeon then left the case, and a second surgeon recorded the anatomic position of each suture from two fixed points. The sutures were then removed, and the first surgeon re-entered the case and was asked to relocate the suture (and thus frozen section) positions. Of 71 total soft tissue points, the 40 peripheral points were off target by a mean of 9 mm (range 0–24 mm), while the 31 central points were off target by a mean of 12 mm (range 2–44 mm), with the variation in position

Table 4.2 Comparison of intraoperative margins to final margin status

	Type of margin	n	Final margin status	P value	3-Year survival	Type of study	Quality of evidence
Amit	Specimen-driven	51	Positive 8 (16) Negative 43 (84)	0.01	Not reported	RCT	High
	Defect-driven	20	Positive 9 (45) Negative 11 (55)				
Chang	Specimen-driven	60	Positive 0 (0) Negative 60 (100)	<0.001	0.90	Retrospective review	Moderate
	Defect-driven	26	Positive 6 (25) Negative 20 (75)		0.73		
Maxwell	Specimen-driven	119	Positive 9 (7.7) Negative 110 (92.3)	<0.001	Not reported	Retrospective review	Moderate
	Defect-driven	100	Positive 23 (24.2) Negative 77 (75.8)				

exceeding 1 cm in 30% of the peripheral and 35% of the central margins [20]. This sampling error may falsely increase the surgeon's confidence that complete tumor resection was performed, resulting in a propensity to undertreat or de-escalate therapy under the assumption that the margins are negative (Table 4.2).

If intraoperative frozen margins are to be utilized, the surgeon should obtain the intraoperative margins from the resected specimen itself, not from the tumor bed. The recommendation for the pathologist is to sample the resection specimen margins even if all margins appear to be already obtained from the tumor bed. (evidence quality moderate, weak recommendation).

A Personal View of the Data

The evolving role of intraoperative frozen margins in oral cavity squamous cell carcinoma is certainly an important topic in the field of head and neck oncology. As evidenced by the AHNS survey, a significant majority of head and neck surgeons use intraoperative frozen margins in oral cavity cancer treatment. While the method of margin sampling differs, most head and neck surgeons (our institution included) obtain margins for frozen analysis from the tumor bed rather than the resected specimen itself. If the tumor bed margins are negative, no further resection is performed at the time of surgery; if margins are positive, further resection is performed at the area of the positive margin, and new frozen margins are sent until negative margins are obtained. Disagreement at tumor board inevitably ensues, as the situation of a positive final specimen margin in the setting of negative tumor bed margins begs the question, "which margin is the true margin?" To avoid this inevitable dissent, the

evidence presented in the prospective and retrospective studies reviewed in this chapter is of sufficient quality to alter the practice habits of surgeons at our institution.

In our review of the literature for this topic, it appears that the question is becoming not only "should margin sampling be obtained from the specimen or from the resection bed in oral cavity cancer?" but is transitioning to "should margin sampling be obtained in oral cavity cancer?" In many cases, the surgical margins are adequate, and the value of intraoperative margin assessment to the surgeon is simply reassurance in the operating room that the margins are clear. From an economic standpoint, this reassurance can be costly, as frozen section analysis costs on average $3123 per patient, with DiNardo et al. demonstrating an estimated cost-benefit ratio of 20:1, as only 4 of the 80 patients in their study who underwent frozen margin analysis potentially benefited from the use of frozen margins [21]. When margins are close or grossly positive, they are revised, with the surgeon removing additional tissue until margins are negative. However, based on the studies reviewed in this chapter, re-resection of positive margins has shown limited value when examining local recurrence and overall survival when compared to negative margins obtained on initial resection [22–27].

An alternative to a pathologist examining frozen margins for evidence of microscopic disease is for the surgeon to perform gross examination of the tumor at the time of resection, a low-cost alternative to frozen section that has been investigated by Chaturvedi et al. in a prospective study of 145 patients at Tata Memorial Hospital in Mumbai, India, 94% of whom were diagnosed with oral cavity cancer [28]. In this study, non-primary surgeons measured the distance between the tumor and margins without stretching the mucosa using a sterile metallic scale, relying on palpation to determine adequacy of deep margins. The specimens were then sent for frozen margin analysis and final histopathology, and the results compared. There was found to be no significant difference in the precision of frozen section and gross examination for intraoperative assessment of margins ($p \leq 0.8$). Addressing the common fear of submucosal spread, the study found that submucosal/microscopic tumor spread changed the margin status from negative on gross examination to positive in only 1.2% of cases, ultimately stating that when 7 mm margins from gross visible tumor were obtained, gross examination was equivalent to frozen section for determining negative margins. The same author performed a retrospective review of 435 patients comparing 239 (54.94%) who underwent gross examination assessment to 196 (45.05%) who underwent frozen section analysis [29]. The overall incidence of inadequate margins in the frozen section group was 6.63% compared to 6.69% in the gross examination group, with only 1.37% of patients having microscopic spread of disease or submucosal disease not seen on gross examination, similar to the finding in the prospective study. No survival benefit was found when frozen section was used for margin analysis, with 14 month disease-free survival of 86.7% in frozen section versus 83.5% in gross examination and 14 month overall survival 90.4% in frozen section and 90.9% in gross examination.

While the gross examination results are encouraging, further research concerning this method is needed, and we are not prepared to change our standard use of

intraoperative frozen margins to gross examination only. However, the evidence described in this chapter concerning the use of specimen-driven versus defect-driven margins is strong enough to support a change to the routine use of specimen-driven margins among our institution's surgeons.

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Should Level IIb Be Addressed Routinely in Clinically Node Negative Oral Cancers?

5

Pankaj Chaturvedi and Akshat Malik

Background

'To be or not to be' was a dilemma in which Prince Hamlet had found himself in Shakespeare's famous play. Centuries down the line, the same question plagues the minds of Head and Neck surgeons; IIb or not IIb. That is whether level IIb nodal station is to be addressed in the clinico-radiologically N0 (cN0) neck during neck dissection in patients with oral cavity cancer.

The American Academy of Otolaryngology & Head and Neck Surgery standardized the neck dissection nomenclature in 1991 [1]. In another update in 2002, neck dissection terminologies were further revised [2, 3]. They included the boundaries of neck node stations as described by the Memorial Sloan Kettering Group. Upper jugular nodes were referred to as level II lymph nodes. The anterior boundary was the stylohyoid muscle and the posterior boundary being the posterior border of the sternocleidomastoid muscle. Superiorly level II starts at the skull base and extends to the inferior border of the hyoid. The spinal accessory nerve divides level II into two parts. The nodes lying antero-medial to it are designated as level IIa, while posterior lateral to it is level IIb.

Elective neck dissection is the procedure of choice for addressing the neck in patients with oral cavity cancer and cN0 neck when the concern for nodal metastasis exceeds 10–20% [4]. This generally means doing a selective neck dissection—level I–III/level I–IV. When addressing level IIB, the traction and manipulation of the spinal accessory nerve may lead to ischemic injury to the nerve and resulting neuropraxia. This can result in shoulder dysfunction and disability. Many investigators have tried to evaluate if level IIb can be omitted while doing selective neck

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dissection. There have been randomized controlled trials that have compared oncologic and functional outcomes of level IIb nodal dissection in clinically node negative oral cavity cancer. Thus there still exists ongoing controversy on whether level IIb should be dissected during selective neck dissection for cN0 necks in oral cavity cancer persists.

Search Strategy

Based on the PICO table (Table 5.1) a thorough literature search was conducted using the Pubmed, Medline and Cochrane Database of Systematic Reviews. We included only English language articles published after 1980 till 2017 in the analysis. Search keywords used were—mouth neoplasms, neck dissection, spinal accessory nerve injury, 11th nerve, sublevel IIb, sub-muscular recess and level IIb.

These keywords were used in different combinations with 'OR' and 'AND' function. The abstracts of the articles obtained via these keyword searches were screened to see whether the article was relevant to our topic of study. Full texts of the articles relevant to the topic were obtained and evaluated. The references of these articles were also evaluated to look for relevant studies.

The search was directed at two aspects—evaluating the occult metastasis at level IIb in cN0 neck in oral cavity cancer patients and secondly to assess whether level IIb dissection actually affected the spinal accessory nerve function.

Results

Incidence of Nodal Metastasis at Level IIb in cN0 Oral Cavity Cancers

After thorough evaluation, we found ten articles which were relevant to our study. There were no randomized controlled trials addressing this issue but there were several prospective as well as retrospective studies. Individually, some of them had limited sample size (<50 patients) and a mixed sub-site cohort. There were two meta-analysis where the incidence of nodal metastases at level IIb in oral cancers have been evaluated. Of the ten studies we considered, six studies had been included

Table 5.1 PICO

Patient	Intervention	Comparison	Outcome
Subjects with squamous cell carcinoma of oral cavity with clinically nodes negative neck, requiring surgery	Unilateral or bilateral neck dissection with level IIb addressed	Patients who did not undergo level IIb nodal clearance	Percentage of occult level IIb nodal metastasis Accessory nerve dysfunction

in the meta-analysis by Lea et al. [5] and nine studies had been included in the meta-analysis by Kou et al. [6].

Lea et al. [5] included nine studies in their analysis. The studies included were heterogenous with respect to the inclusion, exclusion criteria and patient population. Of these, just five studies included only cN0 patients. Together these five studies had a pooled total of 182 patients. Of these, 11 patients were detected to have occult metastasis at level IIb. When analyzing studies in a meta-analysis, the calculations vary depending upon whether fixed effect or random effect model have been considered. In the fixed-effect model it is assumed that the true effect size is the same in all studies, and the summary effect is the estimate of this common effect size. In the random-effects model it is assumed that the true effect size varies from one study to the next, and that the studies in the analysis have a random sample of effect sizes. The summary effect is the estimate of the mean of these effects. Thus using random effects model, 6.04% (95% CI 2.56–9.53) patients were detected to have occult metastasis at level IIb. Amongst these studies level IIb nodal tissue was separated intra-operatively only in two studies. In rest of the studies the specimen were split into different parts during histopathological processing after resection. This would lead to the possibility of incorrect delineation between level IIa and level IIb.

In another meta-analysis and systematic review, Kou et al. [6] included 22 studies in their analysis. In Out of these studies, a total of six were on cN0 patients and nine studies had information about cN0 and N+ numbers. They analyzed level IIb metastasis in the entire cohort of the patients and separately in patients with tongue primary. Considering the random effects and fixed effects model, the pooled estimated cervical level IIb metastases rate for N0 and N+ necks was 6% (95% CI: 4–7%) and 7% (95% CI: 5–10%) respectively. The studies included were heterogenous. The I^2 value for the cohort was 72% indicating high heterogeneity. There was no publication bias in the studies included in the analysis. They also looked at level IIB metastases in tongue cancer patients. As the data regarding sub-sites was not available for all studies only 12 studies were included in this analysis. These included patients with both N0 and N+ necks. For this sub-set, the I^2 value was 0% indicating minimal minimum heterogeneity between the studies. So, a fixed effects model was used and the pooled level IIb metastases rate for tongue cancer was found to be 7% (95% CI: 5–10%).

A systematic review was conducted to analyze the incidence of level IIb metastases in different head and neck cancer sites and sub-sites in patients undergoing neck dissection [7]. They found that for oral cancers, this incidence was 3.9% (11 of 279). But this figure included neck dissections done for N0 as well as N+ necks.

Based on our literature search we shortlisted ten studies which specifically evaluated cN0 oral cavity cancer patients. There were nine prospective studies and one retrospective study. On evaluating the quality of evidence, four studies were ranked as low quality based on the GRADE system and six studies were ranked as being of very low quality. The results of these studies are depicted in Table 5.2. Seven studies exclusively dealt with cN0 patients of oral cavity carcinoma. Three studies had a mixed population of c N+ and c N−ve patients but provided separate data for cN0 oral cancers.

Table 5.2 Incidence of nodal metastasis at level IIb in cN0 oral cavity cancers

Study	Total patients of cN0	Number of cN0 necks addressed	Level IIb metastasis cases	Percentage of level IIb metastasis (out of total number of patient)	Primary site with level IIb metastasis	Isolated level IIb metastasis	Grade of study
Lim et al. [8]	74	119 (29 unilateral, 45 bilateral)	4	5%	Tongue (4)	0	Very low
Maher and Hoffman [9]	71	98 (44 unilateral, 27 bilateral)	4	5.6%	Tongue (3) Retro molar Trigone (1)	2	Very low
Agarwal et al. [10]	231	231	2	0.86%	Buccal Mucosa (2)	0	Low
Elsheikh et al. [11]	48	74 (22 unilateral, 26 bilateral)	5	10.4%	Tongue (5)	0	Low
Chiesa et al. [12]	11	11	1	9.1%	Tongue (1)	0	Very low
Kraus et al. [13]	39	42	0	0%	0	0	Low
Dabholkar et al.[a] [14]	25	25	0	0%	0	0	Very low
Paleri et al. [7]	10	10	1	10%	Floor Of Mouth (1)	0	Very low
Corlette et al. [15]	48	48	2	4%	0	0	Low
Manola et al. [16]	16	16	0	0%	0	0	Very low

[a]Not pure N0 studies

Association with Positive Nodes at Other Levels

Few studies have also tried to find if in cN0 necks nodal metastasis at level IIb was associated with positive nodes present at any other neck level. In a study where cytokeratin and epithelial membrane antigen were used as molecular markers for metastatic lymph nodes no isolated level IIb metastasis were seen. All patients having metastasis at level IIb also had nodal metastasis at level IIa [16]. CK20 has been used for identification of primary and metastatic carcinoma. In another study, polymerase chain reaction was used to detect CK20 as a marker for micrometastasis and once again, no isolated level IIb metastasis was found [11]. In another study, all patients with level IIb metastasis also had co-existing metastasis at level IIa. Additionally, three patients had level I metastasis and one had level III metastasis.

However, isolated level IIb without the presence of nodal metastases in other neck levels has also been reported [9]. In this study, level IIb metastases were seen in four patients. Out of them two had isolated metastasis and one had metastasis at level IIa. They found that perilymphatic and perivascular invasion were significantly associated with sublevel IIb lymphatic metastasis ($p < 0.02$). In contrast, there was no statistically significant relationship between perilymphatic ($p = 0.073$), perivascular ($p = 0.159$) and perineural ($p = 0.228$) invasion and metastases to any other cervical level. But the number of patients with involved level IIb nodes in this study was less and they did not evaluate this association via multivariate analysis [9]. Though there are few other studies which have looked into this aspect but they have included cN+ necks also in their analysis so we have not considered them here [17, 18].

Association with Sub-Site

Many studies on cN0 oral cavity cancers with positive level IIB lymph nodes have found the primary to be in tongue [6, 9, 11]. But such an association of oral cavity sub-sites and level IIb metastasis has not been proven. In one of the studies where molecular analysis for CK20 was done on the nodes it was shown that 22% of tongue tumors may metastasize to level IIb [11]. Another study mentioned that tongue cancers may have 11% chances of level IIb metastasis but even this study had only three patients of carcinoma of tongue with level IIb metastasis. So the number of patients as well as number of positive nodes were too few to draw any meaningful conclusion [9]. In a recent meta-analysis, level IIb metastases in tongue cancer patients were separately evaluated and were found to be 7%. This was 1% higher than for entire oral cavity combined. However the included studies included patients with both N0 and N+ necks [6].

Accessory Nerve Dysfunction

Shoulder dysfunction following neck dissection is a known entity [19]. The term ‘shoulder syndrome’ was given in 1961. Its symptoms include constant pain, shoulder tilt and drop, difficulties in shoulder retraction, limitations in the anterior flexion movements and active shoulder abduction, winged scapula and abnormal electromyographic findings [20].

It has been reported that shoulder pain may be present in up to 70% patients following neck dissection [21]. It has been shown that 100% had shoulder pain and that 80% had shoulder drop after the radical neck dissection surgery [22]. It is believed that the nerve dysfunction varies with the extent of neck dissection. It has been seen that the modified radical neck dissection is associated with shoulder morbidity when compared to selective neck dissection. Selective neck dissection may be associated with shoulder complaints in 29–39% of the patients [22, 23]. Selective neck dissection causes better shoulder function when compared to other types of dissections as

there is less level V manipulation causing less traction to the accessory nerve and the cervical plexus. Nerve traction may occur during pulling the sternocleidomastoid muscle as well [24–27]. Another study has shown that complete or incomplete denervation of the trapezium muscle is caused by the axonal injury to the XI cranial nerve. This may even happen in spite of anatomical continuity of the nerve due to the traction applied onto it [27–31]. It has also been suggested that rather than nerve injury, shoulder dysfunction occurs due to adhesive capsulitis [32, 33].

There are very few studies which have looked at nerve dysfunction with level IIb dissection specifically. Also, most of the studies have been on cohorts of different head and neck cancer-sites. In a study on head and neck cancer patients, it was observed that, action potential had median values of 54.3 μV before surgery and 11.6 μV after it ($p < 0.001$). There was a mean decrease of 70% comparing to preoperative values. The median was 12.5 μV after dissection including level IIb, and 8.9 μV after dissection including levels IIb and V ($p < 0.002$) [34]. Upper limb abduction was significantly more restricted in patients undergoing level V dissection compared to those undergoing level IIb dissection. In another study on laryngeal cancer patients selective neck dissection (including level IIb) and superselective neck dissection was compared using clinical examination, EMG, ENG and a questionnaire. It was seen that group where level IIb was not addressed had better results in EMG, arm abduction and quality of life [35]. In another study where patients either underwent level II–IV or II–V neck dissection for laryngeal and oropharyngeal cancer evaluation of dysfunction was done by using clinical examination, strength and motion tests, EMG, ENG and a questionnaire at 1 year after the surgery. It was showed that nerve impairment occurs even when level V was spared due to level IIb dissection [20]. Electrophysiological changes in muscles however may not always amount to clinical limitation in shoulder movements. In another study, where level IIb was not dissected a temporary deterioration of the accessory nerve function was still seen on electroneurography at 3 weeks with further improvement seen at 6 moths. It was observed that level IIb dissected or level IIb undissected patients showed similar axonal deterioration [22]. In another study, level IIb preserving unilateral or bilateral neck dissection was done. All shoulder movements and muscle strengths were preserved [36]. Neck extension, rotation movements, and flexion strengths were restricted [36]. ENMG values were affected moderately in the early postoperative period (at 1 month) and improved slightly in the late postoperative period (at 6 months). None of the patients developed shoulder syndrome or adhesive capsulitis [36]. A double-blinded randomized controlled trial was conducted upon 57 node negative early oral cancer patients (anterior two-third tongue and floor of mouth) who underwent neck dissections with or without level IIb dissection [37]. They assessed patients undergoing unilateral and bilateral neck dissections separately. They assessed the patients on the basis of EMG or nerve conduction studies, clinical examination (angle of movement) and University of Washington quality of life shoulder function domain. This questionnaire had two sub-scales assessing the physical function and socioemotional function. These were compared with pre-operative baseline values at 6 weeks and 6 months. They found that though trapezius muscle motor amplitudes decreased at 6 weeks and 6 months

post-operatively in both the groups but they were worse in the group undergoing level IIb dissection though this difference was not statistically significant. This decrease in amplitude was also found to be associated with poor outcomes on the shoulder domain of the University of Washington Quality of Life Questionnaire [37]. This study was conducted as feasibility study and the number of patients were too small to draw any meaningful conclusions.

Level IIb metastasis can occur in cN0 oral cavity cancer and it needs to be addressed in all cases (evidence quality low, weak recommendation).

Personal View

Occult metastasis at level IIb can occur in oral cavity carcinoma regardless of T stage. These may occur more often in patients with tongue cancer. Though some degree of accessory nerve dysfunction may occur following IIb dissection, it has not been proven to be of clinical relevance. Needless to say that all precautions should be taken to avoid direct or indirect injury to the spinal accessory nerve. Level IIb should always be addressed in all cN+ necks as well as in patients with locally advanced tumors (T3 and T4). Considering rarity of occult metastases in superficial T1 lesions with cN0 necks, IIb dissection can be avoided. However, it is advisable to explain risk benefit ratio to the patient.

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6 Role and Efficacy of Sentinel Lymph Node Biopsy in Oral Cavity Squamous Cell Carcinoma

Steven B. Chinn and Stephen Y. Lai

Introduction

Oral cavity squamous cell carcinoma (OCSCC) is diagnosed in over 32,000 patients and associated with over 7000 deaths annually [1]. Despite advances in surgical, reconstructive and adjuvant therapy, 5-year overall survival remains at 60% [2]. Surgical resection of the primary tumor is the standard treatment for local control. Management of the neck traditionally was based on presence of clinical adenopathy (cN+) or clinically negative nodes (cN0). Neck dissection is and remains the standard first line regional therapy for cN+ disease in OCSCC [2]. Over the last 2 decades there has been a transition from the "Halstedian" approach to resection with de-escalation from radical neck dissection to modified radical neck dissection to selective neck dissection without a decrease of regional control and improved functional outcomes and quality of life [3].

In the cN0 patient selective neck dissection (SND) is indicated for risk of occult metastasis >20% [4]. Risk of occult nodal disease has been well-studied with depth of invasion (DOI) being one of the most reliable risk factors for occult metastasis in early stage OCSCC; in the oral tongue DOI >2–4 mm and floor of mouth >1.5 mm are the

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most cited indications for neck dissection in cN0 patients based on known regional recurrence rates [2]. Perineural invasion (PNI), perivascular invasion and aggressive tumor patterns are also histologic risk factors associated with occult metastasis and regional recurrence and are suggestive of elective neck dissection [5, 6].

In the clinically negative neck (cN0), risk stratification was critical to balance the risk-benefit ratio for therapy vs. morbidity with regards to elective neck dissection (END) resulting in controversy over observation versus END. However, a recent prospective randomized control trial compared END versus observation with therapeutic neck dissection (TND) [7]. They found overall survival (OS) and disease-free survival (DFS) was significantly higher in the END group versus observation/TND group (OS: 80% vs. 67.5%, $p = 0.01$; DFS 69.5% vs. 45.9%, $p < 0.001$ respectively). In subgroup analysis assessing depth of invasion (DOI) <3 mm demonstrated no difference in risk of occult metastasis between the two groups suggesting that END may not be warranted, however that risks missing nearly 15% of occult disease in their study. Similarly, occult disease was found in 28% of all patients, thus nearly 70% underwent an "unwarranted" neck dissection.

While survival may be improved with SND, there remains functional morbidity associated with this procedure. Several studies have used validated instruments to assess post-treatment shoulder function and QOL after neck dissection: University of Washington Quality of Life (UW-QOL) shoulder domain, Constant's Shoulder Scale, Neck Dissection Impairment Index (NDII) and Disability of the Arm, Shoulder, and Hand (DASH). All have demonstrated neck dissection to be associated with worse QOL, shoulder function, leisure activities and employment status; even with surgical preservation of the spinal accessory nerve [8–16].

In the cN0 neck, is there a better way to assess occult nodal disease to avoid unnecessary neck dissection while maintaining the survival advantage of END? Sentinel lymph node biopsy (SNLB) of the oral cavity offers a well-established method for identifying patients with occult disease who would benefit from END while minimizing unnecessary neck dissections. The objectives of this chapter are to analyze the evidence on the efficacy and outcomes of SNLB in early stage OCSCC.

SLNB Background

SLNB has been extensively studied in breast cancer and melanoma where accurate staging at diagnosis in each of these diseases is critical as it guides therapy and is a strong determinant of long-term prognosis. Practice guidelines for both breast cancer and melanoma recommend lymphatic mapping and sentinel lymph node biopsy for patients with early stage disease [17–20]. Identification and harvesting of sentinel nodes requires a precise set of procedures and involves multiple clinical specialties (nuclear medicine, radiology, surgical oncology and pathology) and specialized pharmaceutical support. While no imaging study can consistently detect lymph node metastases with 100% accuracy, an experienced multidisciplinary team may achieve high rates of accuracy.

Lymphatic mapping occurs prior to the formal pathologic staging of breast cancer and melanoma. Commonly performed with radiotracers, lymphatic mapping can help to assist in the localization of lymph nodes draining a primary tumor site and typically consists of imaging (lymphoscintigraphy) and/or intra-operative

Table 6.1 PICO table

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with clinical node negative oral cavity cancer	Sentinel lymph node biopsy	Elective neck dissection	SLN identification NPV Survival complications Shoulder function

lymphatic mapping (ILM) using a gamma detection device [17–20]. The sentinel lymph node is defined as the first lymph node in the primary nodal draining basin most likely to be the site of regional metastasis. By surgically removing the "sentinel" lymph nodes, the pathologist can more closely examine each lymph node to look for microscopic disease and determine if a cancer has spread [21].

Over the last decade, SLNB has been applied to HNSCC in an effort to reduce treatment related morbidity while maintaining prognostic and therapeutic vigilance.

Literature Search Strategy

To identify relevant publications for the PICO table (Table 6.1), a literature search was performed using PubMed and Google Scholar. The following search terms were used to query all recent publications: "oral cavity cancer," "oral tongue cancer," "floor of mouth cancer" + "sentinel lymph node biopsy," "lymphoscintigraphy" with no restriction on time period for inclusion criteria of articles. We also utilized "oral cavity cancer elective neck dissection" for basic review of recent literature on management of the N0 neck.

Results

Head and Neck Sentinel Lymph Node Biopsy

The cN0 neck remains a challenge for the head and neck surgeon with a need to perform SND to treat and stage occult disease, while minimizing unnecessary morbidity associated with neck dissections in patients who ultimately have pN0 necks. As with breast cancer and melanoma, SLNB in OCSCC offers a less invasive approach to more accurately identify occult metastasis in early stage OCC. Originally described for the head and neck in 1996, the techniques and successes have advanced significantly over the last 20 years [22–24].

Efficacy and Survival Outcomes

There have been many studies looking at SLNB in OCSCC, however many are small retrospective case series. For a focused review and analysis, we included all multi-center prospective trials or large (>100 patients) prospective single institution trials in Table 6.2 [25–30]. We also separately analyzed meta-analyses [31–33].

Table 6.2 Summary of prospective and meta-analyses evaluating SLNB

Study	Study design	Patients	SLN identification	SNLB NPV	Regional recurrence	Quality of evidence
Alkureishi et al. (Canniesburn Trial) [25]	Multicenter prospective	T1/T2: 134	93%	Overall: 94% OT: 98% FOM: 88%	5-Year SLNB-alone: 5.8% SLNB-assisted END: 0%	Moderate quality
Civantos et al. (ACOSOG Z0360) [26]	Multicenter prospective	T1/T2: 140	NR	Overall: 96% OT: 96% FOM: 96%	NR	Moderate quality
Broglie et al. [27]	Prospective single center	111	96%	Overall: 96%	3 years: SLNBneg: 4% SLNBpos: 22%	Moderate quality
Schilling et al. (SENT Trial) [28]	Multicenter prospective	T1/T2 SLNB: 415	99%	Overall: 95% OT: 91–94% FOM: 98%	SLNB: 4.7%[a] CND: 15%[a]	High quality
Agrawal et al. (NEO3-06) [29]	Multicenter prospective	T1–4 SLNB: 83	97.6%	Overall: 97.8%	NR	High quality
Flach et al. (Dutch Multicenter Trial) [30]	Multicenter prospective	T1/T2 SLNB: 62	100%	Overall: 88% FOM: 80% OT 93%	12%	High quality
Meta analyses						
Liu et al. [31]	Meta-analysis	T1/T2: 3566	96.3	Overall: 94%	6%	High quality
Govers et al. [32]	Meta-analysis	T1/T2: 508	NR	Overall: 96.8	3%	High quality
Thompson et al. [33]	Meta-analysis	T1/T2: 593 T3/T4: 38	NR	Overall: 96%	4%	High quality

CND completion neck dissection, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy, *END* elective neck dissection, *FOM* floor of mouth, *NR* not recorded

[a]Significantly different

In the European trial sentinel lymph nodes were identified in 93% of patients, with a greater NPV in oral tongue compared to FOM (98% vs. 88%) [25]. However, the study design was not homogenous, with 59% (79/134) undergoing SLNB alone and 41% (55/134) undergoing SLNB-assisted END. Locoregional Disease-Free Survival and Overall Survival were not significantly different between SLNB-pos and SLNB-neg groups (p = 0.545) nor between SLNB alone and SLNB-assisted END (P = 0.293). It is unclear how the two groups were divided into SLNB alone versus SLNB-assisted END and unexpected that was not a survival advantage in the SLNB-neg group. There may be unintended bias built into the study design, particularly on how patients were selected for the SLNB-assisted END. However, the main takeaway is the feasibility of SLNB in early stage OCSCC.

The US-based trial (ACOSOG Z0360) was a phase II feasibility trial designed to compare SLN findings to those of the neck dissection performed immediately after the SLNB [26]. They found SLNB in the oral tongue to have a 96% NPV overall and 100% NPV for T1 oral tongue lesions. In positive SLN, 51% were the only positive nodes. This finding supports the practice of completion neck dissection following positive SLNB for SCC. There was no difference in NPV of oral tongue relative to FOM.

Flach et al. reported the Dutch Multicenter trial evaluating SLNB in T1/T2 N0 in oral cancer [30]. They analyzed 62 patients who met criteria. Of the patients with lateralized tumors, 13% were found in the contralateral neck and 21% were bilateral. Overall, 32% were positive for occult metastatic carcinoma, all of which occurred in the ipsilateral neck. In subsequent neck dissections for positive SLNB, two patients had non-sentinel nodes positive for metastatic carcinoma. Regional failure in the SLNB-neg group was 12%. Consistent with other trials, they found regional control rates at 97% in SLNB-negative patients and 95% in SLNB-positive patients. The overall NPV was 88%. There was no difference in 5-year DFS, OS or DSS between SLNB-negative and positive patients (72.0% vs. 73.7%, p = 0.916; 92.7% vs. 79.7%, p = 0.134; and 97.4% vs. 85%, p = 0.059 respectively) confirming a therapeutic effect of SLNB for treatment stratification.

Recently, the Sentinel European Node Trial (SENT) analyzed their 3-year results of SLNB in T1 and T2 oral cancers [28]. Occult disease (SLNB-positive) was identified in 23% (94/415) of all patients with only 4.7% (15/321) of SLNB-negative patients developing a regional recurrence in the absence of a local recurrence (false negative rate 14% and NPV 95%). This is in comparison to 15% (14/94) isolated regional recurrence in SLNB-positive patients after SLNB and SND. Single modality treatment with surgery alone was used in 88% of all patients and in only 27% of the SLNB-positive patients. Disease-specific survival is 94% which compares favorably to early stage oral cancer treated with surgery and END (61–85%) [34, 35]. Number of positive sentinel nodes was also predictive of worse OS (Fig. 6.1a). As expected OS and DSS were significantly better in SLNB-negative patients compared to those who were SLNB-positive (Fig. 6.1b). For positive SLNs, the type of metastasis predicted survival; isolated tumor cells had the best OS followed by micrometastasis and then macrometastasis. Given the accuracy and consistent NPV across most studies, SLNB offers an excellent alternative to END in the cN0 patient with early OCC.

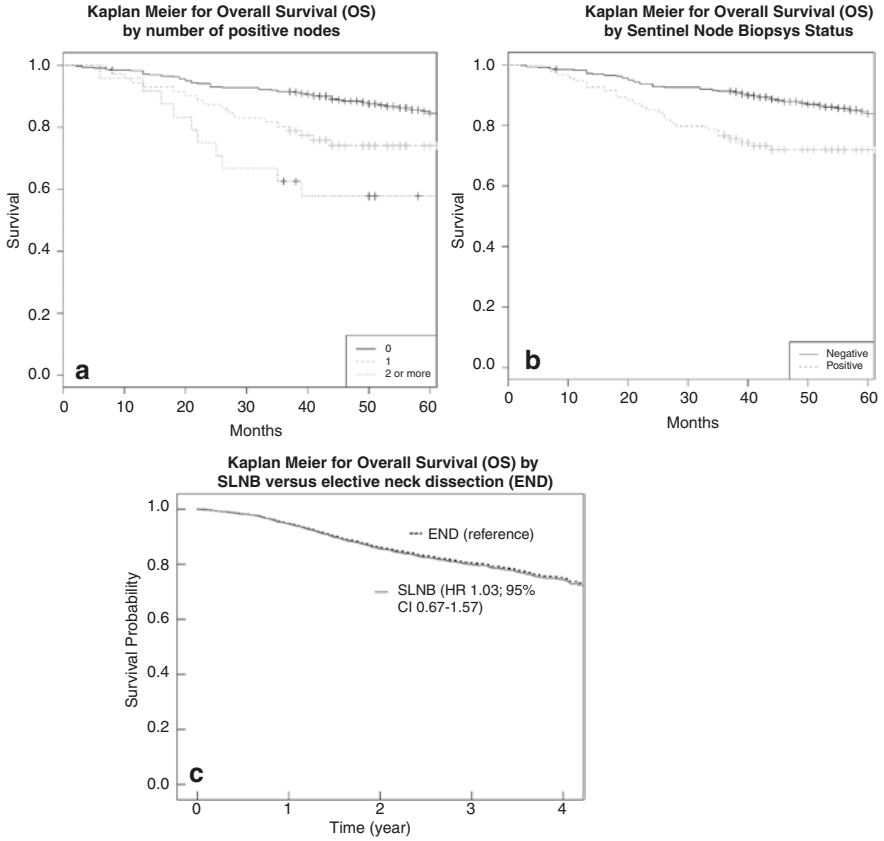

Fig. 6.1 Kaplan Meier Survival Curves. (**a**) Overall Survival (OS) by number of lymph nodes [28]; (**b**) OS by status of sentinel lymph node biopsy (SLNB) [28]; (**c**) SLNB vs. Elective neck dissection [37]

Of interest, for lateralized tumors, the vast majority drained to the ipsilateral neck (88.6%), but 10% drained to bilateral necks and 2.4% exclusively drained to the contralateral neck. Of the nodes identified in the contralateral neck, 14.3% were positive for occult disease. SLNB regional recurrence was significantly better than completion neck dissection (CND), however there is no comparison arm to END and conclusions cannot be made regarding equivalence of SLNB to END as the CND group inherently represents a more unfavorable group with regard to disease stage.

There have been several meta-analyses evaluating the role of SLNB in OCSCC. Liu et al. analyzed 66 studies from 2000–2016 evaluating 3566 patients with early stage oral SCC [31]. They did not differentiate oral cavity versus oropharynx. The pooled SLN identification rate was 96.3% with a pooled NPV of 94%. This NPV implies that only 6% of SLN-negative T1/T2 OCSCC patients would

have a regional recurrence during follow-up with a negative SLNB [31]. Govers et al. looked at 21 studies encompassing 847 cases, of which 17 studies (508 cases) were separately analyzed looking at OCSCC [32]. In OCSCC subset, the pooled sensitivity of SLNB was 92% with a pooled NPV of 96.8%, thus a 3% regional recurrence rate [32, 33]. In addition, there is no difference in regional recurrence between SLNB and END (6.7% and 6% respectively); however, there are limited data evaluating whether SND after positive SLNB has a survival benefit [33, 36]. Thompson et al. also compared 766 patients including all head and neck subsites, with a subset analysis of 631 OC cancers. In their meta-analysis, they found an overall sensitivity of SLNB of 94% with an NPV of 96%. Of patients with a negative SLNB, 2% had a positive node after END. In all meta-analyses, SLNB shows highly accurate results with overall sensitivities ranging from 92–94%, NPV of 94–97%. Regional failures in negative SLNB are relatively low, ranging from 2–6%.

A recent national cancer database analysis found that when SLNB was used, END was avoided in 64% of patients and that SLNB patients had significantly lower peri-operative morbidity. There was no difference in peri-operative mortality or survival. Three-year OS was 82% in the SLNB group and 77.5% in the END group (Fig. 6.1c) [37].

Functional Outcomes

Several studies have compared different techniques for regional control in OCSCC. All have found increasing neck dysfunction scores in order from no neck dissection, SLNB, SND, to MRND [38–40]. Murer et al. compared 33 patients who underwent SLNB and 29 who underwent END. Using the Neck Dissection Impairment Index (NDII) and the Constant Shoulder Assessment, all scores were better in the SLNB group and all complications occurred in the END group. They did not assess survival [40, 41]. Schiefke et al. evaluated 24 SLNB patients compared to 25 END patients. Quality of Life was assessed using the EORTC QLQ-C30 questionnaire, the disease-specific EORTC QLQ-H&N35 module, the Hospital Anxiety and Depression Scale, a fear of progression questionnaire. The functional status was evaluated by scores for cervical scar, extent of lymphedema (Miller score), sensory function, function of facial and hypoglossal nerve, cervical spine, and shoulder (Constant score). There was no difference in QOL measurements but there were significantly fewer swallowing problems, less fear of disease progression, and as expected, had significantly less impairment from cervical scars, sensory dysfunction and better shoulder function. Hypoglossal nerve and facial nerve function as well as cervical spine function were similar between the groups. END patients had worse pain and a negative impact on daily activity, but shoulder mobility and strength was equal [38]. Govers et al. evaluated health status (health utility score), shoulder dysfunction and patient reported QOL (VAS) relative to different neck interventions. Shoulder dysfunction was associated with more aggressive neck surgery resulting in worse health utility (Fig. 6.2) [39].

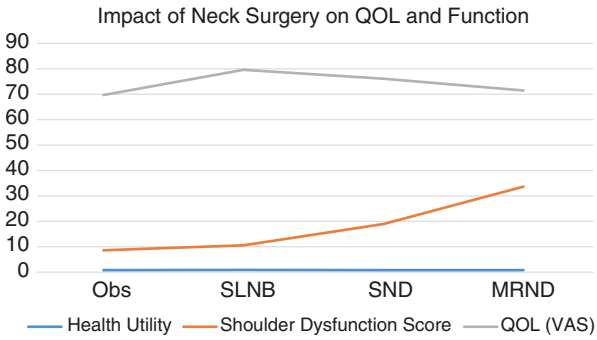

Fig. 6.2 Impact of Neck Surgery on QOL, Health and Shoulder Function. *Obs* observation/watchful waiting, *SLNB* sentinel lymph node biopsy, *SND* selective neck dissection, *MRND* modified radical neck dissection (Adapted from Govers et al., Clin Otolaryngol 2015 [39])

Hernando et al. compared complications of SLNB versus END in a prospective, non-randomized trial. As expected there were increased shoulder dysfunction and scar length with END, but no difference in lymphedema or survival. This supports the argument that SLNB can be done with lower complications and equal outcomes [42]. Unfortunately, this study is underpowered and further studies comparing outcomes are warranted.

In addition to improved functional morbidity, SLNB has also been shown to have higher cost-utility relative to fine needle analysis and END [43].

Technical Advances

Vital blue dyes are a family of colorimetric blue dyes which were among the first agents used clinically to trace the flow of lymph through lymphatic vessels and to visualize lymph nodes during surgery. The blue dye stains the lymph and lymph nodes enabling visibility during intraoperative lymphatic mapping procedures. Their use is limited by the need for direct visualization during surgery, residual staining, and allergic reactions including anaphylaxis [44–46]. Lymphatic mapping procedures usually involve use of a radiolabeled tracer supplemented by intraoperative injection of vital blue dye. In the United States, the only FDA-approved radiotracers are Lymphoseek® [technetium Tc 99m tilmanocept, Navidea Biopharmaceuticals, Dublin, OH, USA] and technetium Tc 99m sulfur colloid (Pharmalucence, Billerica, MA, USA) [Sulfur Colloid PI]. In Europe, additional radiolabeled tracers include Nanocoll® (technetium Tc99m albumin nanocolloid; GE Healthcare S.r.l., Milan, Italy) [Nancoll SPC] and Nanocis® (technetium [99mTc] colloidal sulphide injection; Cis bio international, Cedex France) [Nanocis SPC].

Recently a multicenter phase III trial (NEO3-06) was completed looking at the use of [99mTc]Tilmanocept in OCSCC SLNB to evaluate FNR and accuracy for this receptor-targeted radiotracer [29]. One-hundred and one patients with T1–T4, N0, and M0 HNSCC were enrolled with planned injections, SLNB and planned SND at the time of the SLNB. [(99m)Tc]Tilmanocept identified one or more SLNs in 81 of 83 patients (97.6%). Of 39 patients identified with any tumor-positive nodes

(SLN or non-SLN), one patient had a single tumor-positive non-SLN in whom all SLNs were tumor-negative, yielding an FNR of 2.56%; NPV was 97.8% and overall accuracy was 98.8%. Subset analysis looked at timing of injection and found no difference between injections the day before or same day.

Comparison to Sulfur Colloid

[(99m)Tc]Tilmanocept has not been compared directly to [(99m)Tc]Sulfur colloid in a prospective randomized clinical trial in HNSCC. However, there are several studies comparing [(99m)Tc]Tilmanocept to [(99m)Tc]Sulfur colloid in breast cancer [47–49]. [(99m)Tc]Tilmanocept was shown to have significantly faster injection site clearance rates and clearance half-time compared to sulfur colloid, with no significant difference in primary sentinel node uptake (% of injected dose present in sentinel node(s) at the time of lymphatic mapping. Unkart et al. performed a randomized control trial comparing [(99m)Tc]Tilmanocept versus [(99m)Tc]Sulfur colloid in breast cancer sentinel lymph node and found no technical advantage to either and recommended use based on surgeon preference [48].

Comparative analysis in OCSCC is based on cautious assessment of FNR and overall accuracy (correctness; sensitivity and specificity) from the two main trials looking at SNB in OCSCC: NEO3-06 [(99m)Tc]Tilmanocept (Lymphoseek) and ACOSOG Z0360 ([(99m)Tc]Sulfur colloid) trials [26, 29]. The false negative rate for [(99m)Tc]Sulfur colloid was 9.8% (n = 41) versus 2.56% for [(99m)Tc]Tilmanocept (n = 38) ($P < 0.0006$). The overall accuracy for [(99m)Tc]Sulfur colloid was 97% (n−140) versus 99% for [(99m)Tc]Tilmanocept (n = 82) ($P < 0.0161$).

> Early stage oral cavity cancer can be safely managed SLNB as an alternative to END, however equitable comparative data on survival is lacking (evidence quality moderate, conditional recommendation).

Personal View of the Data

Patients with cT1/T2 N0 oral cavity squamous cell carcinoma of the oral tongue can be safely managed with SNLB as an alternative to END. To date, there is no prospective randomized data comparing SLNB versus END in OCSCC whereas there is strong data supporting a survival advantage using END versus observation [7, 50]. The use of SLNB in early stage OCSCC offers potential for increased survival while minimizing unnecessary neck dissection however this indication remains supposition until randomized trials comparing SLNB versus END are done. Despite SLNB being widely accepted in Europe and several successful US-based trials, adoption of its use in the US has been limited [37]. This may be multifactorial given a steep learning curve, additional pre-operative work-up required and the need for

an experienced multidisciplinary team. In melanoma, it was noted that 30–50 cases are necessary to competency [51, 52]. The evidence on the safety and efficacy of SLNB in early stage OCSCC is excellent. However, with the knowledge that END improves survival in early stage OCSCC, it is prudent that we perform high-quality studies assessing the impact of SLNB on survival; future studies comparing these two options on regional control are imperative to better defining the role of SLNB in the management of early-stage OCSCC.

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Surgical or Non-surgical Treatment for Advanced Oral Cavity Cancer

7

Adam Howard and Zhen Gooi

Introduction

Oral cavity squamous cell carcinoma (OCSCC) remains primarily a surgical disease, despite advancements in organ preservation options for other head and neck cancers. Advanced oral cavity tumors in particular represent a challenge, as surgical intervention can often lead to debilitating morbidity with respect to swallowing, speech, and quality of life. For the last two decades, the 5-year overall survival (OS) has been in the region of 60% for all patients with OCSCC [1]. This falls to about 33% for patients with locally advanced disease, with locoregional recurrence rates ranging from 16–35% [2]. NCCN guidelines currently recommend surgical resection with adjuvant therapy for advanced OCSCC [3]. However, given the morbidity of surgical approaches and the extent of surgery frequently requiring reconstruction for advanced cancer, there is some interest in the field for the utilization of non-surgical treatments involving chemoradiation [4]. Concerns over this approach include the efficacy of definitive CRT compared to surgery, and the risk of complications such as osteoradionecrosis (ORN) of the mandible from high doses of radiation therapy (RT) [5]. The data on this topic remains scarce and conflicting and this chapter aims to review the existing data pertaining to surgical versus non-surgical treatment options for advanced oral cavity carcinoma.

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Table 7.1 Treatment options for advanced oral cavity carcinoma

Population	Intervention	Comparison	Outcomes
Stage III or IV oral cavity squamous cell carcinoma	Concurrent chemoradiotherapy	Surgical resection with or without adjuvant RT or CRT	Overall survival Disease-free survival Locoregional control Distant control

Literature Search Strategy

Based on the PICO table (Table 7.1), PubMed and MEDLINE searches incorporating the terms "oral cavity" and "advanced stage" and "chemoradiotherapy" and "radiation therapy" and ("surgery" or "surgical resection") were used to review the literature. The references sections of applicable articles were also reviewed to identify further studies that met criteria. Studies that included other head and neck cancer sites were included as long as there was sub-site analysis specific to the oral cavity. Preference was given to randomized controlled trials and meta-analyses. The majority of applicable articles are retrospective reviews or institution experience. The outcomes of overall survival, disease-free survival (DFS), progression-free survival (PFS), disease-specific survival (DSS), locoregional control (LRC), and distant control (DC) were identified as the four main outcomes for analysis. The search was limited to studies published in English and the time limit for inclusion criteria was from 2008 up until the time of writing in 2018.

Results

Randomized Controlled Trial

The randomized controlled trial by Iyer et al. randomized a total of 119 patients with stage III or IV head and neck cancer into either a surgery plus adjuvant RT arm or concurrent CRT arm [6]. Sixty patients were randomized into the surgery plus RT, although only 50 patients received the treatment according to protocol. The CRT arm consisted of 59 patients, 41 of which received CRT according to protocol. Overall patient characteristics were similar between the two groups. Oral cavity carcinoma accounted for 32% of the primary disease in the CRT arm, and 22% of the primary disease in the surgery arm. Oral cavity carcinoma accounted for 27% of the primary disease for the entire study, which was the second highest in prevalence after laryngeal cancer. The CRT arm received at least 66 Gy to the primary tumor and 60 Gy to involved lymph nodes, with cisplatin and 5-FU as chemotherapeutic agents. Patients in the surgery arm underwent radical resection of the primary tumor with levels I–V neck dissections on the ipsilateral side or bilateral if indicated. Adjuvant RT consisted of 60 Gy to primary site and 50 Gy to the involved neck when indicated (Table 7.2).

Table 7.2 Summary of comparative studies

Study	Type	OS surgery vs CRT	PFS surgery vs CRT	DSS surgery vs CRT	LRC surgery vs CRT	DC surgery vs CRT
Iyer et al.	Randomized controlled trial	–	–	68% vs 12% at 5-years (p = .038)	No difference (p = .36)	8% vs 50% distant recurrence rates at 5-years (p = .05)
Spiotto et al.	Population cohort study	52% vs 40% (95% CI 8–16%) HR 0.66 favoring surgery (95% CI .61–.71)	–	–	–	–
Cannon et al.	Population cohort study	Mean OS 71 mo vs 35 mo (p < .001)	–	Mean DSS 115 mo vs 63 mo (p < .001)	–	–
Tangthongkum et al.	Retrospective cohort	24% vs 33% at 5 years (p = .19)	–	25% vs 27% at 5 years (p = .86)	–	–
Gore et al.	Retrospective cohort	HR .10 in favor of surgery at 5-years (95% CI .04–.26, p < .001)	–	HR .06 in favor of surgery at 5-years (95% CI .02–.19, p < .001)	LRC higher in surgery group (p = .001 for LC, p = .029 for RC)	–
Sher et al.	Retrospective cohort	85% vs 63% at 2-years (NS)	82% vs 56% at 2-years (p = .03) favoring surgery	–	91% vs 64% at 2-years (p < .01) favoring surgery	94% vs 83% at 2-years (NS)
Elbers et al.	Retrospective cohort	HR 1.5 at 5-years (95% CI .96–2.46, p = .08)	DFS at 5-years HR 1.39 (95% CI .83–2.33, p = .21)	HR 1.52 at 5-years (95% CI .89–2.58, p = .13)	HR 2.88 associated with CRT (95% CI 1.35–6.16, p = .006); favors surgery	–
Stenson et al.	Retrospective cohort	53% vs 65.9% at 5-years (p = .86)	53.6% vs 66.9% at 5-years (p = .87)	–	–	–

OS overall survival, *CRT* chemoradiation, *PFS* progression free survival, *LRC* locoregional control, *DC* distant control, *mo* months, *NS* statistically not significant

For all sub-sites of the head and neck, the trend was surgery followed by adjuvant RT demonstrated an advantage over CRT for overall survival, disease-specific survival, locoregional control, and distant control. However, none of the differences were statistically significant. The authors then report the results for oral cavity, which did demonstrate significant differences between the two arms. The 5-year DSS was 68% for the surgery arm and 12% for the CRT arm ($p = .038$). The 5-year distant recurrence rates were 8% for the surgery arm and 50% for the CRT arm ($p = .05$). There was a trend in locoregional recurrence that favored the surgery arm over CRT for OCSCC, although this was not statistically significant ($p = 0.355$). The authors of this study note a few major issues, including the fact that the study was terminated prematurely due to poor accrual, leading to the study being underpowered. Furthermore, the numbers for each sub-site analysis were small, with 19 OCSCC patients in the CRT arm and 13 OCSCC patients in the surgery arm [6].

Database Reviews

Two large database reviews, one analyzing the NCDB and one the SEER database, were identified as pertinent to this chapter. The first from Spiotto et al. examined the NCDB for patients with stage III or IVa OSCC treated with either definitive CRT or surgery plus adjuvant therapy (RT or CRT) [7]. The authors identified 6900 patients form the database, 4809 of which received surgery and adjuvant therapy, and 1792 received definitive CRT. The authors formulated propensity score-matched cohorts for the two treatment groups to account for potentially confounding demographic and clinical variables. In the propensity score-matched cohorts, the authors found the 3-year OS was 51.8% in the surgery group and 39.9% in the CRT group (difference of 11.9%; 95% CI 7.8–16.0%). On multivariate analysis, surgery was associated with an improved 3-year survival compared to CRT (HR 0.66; 95% CI 0.61–0.71). The authors analyzed the difference in 3-year survival between surgery and CRT for both T1–T2 and T3–T4 disease. They found a 3-year overall survival benefit with surgery and adjuvant therapy compared to CRT in T3–T4 cancers. 3-year OS with surgery was 49.7% compared to 36.0% with CRT (difference of 13.7%; 95% CI 9.1–18.3%). However, for T1–T2 cancers, the 3-year survival was not statistically significant between the two treatment groups. The authors note several limitations to the study, including the fact that there may be bias in favor of the surgery arm if a substantial percentage of patients in the CRT group were considered non-operable candidates due to more advanced disease and comorbidities. Also, only overall survival was included, and data regarding PFS, LRC, DC was not collected or reported [7].

A SEER database review by Cannon et al. analyzed 5856 patients with stage III and IVa OCSCC, 1226 patients were treated with surgery alone, 3361 patients were treated with surgery and adjuvant RT, and 975 patients were treated with non-surgical measures (RT alone or CRT) [8]. After controlling for known confounders on multivariate analysis such as marital status, age, ethnicity, oral cavity subsite, and overall stage, the authors found that surgical intervention with or without

adjuvant RT significantly improved mean DSS compared to non-surgical treatment (115 months for surgery versus 63 months for non-surgical treatment, $p < .001$). Similarly, mean OS was 71 months for surgical intervention compared to 35 months for non-surgical treatment ($p < .001$). There are several limitations to this study. One major limitation is the fact that the review does not document the percentage of non-surgical patients treated with RT versus CRT. Also, more advanced or unresectable disease could introduce selection bias to the study in favor of surgery, as these patients will often opt for non-surgical approaches to avoid significant morbidity associated with radical surgery [8].

Retrospective Cohort Reviews

A retrospective comparative cohort study by Tangthongkum et al. compared surgical intervention to CRT in stage III and IVa OCSCC [9]. The surgical group consisted of 128 patients who had adjuvant RT or CRT, and the CRT arm consisted of 61 patients. The 5-year overall survival (OS) rates for all patients were 24% for the surgery arm and 33% for CRT arm ($p = 0.191$). The authors report 5-year disease-specific survival (DSS), which was 25% for the surgery arm and 27% for CRT arm ($p = 0.857$). Only 3.1% of patients in the surgery arm and 3.3% of patients in the CRT arm developed ORN ($p = 0.999$). The authors conclude CRT is an effective alternative to surgical intervention in advanced OCC [9].

A retrospective cohort study by Gore et al. analyzed patients with oral cavity carcinoma treated with either surgery and adjuvant RT or definitive CRT [10]. This study does include all stages of OCC, however 80% of the patients were stage III or IV. There were 54 patients in the surgery arm and 50 patients in the CRT arm. There was a significant difference in 5-year OS in favor of the surgical arm, with a HR of 0.10 (95% CI 0.04–0.26, $p < .001$). The 5-year DSS also favored the surgery group, with a HR of 0.06 (95% CI 0.02–0.19, $p < .001$). Local control was higher in the surgery arm ($p = .001$) and regional control was higher in the surgery arm ($p = 0.029$). The authors found no significant difference in ORN rates between the two groups (12% in CRT group versus 13% in surgery group, $p = 0.88$). This study does not adequately break down survival outcomes based on stage, which is a significant limitation for the purposes of this review, as it makes it difficult for fully extrapolate the data to only advanced OCSCC [10].

A retrospective review by Sher et al. analyzed 42 patients with OCSCC, 30 patients were treated with surgery with adjuvant RT or CRT and 12 patients were treated with non-surgical approaches (CRT or RT alone) [11]. All stages of OCSCC were included in the study, although 64% of the patients had either stage III or IV disease. The 2-year survival outcomes for patients treated with surgery are as follows: 85% OS, 82% progression-free survival (PFS), 91% locoregional control (LRC), and 94% distant control (DC). The 2-year survival outcomes for patients treated with non-surgical approaches were as follows: 63% OS, 56% PFS, 64% LRC, and 83% DC. There was a statistically significant survival advantage in terms of PFS and LRC between the two groups in favor of surgery ($p = 0.03$ and $p < 0.01$,

respectively). However, the difference in OS and DC between the two groups was not statistically significant. One major limitation to this study is the number of patients analyzed, as the non-surgical group only included 12 patients and there was not a standardized CRT protocol for all of these patients. Furthermore, this study includes all stages of OCSCC, and close to 40% of the patients had stage I or II disease [11].

A retrospective cohort review from Elbers et al. compared outcomes of 109 patients with advanced OCSCC treated with surgical intervention and post-op RT or CRT to 100 patients treated with definitive CRT for advanced OCC [12]. The median OS was 46 months for the surgery group and 13 months for the CRT group, and 5-year OS was 45% versus 22%, respectively ($p = 0.002$). However, after multivariate analysis controlling for confounding factors such as age, gender, smoking status, ASA status, and TNM staging, these results were not statistically significant (adjusted HR = 1.5; 95% CI 0.96–2.46; $p = 0.08$). The disease-free survival (DFS) rates at 5 years were 45% for the surgery arm and 22% in the CRT arm ($p < .001$). The DSS rates at 5 years were 64% in the surgery arm and 39% in the CRT arm ($p = .001$). However, once again with adjustment for confounding factors, these differences in DFS and DSS were no longer statistically significant. The 5-year LRC was 77% for surgery and 49% for CRT ($p < 0.001$). For this comparison, there was a statistically significant increased risk of developing locoregional recurrence in the CRT group, even after controlling for confounders and prognostic factors (adjusted HR = 2.88; 95% CI 1.35–6.16; $p = .006$). There were similar rates of ORN between the two groups as well, with 4% of CRT patients developing ORN versus 7% of surgery patients developing ORN. One important fact about this study is that the CRT group had more T stage III–IV tumor compared to the surgery cohort (90% versus 66%, $p < .001$), and larger median tumor diameter (4.1 cm versus 3.0, $p < .001$) [12].

A retrospective review by Stenson et al. analyzed a total of 138 with stage III or IV OCSCC who were treated with either definitive CRT (111 patients) or surgery followed by CRT (27 patients) [13]. The 3 and 5-year overall survival outcomes for the CRT group are 69.6% and 65.9%, respectively. The 3 and 5-year OS for the surgery group are 67.1% and 53.0%, respectively. There were no statistically significant differences in overall survival between the two groups ($p = 0.86$). The 3 and 5-year progression-free survival rates for the CRT group was 70.6% and 66.9%, respectively. For the surgery group, the 3 and 5-year PFS rates were 63.0% and 53.6%, respectively. There was no significant difference in PFS between the two groups ($p = 0.87$). The authors state that they encountered an 18.4% rate in ORN for patients with documented ORN status (only 49 of the 138 patients) [13].

A retrospective review from Cohen et al. identified 39 patients with T4 OCSCC that were treated with definitive CRT from 1993–2001. All patients received concomitant 5-FU, hydroxyurea, and radiation therapy (FHX) as the treatment regimen. Overall survival at 3-years was 62% and at 5-years was 56%. The 3-year and 5-year PFS were 59% and 51%, respectively. Locoregional control at 3 and 5-years was 82% and 75%, respectively. The authors report 11 of the 38 subjects (29%) developed long term complications. There was an 18% rate (7 of 38 subjection) of ORN. Of the 38 patients, 2 of them (5%) remained gastrostomy-tube dependent for years after treatment [14]. Another retrospective review from the University of

Chicago by Foster et al. analyzed the results for 140 patients with advanced OCSCC treated with definitive CRT from 1994–2014. The patients received FHX for their chemotherapeutic regimen and 70–75 Gy of RT (IMRT used exclusively after 2004) concurrently. The authors report 5-year OS, PFS, LRC, and distant control as 63.2%, 58.7%, 78.6%, and 87.2%, respectively. The authors report an ORN rate of 20.7% for the patients with known ORN status. Only the floor of mouth subsite was demonstrated to significantly increase the risk of developing ORN (OR 5.53; 95% CI 1.69–18.1; $p < .01$). Gastrostomy tube dependence was determined through post-CRT SPSS scores. A score ≥6 indicated feeding tube dependence. This information was only available for 64% of the patients in the study, however it showed that 10.0% of patients had long term dependence on feeding after treatment [15].

A retrospective study from Crombie et al. analyzed the outcomes of 54 patients with all stages of OCSCC (89% had stage III or IV disease) treated with primary concurrent CRT from 2000–2007. There was a range of CT and RT regimens used instead of a strict protocol. The reported 5-year OS and DSS was 29% and 30%, respectively. The overall rate of ORN was 11%, and the rate of ORN amongst survivors was 36% [16]. A final retrospective review from Scher et al. analyzed 73 patients with all stages of OCSCC (79% stage III or IV) treated with definitive CRT between 1990–2011. Again, there was a range of CT and RT regimens used instead of a strict protocol. Only 45 (61.6%) of patients received concurrent CRT, as routine use of concurrent CRT began after the year 2000. The authors report 5-year OS, LRC, and distant control rates of 15%, 37%, and 70%, respectively. Disease-specific survival at 3-years was 38% and the incidence of ORN was 6.8% [17].

Surgical resection followed by adjuvant therapy dictated by final pathologic status should be the prefered treatment option over chemoradiation for advanced stage oral cavity squamous cell carcinoma (quality of evidence moderate, strength of recommendation conditional).

Personal View of the Data

Using definitive concurrent CRT for advanced stage head and neck cancer is a controversial subject that is still evolving. Specifically in oral cavity carcinoma, concerns over complications such as osteoradionecrosis are valid. Our institutional experience reviews suggest that more aggressive CRT regimens may lead to comparable survival rates, at the expense of a higher incidence of ORN compared to surgery and adjuvant therapy. For certain oral cavity subsites with advanced stage classification, there is a clear benefit more for up-front surgical resection and reconstruction, such as the floor of mouth, retromolar trigone region and alveolar ridge with gross extension into the mandible. On the other hand, for oral tongue cancers with marked extension across midline and involving the base of tongue, there is a significant functional impact that is incurred with a subtotal/total

glossectomy, even with reconstruction. In these patients, the surgical oncologist must also consider the possibility of needing to carry out a total laryngectomy in addition to glossectomy in order to avoid mitigate the risk of dysfunctional larynx and subsequent aspiration. The combination of these surgical resections incurs a life changing impact on the patient in terms of both speech and swallowing, and in these scenarios, it is reasonable to consider definitive chemoradiation as the primary treatment approach.

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Part II

Oropharynx

8 Surgical Versus Non-surgical Management of Early T-Stage Oropharyngeal Cancer

Joseph Zenga and Jeremy D. Richmon

Introduction

During the past century, the care of head and neck cancer has evolved considerably, in both treatment approach and technological innovation. Some management decisions are based on meta-analyses of randomized trials, others on observational prospective data, and still others on retrospective evidence or on tradition alone. Although the National Comprehensive Cancer Network (NCCN) guidelines [1] provide a coherent and generalizable framework for the treatment of head and neck cancer, applying these guidelines to any individual patient is often more nuanced, requiring clinical judgement and careful interpretation of the evidence.

Further complicating management decisions has been the increased incidence of human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinomas (OPSCC) [2–4]. HPV-associated disease carries a significantly improved prognosis across different tumor stages, patient populations, and therapeutic treatment modalities [5, 6]. While HPV-association has not yet affected current treatment guidelines [7], it has profoundly changed disease staging as reflected in the eighth edition of American Joint Committee on Cancer (AJCC) staging manual, emphasizing the importance of HPV status on outcomes [8].

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This review will examine management options for patients with early T-stage OPSCC, and will specifically examine the subset of patients without clinical nodal metastases. Such patients represent a unique subset of AJCC eighth edition Stage I disease who may be treated with single modality therapy, whether surgery or definitive radiotherapy [7]. Treating these patients surgically, however (e.g. transoral resection and neck dissection), provides histological staging information for the primary site and cervical lymphatic basin and if adverse features or occult pathological nodal disease is identified, these patients may be stratified for adjuvant therapy. Such variable upstaging and changing treatment strategies make interpretation and comparison of oncologic and functional outcomes between surgical and non-surgical therapy challenging. The majority of available evidence often intermixes patients with various N-stages and may contain several different treatment paradigms. The decision to pursue definitive non-surgical therapy or an upfront surgical-based strategy for patients with early T-stage OPSCC must incorporate potential high-risk features of the disease process, expected functional outcomes, feasibility and logistics of treatment, and patient preference. As technology improves and treatment paradigms change, in both surgical and non-surgical modalities, this discussion will continue to evolve.

Literature Search Strategy

Based on the PICO table (Table 8.1), a structured review of available pertinent databases (Ovid Medline, Embase, Scopus, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and Clinicaltrials.gov) was performed. Search terms included all permutations of relevant keywords including "oropharyngeal, oropharynx, tonsil, tongue base, soft palate, pharyngeal, Human Papilloma Virus (HPV), early stage, T1, T2, squamous cell carcinoma, cancer". Included studies for analysis of oncologic results, functional outcomes, complications, and cost-effectiveness for transoral surgery and intensity-modulated radiotherapy (IMRT) were published between 1997 and 2017 for early T-stage oropharyngeal squamous cell carcinoma. Studies were excluded if they reported on outcomes of other histologies besides squamous cell carcinoma, recurrent disease, previously treated patients, those with metastatic disease on presentation, or patients not treated with curative intent. Additionally, advanced T-stage disease has significant differences in treatment modality and functional outcomes from early T-stage disease and is beyond the scope of this review. Preference was given randomized data, meta-analyses, and systematic reviews. Other critical high-quality retrospective studies were included as appropriate.

Table 8.1 Outcomes for early T-stage oropharyngeal squamous cell carcinoma

Population	Intervention	Comparison	Outcomes
Adults with early T-stage oropharyngeal squamous cell carcinoma	Surgical treatment	Non-surgical-based therapy	Oncologic Functional complications Cost-effectiveness

Oncologic Outcomes

Transoral Surgical Approach vs IMRT: Concepts

While both modern definitive radiation and upfront transoral surgical approaches appear preferable to open surgery for OPSCC, no randomized trials have been performed comparing radiotherapy and transoral surgery for early stage OPSCC [9]. An inherent difficulty in this comparison is the absence of pathological staging for patients undergoing definitive radiotherapy. It is not uncommon that despite early clinical staging, after surgical resection many patients will demonstrate adverse pathological features requiring the addition of adjuvant radiotherapy [10]. In a review of the National Cancer Database, involving 2570 patients with clinical T1–2 N0–1 OPSCC, 47% had a least one high-risk pathological feature identified after surgical resection, including upstaging of the primary tumor, multiple nodal metastases, or extracapsular extension [11]. In that way, when evaluating outcomes of early stage OPSCC, the pre-treatment decision, in reality, is between definitive radiotherapy and upfront transoral surgery *with risk-based adjuvant therapy*. Surgery provides advanced prognostic information that enables treatment to be tailored to the nature of the disease but comes at the price of multi-modality management in many cases. In early stage patients managed with definitive radiation, however, it is unknown how many may have had occult regional metastases or aggressive histological features at the time of treatment. This lack of prognostic information, in the absence of randomization, makes observational comparison between surgical and non-surgical treatment for early stage OPSCC inherently limited. Nonetheless, meta-analyses of observational data comparing transoral surgery with risk-based adjuvant therapy and definitive radiotherapy for early stage OPSCC have shown generally equivalent recurrence and survival outcomes (Table 8.2) [12, 14]. Notable in these reviews, however, is an absence of known HPV status. Given the dramatic prognostic effect of HPV-association, such absence of data further limits the strength of comparative studies [15].

Transoral Surgical Approach vs IMRT: Outcomes of Single Modality Therapy

While comparative systematic reviews and meta-analyses provide a valuable global estimate of outcomes, they group a wide variety of disease stages and treatment paradigms in analysis, a necessary limitation when comparing definitive radiation and surgery with risk-based adjuvant therapy. Understanding the oncologic outcomes for single modality therapy alone, however, is equally important for pre-treatment decision-making. In the absence of high-risk characteristics, it appears that both transoral surgery alone and definitive radiotherapy demonstrate similar and excellent locoregional control and survival. Garden et al. [16] reviewed outcomes of 217 patients with low-volume OPSCC (T1–2, N1–2a) treated with radiation alone and reported a 5-year locoregional control of 98%. In a prospective clinical trial of hypofractionated radiation in early stage OPSCC (T1–2, N0–1), RTOG 00-22, Eisbruch et al. [17] reported a 91% 2-year locoregional control.

Table 8.2 Systematic reviews for oncologic outcomes of surgery and radiotherapy in early T-stage oropharyngeal squamous cell carcinoma in the past 5 years

Study	n	Studies	Inclusion	cN0	HPV	Treatment	LRC	Survival
de Almeida [12]	TORS: 772 RT: 1287	20	T1–2, any N[a]	TORS: 17%[b] RT: 11%[c]	NR	TORS: 67% adjuvant therapy RT: 56% RT alone, 44% CRT	TORS: 2-year LRC 94%[d] RT: 2 year LRC 91–96%[e]	TORS: 2-year OS 82–94%[f] RT: 2-year OS 84–96%[g]
Kelly [13]	TORS: 190	11	T1–2, any N	NR	NR	TORS: adjuvant therapy NR	TORS: LC 96%[h]	TORS: OS 95%[h]
Morisod [14]	TOS: 276 RT: 729	12	T1–2, N0	100%	NR	TOS: adjuvant NR RT: addition of chemotherapy NR	TOS: 5-year LRC 79–94%[i] RT: 5-year LRC 71–88%[j]	TOS: 5-year DSS 82–97% RT: 5-year DSS 86–95%
Howard [9]	No data	No data	T1–2, N0–2 RCTs	No data	No data	No data	No data	No data

TORS transoral robotic surgery, *RT* radiotherapy, *LRC* locoregional control, *OS* overall survival, *DSS* disease specific survival, *NR* not reported, *TOS* transoral surgery, *RCT* randomized controlled trials

[a]Studies were included if they contained at least 75% T1–2

[b]N-stage not reported in three studies

[c]N-stage not reported in four studies

[d]Reported in one study

[e]Reported in three studies

[f]Reported in two studies

[g]Reported in four studies

[h]Aggregate estimates from seven studies with mean follow up 20 months

[i]Reported in two studies

[j]Reported in four studies

Similarly, pathologically low-risk OPSCC patients have shown excellent disease control with transoral surgery alone, regardless of HPV status. Cosmidis et al. [18] reviewed 53 patients with T1–2, N0–1 disease without extracapsular extension and reported a 91% 5-year locoregional control rate. In a recent prospective clinical trial, Dabas et al. [19] managed 49 patients with T1–2, N0 HPV-negative OPSCC with TORS alone and found a locoregional control rate of 96% at an average follow up of 29 months. Proponents of radiotherapy in early stage OPSCC, however, express concern about the inability of surgery to address the retropharyngeal nodal base. In early clinical stage disease, however, involvement of the retropharyngeal nodal basin is rare. Moore, et al. performed retropharyngeal nodal dissections on 72 patients with OPSCC and found that those with early T- and N-stage disease with a clinically negative retropharyngeal nodal basin had no occult retropharyngeal metastases [20]. In select patients at higher risk for retropharyngeal involvement (e.g. those with radiographic concern, posterior pharyngeal wall involvement, or N1 disease in the lateral neck), surgically staging the retropharyngeal nodal basin may inform decision-making for postoperative adjuvant therapy [21, 22].

Where primary transoral surgery and definitive radiotherapy may differ is in their respective ability to salvage those rare failures of initial treatment. In a review of 175 patients with T1–2 N0 OPSCC treated with radiotherapy alone, Selek et al. [23] reported successful surgical salvage in 32% of failures. A recent systematic review of surgical salvage for all stages of OPSCC initially treated with non-surgical therapy reported similar results, with 3-year disease-free survival rates of 26–55% [24]. The surgical trial by Cosmidis et al. [18], however reported a 5-year disease-free survival of 100% despite an 11% locoregional failure rate. In a multi-institutional review of 53 patients with intermediate and high-risk OPSCC managed with surgery alone, although Routman et al. [25] reported a 3-year locoregional relapse rate of 23%, of these patients 83% successfully underwent salvage therapy. In the setting of locoregional recurrence after treatment for early stage OPSCC, patients initially treated with surgery alone are often candidates for definitive (chemo)radiotherapy with or without additional surgical salvage [14, 26]. Those who have received radiotherapy previously, however, must often rely on surgical salvage alone. While adjuvant re-irradiation may improve locoregional control in select patients, it comes with substantial morbidity and has not been shown to improve survival in this setting [27].

Therefore, given the current status of best evidence demonstrating oncologic equivalency of these treatment modalities the choice between surgical and non-surgical management of early stage OPSCC becomes more nuanced than solely recurrence and survival statistics. This decision becomes primarily driven by patient selection, functional outcomes, cost-effectiveness, and patient preference.

In the absence of randomized data, overall oncologic control for early stage OPSCC appears relatively similar between definitive radiotherapy and transoral surgery with risk-based adjuvant therapy (quality of evidence moderate; conditional recommendation).

Functional Outcomes

While clinically significant differences in functional outcomes between treatment modalities for early stage OPSCC may exist, there are important limitations in the available data that make such comparisons problematic. The most critical limitation is heterogeneity in outcome reporting. Different studies, including different treatment modalities and unique patient subsets, have variable objective and subjective outcome measures. These often employ a wide variety of functional and quality of life instruments, assessed at different time points, with limited ability to compare results across studies. Many lack pre-treatment data for evaluation and often have poor follow up and compliance with quality of life questionnaires.

While not limited to only early stage disease, Dawe et al. [28] recently reviewed the available literature in an attempt to compare functional swallowing outcomes between transoral surgery and non-surgical therapies in the management of OPSCC. The authors identified 37 studies including 1377 patients managed with definitive (chemo)radiotherapy and 768 patients treated with TLM or TORS with risk-based adjuvant therapy. Overall, less than 50% of studies included an objective measure of swallowing, such as videofluoroscopy or endoscopic exam. Those that did measured these at varying time points and included a wide variety of both validated and non-validated outcomes scales. While a greater number of studies included subjective measurements of swallowing function and quality of life, in these reports 19 different outcomes instruments were used, many with little overlap and little ability to compare measurements. The most commonly used outcome measure was the MD Anderson Dysphagia Index (MDADI), reported in 13 studies. These studies, however, include heterogeneous populations with variable treatment paradigms and many lack pre-treatment data. Ultimately, at 24 months post-treatment, MDADI scores were similar for patients who underwent (chemo)radiotherapy as compared with those treated with TLM or TORS with risk-adjusted adjuvant therapy.

Despite such heterogeneity, certain trends have emerged, particularly in the management of early stage OPSCC. Several recent reports have shown excellent long-term functional outcomes of patients who can be managed with transoral surgery alone [29–35]. Choby et al. [31] investigated the functional outcomes of 34 patients managed with TORS alone using the University of Washington Quality of Life (UW-QoL) questionnaire. These authors found that pain and swallowing outcomes continue to improve over first post-operative year and only 6% required a temporary tube feeding with no patients requiring a long-term gastrostomy tube. Several other reports have directly compared functional outcomes of TORS alone with TORS plus adjuvant radiotherapy [29, 30, 34, 35]. Although these outcome measures differ, all have found negative functional effects of adjuvant therapy, particularly adjuvant chemoradiotherapy, and have reported long-term return to baseline or near-baseline functional outcomes in patients undergoing transoral surgery alone [29, 35, 36]. An important consideration, however, is tumor subsite and extent, even in early stage disease. In a review of reconstructive algorithms for oropharyngeal

defects, de Almeida et al. [37] found that patients with soft palate defects greater than 50% required regional or free tissue transfer, which may have substantial impacts on post-operative function.

While many studies have shown largely excellent functional outcomes for early stage OPSCC managed with definitive radiotherapy, when compared with transoral surgery alone, more patients require gastrostomy tube placement during treatment and a small percentage may demonstrate severe radiotherapy-related dysphagia with long-term feeding tube dependency. In series reporting specifically on early stage OPSCC, temporary gastrostomy tube rates often exceed 40% [16, 38]. In a recent study involving 46 patients with low-volume OPSCC treated with definitive IMRT, Geopfert et al. [39] reported overall excellent MDADI scores but found that 15% experienced poor swallowing function at 2 years post-treatment. While the exact etiology of such long-term swallowing dysfunction is unclear, it is likely multifactorial including radiotherapy dosing and delivery, tumor site and size, and individual patients' susceptibility to the effects of radiation.

In this way, while it appears functionally preferable to undergo surgery alone as compared with definitive radiotherapy in the appropriately selected surgical candidate, many patients with clinical early stage OPSCC undergoing an upfront surgical approach will have pathological findings necessitating adjuvant therapy. How, then, do the functional outcomes of transoral surgery plus adjuvant radio- or chemoradiotherapy compare with those of definitive radiotherapy alone? When considering patients managed with primary surgery, adjuvant chemoradiation, compared with radiotherapy alone, has been a consistent significant risk factor for poor post-operative swallowing outcomes [34, 35, 40]. Few studies, however, have directly compared functional outcomes of patients undergoing an upfront transoral approach plus risk-adjusted adjuvant therapy with definitive non-surgical management in patients with early stage OPSCC (Table 8.3). Although several have shown improved long-term swallowing outcomes for patients treated with a primary transoral approach, there are substantial limitations in these data [36, 42, 43]. Although the majority of patients had early clinical T-stage tumors, many had advanced nodal disease based on older staging criteria and as a result most were treated with multi-modality therapy. These studies were observational in design and non-randomized matching can lead to important differences between treatment groups. Such differences can contribute to inconsistent and variable results [33, 36, 39, 42].

While TORS alone in the appropriately selected patient has improved overall functional results as compared with definitive radiotherapy, when adjuvant (chemo)radiotherapy is needed after TORS functional outcomes are worse and do not appear better than definitive radiotherapy alone (quality of evidence low; conditional recommendation).

Table 8.3 Studies comparing functional outcomes of surgery and radiotherapy in early T-stage oropharyngeal squamous cell carcinoma

Study	n	cT1–2	cN0–1	Surgical treatment	Non-surgical treatment	Long-term gastrostomy tube rates	Functional outcomes
Genden [41]	TORS: 30 CRT: 26	97%	63%	TORS – 47% adjuvant CRT – 36% adjuvant RT alone – 17% no adjuvant – Median RT dose 60 Gy	CRT – 42% IC + CRT – 59% CRT alone – Median RT dose 70 Gy	12 months: – TORS 0%, CRT 4%	No significant differences at 12 months in PSS-HN or FOIS
More[a] [42]	TORS: 20 CRT: 20	65%	43%	TORS – 60% adjuvant CRT – 40% adjuvant RT alone – Cisplatin for CRT group – Median RT dose 56 Gy	CRT – Median RT dose 70 Gy	6 months: – TORS 0%, CRT 60% 12 months: – TORS 0%, CRT 5%	MDADI higher in TORS at 12 months: – TORS 78, CRT 60 (p = 0.006)
O'Hara [43]	TLM: 25 CRT/RT: 33	66%	81%	TLM – 16% adjuvant CRT – 68% adjuvant RT – 16% no adjuvant – RT dose 60–65 Gy	88% CRT, 12% RT alone – Median RT dose 63 Gy	NR	Greater decrease from baseline in CRT/RT compared to TLM group at 12 months in MDADI (p = 0.003), WST (p = 0.003), and PSS-HN (p = 0.006)
Chen [36]	TOS: 31 CRT: 31	84%	16%	TOS – 16% adjuvant CRT – 84% adjuvant RT alone – Median RT dose 60 Gy	CRT – Median RT dose 70 Gy	3% TOS 10% CRT	UW-QoL swallowing domain higher in TOS group at 12 months: – TOS 91.5, CRT 72.1 (p = 0.01)
Ling [33]	TORS: 92 CRT: 46	100%	41%	TORS – 40% adjuvant CRT – 16% adjuvant RT alone – 43% no adjuvant	CRT – Median RT dose 72 Gy	NR	UW-QoL saliva and chewing domains higher in TORS group at 12 months: – Saliva: TORS 65, CRT 53 (p = 0.017) – Chewing: TORS 95, CRT 83 (p = 0.029)
Sharma [44]	TORS: CRT/RT: 88	84%	21%	TORS – 28% adjuvant CRT – 62% adjuvant RT alone – 10% no adjuvant	93% CRT, 7% RT alone – Median RT dose 70 Gy	6 months: – TORS 3%, CRT/RT 25% 12 months: – TORS 3%, CRT/RT 11%	NR

TORS transoral robotic surgery, *RT* radiotherapy, *CRT* chemoradiotherapy, *TOS* transoral surgery, *TLM* transoral laser microsurgery, *PSS* Performance Status Scale, *MDADI* MD Anderson Dysphagia Index, *UW-QOL* University of Washington Quality of Life scale

[a]Included three patients with primary epiglottic tumors, TOS: TLM (n = 16), TORS (n = 15)

Complications

Apart from swallowing-related dysfunction discussed above, the incidence of severe treatment-related complications appears low for both transoral surgery and non-surgical therapies [12]. Although not consistently reported, each treatment modality, has a unique set of potential adverse effects and associated risk factors. While rare, these complications have important implications for treatment choice.

Transoral Surgery

The most important potentially severe complication is postoperative oropharyngeal hemorrhage. Although the overall incidence is approximately 8%, life-threatening bleeding occurs in less than 2% of cases [45, 46]. Higher T-stage tumors and antithrombotic medications have been associated with increased bleeding rates while prophylactic transcervical ligation of major feeding arteries to the resection bed has been shown to decrease the severity of postoperative hemorrhage [46–48]. Pharyngocutaneous fistula rate has been reported in approximately 3% of cases, although local tissue rearrangement in cases of intraoperative orocervical communication has been shown to be highly effective in preventing postoperative fistula [12, 49]. The incidence of severe complication during neck dissection, including cranial nerve or great vessel injury, is less than 2% [50]. Early post-operative pain during the acute healing period is more common, however, and may result in hospital readmission in up to 15% of patients [45].

Radiotherapy

Short-term severe complications of radiotherapy are uncommon although treatment-related pain and mucositis can lead to hospital admission in up to 10% of patients [12]. In certain patient populations, however, including those with systemic collagen vascular diseases or DNA repair disorders such as Fanconi anemia, the acute effects of radiotherapy may be particularly severe and even life-threatening [51, 52]. There also are several long-term effects of radiotherapy which have important implications for quality of life. Despite improvements in salivary gland-sparing IMRT, severe xerostomia can still affect over 40% of patients treated with definitive radiotherapy [53]. Osteoradionecrosis is a multifactorial late complication of radiotherapy, related to both radiation dose and delivery as well as environmental factors including dental health and tobacco use. Reported incidence ranges from 0% to 7% with modern IMRT techniques, however, osteoradionecrosis may occur many years after treatment and incidence appears to increase proportionally with time [54, 55]. In addition to radiation-related bone injury, late soft tissue damage may occur as well, in particularly delayed cranial nerve palsy which has been reported in long-term follow up in as many as 5% of patients who underwent IMRT for OPSCC [56].

The overall complication rates of both surgery and radiotherapy are low in the treatment of early stage oropharyngeal cancer (quality of evidence moderate; conditional recommendation).

Cost-Effectiveness

With presumed oncologic equipoise and remaining questions regarding functional outcomes of transoral surgery and definitive radiotherapy, the next logical investigation in decision analysis is the comparative cost-effectiveness of these two treatment modalities. This line of research is relatively recent with few studies in the current literature, each with differing findings and conflicting results [57–60]. The main limitation of such investigation is the great dependency on the validity of numerous baseline assumptions, including the need for adjuvant therapy after transoral surgery, the overall costs of treatment, the costs and incidence of complications and late toxicities, the costs and incidence of locoregional and distant recurrence, as well as the relative health utilities of different disease states. Such assumptions are often based on retrospective data from other reports which themselves have significant methodological limitations. Implicit in such cost assessments is the critical importance of the percentage of patients who require adjuvant therapy after TORS. Patients managed with TORS alone is highly cost-effective. These patients can be treated in a single surgical setting with a short recovery time and minimal lost productivity in their workplace. Costs substantially increase, however when adjuvant therapy is needed. Patients managed with definitive or adjuvant radiotherapy are generally treated 5 days per week for 6 or 7 weeks, often including significant travel commitments.

The true cost-effectives of TORS with risk-based adjuvant therapy compared to definitive radiotherapy for early stage OPSCC remains unclear and is highly dependent on baseline assumptions including treatment costs, complications, and percentage of patients requiring adjuvant therapy after transoral surgery (quality of evidence low; conditional recommendation).

Our Personal View

With the available evidence, there is no clear disease control or survival difference between surgery- and radiotherapy-based treatment of early stage OPSCC. The majority of patients undergoing either treatment modality have high disease control rates and good post-treatment function. Overall, however, transoral surgery alone likely has the best functional outcomes, is most cost-effective, has the shortest treatment duration, and allows non-surgical management to be reserved in case of recurrence, but is highly dependent on appropriate patient selection. When deciding if a patient is a good candidate to undergo an up-front surgical approach,

we ask the following questions—*Are the location, access, and instrumentation appropriate?* Advanced techniques are often required and experience with transoral laser or robotic surgery is prerequisite. Patients with extensive soft palate defects often require advanced reconstruction and may limit functional outcomes. *Is the patient medically appropriate for transoral surgery?* Poor candidates include patients with severe comorbidities, those on necessary anti-thrombotic medications which may increase the risk of post-operative hemorrhage, and those with poor pre-operative pulmonary or swallowing function who are at high risk of an aspiration-related complication. *What are the chances the patient can be successfully managed with surgery alone?* Despite early clinical stage, a significant proportion of surgical patients will require adjuvant therapy, related to pathological upstaging or other adverse histological features. The functional differences between surgery with adjuvant therapy and definitive radiation, however, remain unclear. The functional effects of de-escalated adjuvant radiation are complex and involve delivery and treatment plan, in addition to overall dosing. Those requiring adjuvant chemoradiotherapy may have particularly poor postoperative function among surgically-managed patients, and consistently identifying those patients who would most benefit from an upfront surgical approach (i.e. be able to avoid triple modality therapy) pre-operatively remains a distinct challenge. This discussion, however, will continue to evolve with further surgical and non-surgical innovation and as de-escalation paradigms change the management of HPV-associated OPSCC.

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Management of Unknown Primary Cancer of the Head and Neck

9

Jennifer Christenson and Ryan J. Li

Introduction

Head and neck cancer of unknown primary (CUP) often presents as a painless enlarging neck mass alone. A subsequent fine needle aspiration (FNA) frequently confirms malignancy. After a thorough evaluation with no identification of a primary tumor, the designation of CUP is confirmed. This represents about 1–4% of all head and neck cancers [1]. In patients over age 40, any painless, cystic or solid neck mass should be considered cancer until proven otherwise [2]. In the era of high-risk HPV (HR-HPV) associated head and neck cancers, the oropharynx is the most common site of the primary tumor [3]. It is likely that the incidence of CUP is rising along with the rise in HR-HPV associated head and neck cancers [4]. The majority of patients presenting with CUP will have a detectable primary after thorough evaluation. An algorithm for management of CUP has been described in the National Comprehensive Care Network Version 1.2018 guidelines. While the primary tumors in 50–80% of cases presenting as CUP are eventually discovered in the tonsils and base of tongue [5], metastatic nodal disease in the neck also requires consideration of other primary sites beyond the oropharynx, including cutaneous, thyroid, hematologic, thoracic, and rarely abdominal-pelvic sites. The benefit of primary site identification is targeted therapy with reduced morbidity to uninvolved sites, as CUP has become a highly curable disease. For the patients whose diagnosis remains CUP after comprehensive examination and imaging—difficult decisions focus on

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anatomical sites for treatment targeting. Radiotherapy to the nasopharynx, oropharynx, larynx, and hypopharynx for CUP has been supplanted in select HR-HPV associated (or p16 positive) cases by directed therapy towards the oropharynx, and at times the nasopharynx. Advances in radiotherapy such as intensity modulated radiotherapy (IMRT) have further reduced treatment morbidity compared to conventional external beam radiotherapy and 3D conformal techniques. Additionally, molecular testing for HR-HPV, p16 expression, Epstein Barr Virus (EBV), and other biomarkers are important diagnostic aids for localization of primary tumors.

The primary focus of this chapter is to review the contemporary evaluation and management of patients with CUP. The majority of the focus is on head and neck squamous cell carcinoma with unknown primary site, as this presentation has become the most commonly encountered CUP in practice. The role of imaging, diagnostic and therapeutic surgery, and the role of radiotherapy with or without systemic chemotherapy are explored. The balance of functional and oncologic outcomes in the treatment of CUP is reviewed. Because all cited literature was published prior to implementation of the American Joint Commission on Cancer (AJCC) eighth Edition Staging Manual, we continue to refer to TNM staging as defined in the seventh Edition.

Search Strategy

We performed a broad search in Pubmed with keywords (unknown primary head neck) to identify relevant literature available in English, regarding the epidemiology, evaluation, and treatment of CUP (see Table 9.1).

Results

Our focus is primarily on CUP diagnosed by FNA or open biopsy results of a neck mass showing squamous cell or undifferentiated carcinoma, wherein a primary site is not identified after thorough work up. Tables are provided to summarize the more contemporary literature at the time this book's publication, with the results section providing examples of data that substantiate the general approach to CUP. The included studies, mostly with small sample sizes, generally showed good agreement with regards to oncologic and functional outcomes (Table 9.2). While HR-HPV or p16 positive CUP comprise the majority of unknown primaries and are mostly of

Table 9.1 Search strategy (PICO table)

Population	Intervention	Comparison	Outcomes
Patients with head and neck cancer with unknown primary	Endoscopy with mucosal biopsy Definitive transoral surgery Radiation therapy or chemoradiation	Transoral surgery ± radiotherapy ± chemotherapy versus primary radiotherapy ± concurrent chemotherapy	Overall survival Disease-specific survival Locoregional control Quality of life Functional outcomes

Table 9.2 Outcomes based on treatment modality in patients with head and neck squamous carcinoma with unknown primary

	Intervention	Overall survival (years)	Disease specific survival (years)	Locoregional control (years)	Type of study (number of patients)
Mizuta et al. [6]	All	72.5% (3)	80.3% (3)	89.7% (3)	Retrospective cohort study (80)
	ND	71% (3)	81.8% (3)	83% (3)	
	ND → RT/CRT	71.9% (3)	79.5% (3)	91.1% (3)	
	RT/CRT ± ND	83.3% (3)	83.3% (3)	100% (3)	
Balaker et al. [7]	All	48.6% (5)			Systematic review (1726)
	Sx + RT/CRT	59.8% (5)			
	RT/CRT	46.6% (5)			
Argiris et al. [46]	ND → CRT	75% (5)		87% (5)	Retrospective cohort study (25)
Nieder et al. [5]	Bilateral RT Unilateral RT	50% (5) 36.4% (5)		81–91% (5) 48.5–92% (5)	Systematic review (122)
Grau et al. [1]	All	36% (5)	48% (5)	44% (5)	Prospective cohort study (260)
	Sx	65% (5)	76% (5)	29% (5)	
	RT	37% (5)	45% (5)	44% (5)	
	RT + Sx	28% (5)	49% (5)	59% (5)	
Kamal et al. [8]	ND + IMRT	84% (5)		91% (5)	Retrospective cohort study (260)
Wallace et al. [9]	RT ± ND	52% (5)	73% (5)	81–92% (5)	Retrospective cohort study (179)
Aslani et al. [10]	Bx + RT	64.8% (8)		76.3% (5)	Retrospective cohort study (61)
	ND + RT	67.6% (8)		85% (5)	
Demiroz et al. [47]	ND + RT	85.3% (4)		90.9% (4)	Retrospective cohort study (41)
	RT	85.6% (4)		88.8% (4)	
Huo et al. [48]	Mucosal (RT)	79.6% (5)		88.5% (5)	Retrospective cohort study (63)
	Cutaneous (Sx + RT)	66% (5)		91.9% (5)	
Chen et al. [11]	Ipsilateral IMRT ± Sx	92% (2)	87% (2)	91% (2)	Retrospective cohort study (25)
De Ridder et al. [49]	IMRT ± ND/ Chemo	62% (5)	78% (5)	90–100%	Retrospective cohort study (80)
McDowell et al. [50]	Sx ± RT	45% (5)	65% (5)	37% (5)	Retrospective cohort review (105)[a]
Cuaron et al. [51]	All	74.5% (5)		86.4% (5)	Retrospective cohort study (85)
	Sx/RT + Chemo	76% (5)		79.4% (5)	
	Sx/RT − Chemo	74.9% (5)		91% (5)	

Abbreviations: *Sx* surgery, *RT* radiation therapy, *CRT* chemoradiation therapy, *ND* neck dissection, *IMRT* intensity-modulated radiation therapy, *Bx* biopsy

Bolded results indicate statistically significant comparative results

[a]All study patients had squamous cell carcinoma parotid metastases. From this it was inferred that all patients had cutaneous unknown primaries. 105 of 143 patients underwent treatment with curative intent

oropharyngeal origin—less common putative sites including cutaneous malignancies, thyroid malignancies, melanoma, lymphoma, and non-head and neck primaries need to be considered. We do not examine these in depth. We will discuss:

1. Imaging modalities in the evaluation of CUP.
2. Molecular testing.
3. Surgical management of the neck and nodal assessment.
4. The role of transoral surgery for diagnosis and treatment.
5. Role of radiotherapy to the neck and mucosal sites for oncologic treatment.
6. Dysphagia after treatment.

Imaging Modalities in the Evaluation of CUP

A brief overview of diagnostic imaging in CUP focuses on cross-sectional and functional imaging, obtained after thorough in-office head and neck examination [12–14]. Imaging aids identification of the primary site and feasibility of neck dissection. Neck magnetic resonance imaging (MRI) and computed tomography (CT) can increase primary detection rate beyond physical exam by 25–30%, and suspicious imaging findings may double the rate of primary detection over negative imaging studies [13, 15]. If anatomical imaging should fail to suggest a primary site, or if distant metastases are strongly suspected, a skull base-to-mid thigh positron emission tomography fused with computed tomography (PETCT) scan is recommended prior to endoscopic evaluation under general anesthesia [16]. One Review article concluded that PET/CT identified primary sites after negative anatomical Imaging in 25% of patients, [45] and in another small study suspicious PETCT findings doubled primary detection rates during endoscopy, compared to endoscopic without such imaging [17]. PETCT is a valuable complement to transoral surgery (discussed below) in the identification of the primary site in CUP [18, 19].

> As cost and institutional availability allows, PETCT should be obtained as part of the diagnostic work-up for head and neck cancer with unknown primary. It is superior to PET or CT alone, and increases the detection rate of primary lesions, modifying therapy in a significant number of patients (quality of evidence moderate, conditional recommendation).

Molecular Testing

Malignant FNA cytology of a neck mass without a clear primary site should prompt testing for expression of p16 on immunohistochemistry (IHC). It is now well-established that up to 90% of p16 positive FNA samples will test positive for HR-HPV, and the majority are associated with primary oropharyngeal cancers [4, 16, 20, 21]. More rarely p16 positivity may indicate a cutaneous or nasopharyngeal

primary [22–25]. An oropharyngeal primary site is less likely to be the primary candidate when the nodal metastasis is in a lower (levels 3, 4, or 5) or higher (parotid) nodal echelon than level 2, requiring consideration of thyroid, nasopharyngeal, cutaneous, and primary parotid malignancies. Molecular and imaging testing for these are beyond the scope of this chapter.

An FNA with cytopathology should be obtained for all patients with a neck mass and no evidence of a primary lesion. FNA should be sent for cytopathology, and a cell block prepared for p16 IHC staining. Depending upon clinical suspicion, EBV titer, thyroglobulin, calcitonin, PAX8 and or TTF should also be tested. Obtaining adequate sample for a cell block is essential, as IHC has important diagnostic and prognostic value (quality of evidence—high, strong recommendation).

Surgical Management of the Neck and Nodal Assessment

A minority of CUP patients can be cured with neck dissection alone. NCCN guidelines recommend neck dissection for definitive treatment of patients with N1 disease [2]—a solitary metastatic node less than or equal to 3 cm diameter (AJCC seventh Edition). For CUP with N1 disease that is HR-HPV or p16 positive with no extracapsular extension (ECE) on final pathology, observation is considered without adjuvant radiation. However the delineation between N1 and N2a disease may be inconsequential in HR-HPV related cancers—N2a disease (i.e. solitary node greater than 3 cm, less than 6 cm, AJCC seventh Edition) without ECE may also be adequately treated with neck dissection alone. Prognostically, this is recognized in the AJCC eighth Edition for p16 positive tumors. Clinical N stage now designates one or more ipsilateral nodes 6 cm or less in size as N1. Pathologic staging now designates four or fewer metastatic nodes as N1, and greater than four metastatic nodes as N2—without incorporating nodal size into pathologic staging classification.

No prospective comparisons between CUP patients whose management of the neck included surgery, and patients who received radiotherapy or chemoradiotherapy alone, are available to assess the true effect of neck dissection on regional control and survival. One retrospective review of 179 CUP patients reported improved regional control for those patients who underwent neck dissection [9], while no benefit of surgery was observed in another series of 61 patients [10]. In both studies, all patients received radiotherapy as part of their overall treatment. A 2001 systematic review of outcomes in CUP patients reported the highest locoregional control rates were achieved in patients who underwent upfront neck dissection followed by adjuvant radiation to the neck and potential primary sites [5]. The period of interest for the aforementioned studies was largely prior to the recognition of HR-HPV in oropharyngeal cancer. The potential heterogeneity in HR-HPV status of the

analyzed patients may have obscured any oncologic benefit of neck surgery. While HPV data will become more readily available in future studies, even large contemporary studies have significant gaps in reporting of this important predictor. One of the largest recent retrospective studies in CUP by Kamal et al. in 2018 reported their experience with treatment of 260 CUP patients that included IMRT—less than 50% of patients had known HPV or p16 status. This study also saw no increase in overall survival in patients who underwent neck dissection as a component of treatment [8].

Whether neck dissection improves oncologic outcomes in CUP with advanced nodal disease remains unclear—perhaps more importantly, increased nodal burden itself appears associated with worse regional control, overall and disease specific survival [6, 8]. Mizuta et al. [6] reported a retrospective multi-institutional study of 80 patients with CUP, comparing patients treated with neck dissection alone (27 of 80, 33.8%), neck dissection followed by RT or CRT (41 of 80, 51.3%), and radiotherapy followed by neck dissection (12 of 80, 15%)—i.e. all patients underwent neck dissection. For the entire group the 3-year overall survival and disease specific survival were 72.5% and 80.3%, respectively. On multivariate analysis the only predictor of OS, DSS, regional relapse free survival (RFS), and distant metastasis free survival (DMFS) was nodal burden (N1–N2a versus N2b–N3) [6].

Interestingly neither the Kamal et al. [8] or Mizuta et al. [6] studies found ECE to be a significant predictor of any oncologic outcome on multivariate analysis. Minimal ECE (e.g. 1 mm capsular invasion) may not have a prognostic impact in the HR-HPV era, unlike gross ECE or diffuse microscopic ECE [5, 7, 8, 26, 27].

While primary radiotherapy is an option for most CUP patients, surgical management of the neck is considered for low nodal burden, especially in the absence of obvious extracapsular spread. Some of these patients will be able to avoid adjuvant radiotherapy to the neck, and dose de-escalation will likely be an option supported by clinical trials in the near future. Nodal burden remains the greatest prognostic predictor in CUP. The AJCC eighth Edition staging system for HPV/p16 positive oropharyngeal cancers reflects a need to redefine early and advanced disease and investigate safe deintensification of treatment (quality of evidence- moderate, conditional recommendation).

Role of Transoral Surgery for Diagnosis and Oncologic Treatment

If a malignant neck mass FNA tests positive for HR-HPV or p16 expression, an oropharyngeal primary is most likely. Transoral surgery—most commonly either TORS or TLMS—may identify the primary site (Table 9.3). For CUP patients the tongue base and palatine tonsils should be thoroughly evaluated for an occult primary. The surgeon's expertise dictates the actual transoral technique. In the absence of a grossly suspicious palatine tonsillar lesion, tonsillectomy is recommended over simple incisional biopsy. If a frozen section of the ipsilateral tonsil is negative for

Table 9.3 Outcomes of transoral surgery for the evaluation of CUP

Study	Patients	Intervention	Outcome classification	Detection rate after TORS/TLMS	HR-HPV or p16 status	Quality of Evidence
Patel et al. [18]	CUP patients who underwent TORS in search of primary tumor	Imaging (multiple modalities) followed by TORS	Localization of primary tumor site	12 of 15 (80%) of patients with no preoperative physical exam or radiologic suspicion	26 positive of 47 tested; in this study 32 patients had suspicious exam and/or radiologic findings prior to TORS	Moderate quality
Patel et al. [28]	CUP patients who underwent TORS in search of primary tumor	Imaging (multiple modalities) followed by TORS	Localization of primary tumor site	26 of 35 (74%) of patients with no preoperative physical exam or radiologic suspicion	18 positive of 24 tested, no difference in HPV status between detected and undetected	Moderate quality
Kuta et al. [19]	CUP patients who underwent PETCT and TLMS[a] in search of primary tumor	PETCT followed by TLMS[a]	Localization of primary tumor site	25 of 27 (92.6%) of patients with no preoperative physical exam or radiologic suspicion	25 positive of 27 (92.6%)	Moderate quality
Geltzeiler et al. [29]	CUP patients who underwent TORS in search of primary tumor	Direct laryngoscopy and TORS[b]	Localization of primary tumor site	37 of 50 (74%) of TORS patients (excludes 14 additional CUP with primary found on direct laryngoscopy)	48 positive of 50 (96%) who underwent TORS	Moderate quality
Hatten et al. [52]	CUP patients who underwent TORS in search of primary tumor	TORS assisted examination for primary tumor	Localization of primary tumor site	48 of 60 (80%) undergoing TORS surgical protocol. 32 of 59 (54%) had preoperative PET-CT without suspicious findings	55 positive of 60 (92%)	Moderate quality

[a]*TLMS* transoral laser microsurgery

[b]Various TORS techniques were used on an individual patient basis: unilateral, versus bilateral lingual tonsillectomy, bilateral versus ipsilateral palatine tonsillectomy

tumor, a unilateral or bilateral lingual tonsillectomy may reveal the primary. Numerous small retrospective studies of CUP have reported success rates from 50–100% in detection of the primary using transoral surgery beyond palatine tonsillectomy [18, 28–33]. The preoperative evaluation for a primary site amongst these studies reported various positive or negative exam and imaging findings. This in part explains the range of detection rates during transoral surgery. In these cases, presumably the primary is either very small or nonexistent, and either TORS or TLMS can facilitate a more comprehensive biopsy survey than endoscopic random biopsies alone—especially along the lingual tonsillar base of tongue. While all experienced surgeons who employ these techniques recognize the seriousness of bleeding complications, rarely are other adverse events encountered, including long term speech or swallowing impairment. The opportunity to completely excise a small primary may obviate the need for pharyngeal radiation. Similarly the identification of a lateral-positioned primary can reduce the radiation volume to midline and contralateral mucosal sites that otherwise would be considered at-risk. Lastly, a negative TORS or TLMS exploration most likely indicates a small primary, or no primary exists—and with a low probability of long-term complications, this should be a considered a worthwhile confirmation of a true unknown primary that usually portends a good prognosis.

Transoral surgery (TORS or TLMS) should be considered, beyond direct laryngoscopy, to search for, and potentially cure small occult primary lesions. This approach can be combined with neck dissection for clinically N1 patients. In selected patients without adverse features, adjuvant therapy can be avoided (quality of evidence-moderate, conditional recommendation).

Role of Radiotherapy to the Neck and Mucosal Sites

While similar outcomes between neck dissection and primary radiotherapy for early nodal disease have been observed, radiotherapy is indicated for all advanced nodal disease. The planned treatment volume, and dose of radiotherapy delivered is evolving. Historically patients with CUP would receive radiotherapy to bilateral necks and all pharyngeal mucosal levels. Individual case decisions might spare the larynx and/or hypopharynx [34]. While locoregional control was achievable, the technique was not sparing of potentially uninvolved pharyngeal structures.

Numerous retrospective studies have examined treatment outcomes comparing ipsilateral and bilateral neck radiation, sparing low risk mucosal levels—but no prospective data is available. Poor accrual led to closure of a prospective trial EORTC 22205 that was designed to answer these questions. Numerous retrospective studies have included small numbers of patients who received ipsilateral radiotherapy, with low rates of contralateral neck recurrence similar to patients who received bilateral neck radiation [1, 3, 9, 35–42].

The largest retrospective CUP study reporting on 352 patients observed one contralateral neck recurrence in patients treated with ipsilateral radiotherapy (1%), compared to five contralateral recurrences when bilateral necks were radiated (4%) [1]. No HPV data, and limited ECE data was available for detailed description of these patients. Furthermore at most only 38% of patients underwent either neck CT or MRI, or PET scan as part of their diagnostic evaluation. Without anatomical imaging the designation of a true unknown primary may have differed between studies and affected survival analyses.

Mourad et al. reported that sparing the larynx, hypopharynx and nasopharynx does not compromise locoregional control and survival in select patients [35].

Kamal et al. reported treatment of 260 patients with CUP that included IMRT—79% of patients had N2b disease or greater [8]. Radiation to mucosal at-risk sites was administered in 245 of 260 (94%) of patients, and only 4% of patients had emergence of a primary tumor after treatment. Regional control (91%), distant metastasis free survival (94%) and overall survival (84%) were excellent 5 years after treatment. In this study, systemic therapy did not improve these outcomes regardless of nodal stage, either when given concurrently with IMRT, or as a neoadjuvant regiment. While fewer than 50% of the study patients had available HPV or p16 data, presumably the majority had HR-HPV associated cancers—the more favorable biology and response to treatment in these patients compared to other head and neck cancers suggests systemic therapy has a more limited role in treatment.

Dysphagia After Treatment

Dysphagia is a major acute and long-term concern for treatment of CUP. Refinement of radiotherapy volume is critical for acceptable long-term swallow function. While an imperfect metric for severity of dysphagia, gastrostomy tube placement is frequently studied. The majority of patients will have their gastrostomy tube removed in the year following treatment, irrespective of radiated pharyngeal levels and addition of systemic therapy [8]. Even those patients with chronic radiation-associated dysphagia (RAD) are often free from gastrostomy tube dependence [8, 43]. Small studies of patients with CUP treated with radiation have variably reported a minority or no patients with grade 3 (severe) or greater dysphagia and a majority of patients self-reporting that they swallow ‘as well as ever’ 6 months following treatment [11]. Still, another small study observed most patients reporting no difference in pre and post-treatment speech, but worse satisfaction with eating 12 months post-treatment [44].

Recommendations Based on the Data

The evaluation and management of CUP is well described in the NCCN 2018 guidelines based upon available evidence. Additionally, the implementation of the AJCC eighth edition staging system—which contains different stage reporting

guidelines for HPV+ and HPV− tumors, reflects the prognostic importance of HPV or p16 testing. Patients presenting with HPV and/or p16 positive CUP are designated T0, while HPV or p16 negative CUP is not assumed to harbor an oropharyngeal primary.

Based upon the preceding data and historical studies, the following summary of recommendations can be made for the management of CUP patients:

1. Transoral surgery (TORS or TLMS) should be considered, beyond direct laryngoscopy, to search for, and potentially cure small occult primary lesions. This approach can be combined with neck dissection for clinically N1 patients. In selected patients without adverse features, adjuvant radiotherapy can be avoided. More advanced nodal disease requires radiotherapy as a component of treatment. The AJCC eighth Edition staging system for HPV/p16 positive oropharyngeal cancers reflects a need to redefine early and advanced disease and investigate safe deintensification of treatment (quality of evidence—moderate, conditional recommendation).
2. In the study of patients with CUP who have HPV-related disease, ECS has likely included a heterogeneous group ranging from minimal microscopic to gross extranodal extension of disease. Patients with a solitary pathologic node and minimal ECS can be considered for neck dissection and adjuvant radiotherapy without the addition of systemic therapy, although definitive data is not yet available (quality of evidence—moderate, conditional recommendation).
3. Primary radiotherapy with or without chemotherapy is recommended for CUP patients with advanced nodal disease (N2b, N2c, N3, or with gross ECE) [2]. The planning target volume (PTV) for radiotherapy in patients with CUP should be strongly informed by HPV or p16 testing, and EBV testing when clinically suspected. Primary radiotherapy for patients with undetected primaries should include high-risk nodal levels and mucosal sites. With respect to mucosal target volume, HPV or p16 positive CUP patients should receive radiation primarily to the oropharynx and consider inclusion of the nasopharynx, limiting radiation to other pharyngeal levels (quality of evidence—moderate, conditional recommendation).

Personal View of Data in the Management of CUP

There is a wealth of valuable experience in the treatment of patients with CUP as evidenced by the previously cited studies. It is clear that the majority of patients with CUP have HPV-associated disease of likely oropharyngeal origin. As such, we counsel them appropriately that the disease is life threatening, but with appropriate treatment there is a high probability of cure.

Limitations of the cited research are common in retrospective studies. Radiation volume was often only broadly described, and comorbidity status was often unreported. Both of these variables may have a powerful influence on overall survival. Comorbidity status in particular has a significant role in treatment selection.

It is important to convey a balanced perspective on treatment options—primary surgery with or without adjuvant therapy, versus primary radiation-based protocols. Patients rightfully focus on which treatment is the 'right' choice, and there is a great deal of comfort that the clinician can provide by describing the excellent outcomes experienced by most patients—regardless of the treatment protocol employed. Centers with a high volume of transoral surgical experience have the opportunity to both detect primary tumors and fully treat the neck and mucosal disease, when nodal burden is low. This will be a small proportion of CUP patients that can avoid radiotherapy, however this subgroup benefits greatly from the low long-term morbidity of surgery. Conversely, we counsel most patients regarding the excellent oncologic outcomes even if a primary site is not discovered, when primary radiotherapy or chemoradiotherapy is chosen. Future research needs to clearly define and distinguish between HPV positive and negative CUP—the study of planned radiation volumes, success of transoral surgical approaches, and prognostic significance of nodal burden need to be considered within these two subgroups separately.

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Part III

Larynx

Early Oral Feeding Following Primary Total Laryngectomy

10

Johannes J. Fagan

Introduction

This chapter reviews the evidence relating to early vs. delayed oral feeding of patients who have undergone primary total laryngectomy and its relevance to clinical practice.

When to introduce oral feeding following primary total laryngectomy has been contentious for many years. Early oral feeding potentially leads to quicker psychosocial rehabilitation, improvement in patient comfort by dispensing with a nasogastric tube (NGT), less nursing care, reduced treatment costs, and earlier discharge from hospital.

Alonso already reported in 1954 that he commenced oral feeding of total laryngectomy patients on Day 2 or 3 [1]. Yet Boyce and Meyers [2] found that 84.5% of American head and neck surgeons delayed oral feeding for at least 7 days, and that only 2.8% fed patients by Day 4; and Cotton and Parry [3] reported that most Australian surgeons delayed oral feeding for 7–10 days. Biases against instituting early oral feeding are no doubt rooted in adverse experiences that every head and neck surgeon has had of a pharyngocutaneous fistula (PCF) following total laryngectomy, and its associated complications such as loss of soft tissue cover, jugular and carotid blowouts, complex reconstructions, prolonged hospitalisation, delayed adjuvant radiotherapy, and long-term swallowing problems.

As will become clear from the data presented in this chapter, all published studies that compare early and delayed oral feeding following primary total laryngectomy show comparable PCF rates.

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Table 10.1 PICO terms used in search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Laryngeal cancer	Total laryngectomy	Early vs. delayed oral feeding	Pharyngocutaneous fistula

Search Strategy

Table 10.1 lists the PICO terms used in a search of English publications listed on Pubmed, from 1960 to 2017. Keywords used included a combination of 'and' or 'or' for laryngeal cancer, total laryngectomy, early oral feeding, delayed oral feeding, pharyngocutaneous fistula. References quoted in these publications were searched for additional relevant studies.

Results

Eleven studies were considered worthy of inclusion. The quality of the evidence is classified using the GRADE system. The quality of evidence classifications of the first four studies in Table 10.2 refer to the risk of PCF, whereas the quality of classifications of the remaining studies refer to the incidence of PCF in early vs. delayed feeding.

Even though the primary question being addressed is early feeding in primary laryngectomy patients, half of the studies include patients that had had previous radiotherapy (Table 10.2). Medina and Khafif only included patients who had had small radiation fields for early cancers [9]. None of the studies included patients having salvage surgery following organ sparing chemoradiation. All excluded patients that required pharyngeal reconstruction with free or pedicled flaps.

The first four studies [4–7] listed in Table 10.2 are retrospective chart reviews of patients that commenced oral feeding between days 1 and 4 following total laryngectomy. When the PCF rates of 9.1–21% are compared to published laryngectomy PCF rates of 3–76% [9], one can conclude that early feeding is associated with acceptable PCF rates. Being retrospective reviews spanning periods of up to 21 years [4], selection biases of cases favourable for early feeding cannot be excluded that may potentially affect the quality of the evidence.

The next four studies listed in Table 10.2 are non-randomized case series that compare PCF rates of early vs. delayed oral feeding [8–11]. The PCF rates for early feeding of 3.6–20% again compare favourably to published laryngectomy PCF rates. The differences in PCF rates between the early vs. delayed oral feeding cohorts were statistically not significant. Comparing sequential series of patients that were fed either early or late minimizes selection bias [8–11].

The last three studies listed in Table 10.2 are prospective randomized studies of PCF rates with early vs. delayed oral feeding [12–14]. Only the study by Seven et al. included post-radiotherapy patients, none of whom developed PCFs [12]. Again, the differences in PCF rates between the early vs. delayed oral feeding cohorts were statistically not significant.

Table 10.2 Studies of early and delayed feeding

Study	Patients	Design	Outcome	Therapy A Early feeding	Therapy B Delayed feeding	Result PCF (%)	Quality of evidence
Aprigliano [4]	625 (Post-RT: 52)	Retrospective chart review	PCF	Day 3	–	Overall: 9.1% Primary: 8.5% Post-RT: 15.3%	Moderate
Akyol et al. [5]	110 (No RT)	Retrospective chart review	PCF	Day 1	–	21%	Moderate
Saydam et al. [6]	48 (Post-RT: 10)	Retrospective chart review	PCF	Day 1/2	–	Overall: 12.5% Primary: 7.9% Post-RT: 30%	Moderate
Süslü and Şefik Hoşal [7]	602 (No RT)	Retrospective chart review	PCF	96% by Day 3	–	11.9%	Moderate
Soylu et al. [8]	295 (Post-RT: 21)	Retrospective sequential	PCF	Day 3	Day 10	A: 13.1% B: 9.3%	Moderate
Medina and Khafif [9]	73 (Post-RT: 12)	Prospective sequential	PCF	Day 3	Days 7–10	A: 3.6% B: 11%	Moderate
Prasad et al. [10]	70 (No RT)	Prospective sequential	PCF	Day 2	Day 10	A: 2.7% B: 6%	Moderate
Aswani et al. [11]	79 (Post-RT: 4)	Prospective, retrospective sequential	PCF	Day 2	Days 7–10	A: 20% B: 15.4% (p = 0.59)	Moderate
Seven et al. [12]	65 (Post-RT: 5)	Prospective randomized	PCF	Day 1	Day ≥7	A: 6.2% B: 9%	High
Sharifian et al. [13]	25 (No RT)	Prospective randomized	PCF	Day 3	Day 7	A: 7.7% B: 8.3%	High
Sousa et al. [14]	89 (No RT)	Prospective randomized	PCF	Day 1	Day 7	A: 27.3% B: 13.3% (p = 0.10)	High

PCF pharyngocutaneous fistula, *RT* radiotherapy

Antireflux and/or antacid medications were administered to Prasad et al.'s and Sharifian et al.'s patients [10, 13]. This could potentially have reduced the incidence of PCF compared to other studies as administration of proton pump inhibitors (PPIs) has been found to reduce the incidence of PCF [15].

The use of nasogastric tubes (NGTs) following total laryngectomy is contentious [12]. NGTs were avoided in patients on early feeding protocols by Aprigliano [4], Akyol et al. [5], Saydam et al. [6], Süslü and Şefik Hoşal [7] (99% of patients), Soylu et al. [8] (85.5% of patients), Medina and Khafif [9], and Sharifian et al. [13] Aswani et al. [11] and Seven et al. [12], initially inserted stomagastric tubes through the tracheoesophageal fistulae, later to be replaced by speaking valves. Prasad et al. [10] and Sousa et al. [14] routinely inserted NGTs. Sousa et al. [16] reported in a subsequent study that patients subjected to early oral feeding fail to meet caloric and protein requirements in the first 4 postoperative days, and suggested that they receive complementary enteral nutrition.

Medina and Khafif [9], Prasad et al. [10], and Aswani et al. [11] reported shorter hospitalization in the early feeding group, although Seven et al. [12] found no difference. However, data about lengths of hospitalization must be treated with caution as the criteria for discharge were not standardised across the studies, and discharge from hospital can be delayed by many factors other than surgical complications such as social issues, availability of transport and speech therapy. Based on the data from the quoted studies, the following conclusions can be derived. Firstly, early oral feeding is not associated with an increased risk of PCF. As such, early oral feeding can be commenced in patients undergoing primary total laryngectomy. Secondly, the surgeon should pay close attention to nutritional requirements in patients on early oral feeding protocols who are not being supplemented via nasogastric or stomagastric feeds. Lastly, there is insufficient evidence to determine if early oral feeding is helpful in the setting of pharyngeal reconstruction with free or pedicled flaps, or salvage total laryngectomy following radiation or chemoradiation therapy.

> Early oral feeding is recommended in patients undergoing primary total laryngectomy with primary pharyngeal closure (evidence quality—high; strong recommendation).

A Personal View of the Data

Early oral feeding following primary laryngectomy has been the standard of care in my hospital for 15 years. Oral feeding is initially supplemented via a stomagastric tube in patients to be subsequently to be fitted with a voice prosthesis, or by NGT, or by passing a fine-bore tube through the voice prosthesis. Early oral feeding potentially leads to quicker psychosocial rehabilitation, improvement in patient comfort by dispensing with a nasogastric tube, less nursing care, reduced treatment

costs, and in our clinical setting, earlier discharge [11]. PPIs are administered peri- and postoperatively to reduce the incidence of PCF [15]. Pending the results of future studies, we generally do not employ early feeding for patients with pharyngeal reconstructive surgery, or following previous (chemo)radiation therapy.

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Primary Surgery Versus Organ Preservation in Advanced Laryngeal Cancer

11

Nathan Nickel, Deepa Danan, and Peter T. Dziegielewski

Introduction

Over 4500 North Americans will be affected by advanced laryngeal cancer in 2018 [1]. The disease and its treatment often cripple functions essential to daily life including speech, breathing and swallowing. As cancer treatments have progressed, oncologists have changed the mantra from "survival at all costs" to "survival with maximum functional and quality of life outcomes;" the treatment of advanced laryngeal cancer hangs delicately in this balance.

Treatment paradigms for locally advanced laryngeal cancer stem from multiple large-scale studies designed to determine the most effective and least morbid means of accomplishing oncologic cure. The following discussion will be directed towards the curative treatment of locally advanced (T3–T4a) laryngeal cancer with a focus on comparing nonsurgical organ preserving therapies (NOP) to total laryngectomy plus adjuvant therapy if indicated (TL + A). A review of the literature was performed to this end. Overall survival (OS) was selected as the primary endpoint for comparison as it was the most uniformly documented outcome and was available for review in multiple studies. Secondary outcomes include recurrence-free survival (local/locoregional control), disease-specific survival and functional outcomes following treatment. Functional outcomes were examined as non-surgical treatments were considered to be "organ preserving", and thus, assumed to be "function preserving". However, this notion has been challenged by many studies.

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Search Strategy

Search parameters and keywords were: total laryngectomy and survival and either organ preservation or radiation (Table 11.1). Search results were generated from PubMed, BioMed Central, and Cochrane Database. Inclusion criteria were limited to full text publications in a peer-reviewed journal with an English language text available for review. No limitation was placed on time period of publication. Abstracts were reviewed for applicability to the clinical question. Full text articles and bibliographies of the selected studies were reviewed to obtain additional studies applicable to the current clinical debate.

Results

Treatment strategies began shifting in the 1990s with the publication of a randomized controlled study through the Department of Veterans Affairs (aka "the VA study") to compare definitive chemo-radiotherapy, radiotherapy and total laryngectomy with adjuvant therapy as indicated in patients with advanced stage laryngeal cancer [2]. The study design compared overall survival of the treatment arms, but was structured to provide early salvage laryngectomy to patients deemed "non-responders" to induction chemotherapy, or to those with residual disease following radiation therapy. Their study showed 2-year overall survival to be equivalent at 68% with either induction chemotherapy followed by radiation therapy or total laryngectomy with recommended adjuvant therapy. Radiation therapy without chemotherapy had inferior results. There were several limitations of this study. The patient populations were characterized according to a previous staging system, and therefore, may have been under-staged in many cases. Additionally, T2 cancers, which likely would not have undergone a total laryngectomy, were included and were limited to the NOP arm. The study also suffered from additional biases that have limited its generalizability. The study intervention required a coordinated multidisciplinary team to reassess and refer patients for TL if they failed the primary treatment modality. This limits external validity by the introduction of complexity bias, present in RCTs when outcomes depend upon multiple groups to perform separate interventions to achieve the studied outcome which may be widely variable outside of the study [3]. There is also sampling bias as the data collection was limited to VA patients,

Table 11.1 PICO table

Patient	Intervention	Comparator	Outcome
Patients with locally advanced laryngeal cancer (T3–T4a)	Organ preservation therapy	Total laryngectomy	Overall survival, disease specific survival, functional aspects following treatment

which may not be representative of the population at large. Additionally, the results of this study and others of similar design may not be applicable to the general population as the VA and other similar large health systems have a more complete and consistent provision of care, whereas patients referred from the community or at institutions with low volumes are subject to unforeseen events such as lapses in insurance coverage, transportation difficulty, or loss to follow-up at a higher frequency.

The VA study demonstrated equivalence in overall survival over a follow up period of 10 years, ushering other studies with similar design to compare secondary endpoints and validate the previous results. In 2003, the successor to the VA trial was published—the Radiation Therapy Oncology Group (RTOG) 91-11 study, which compared three modes of NOP and found that concurrent chemoradiotherapy (CCRT) was superior in locoregional control and laryngeal preservation than radiation alone or induction chemotherapy plus RT [4]. The conclusion was that most T2, T3 and low volume T4 laryngeal cancers should be treated with CCRT [5, 6].

In 2006, Hoffman et al. revisited the issue of laryngeal cancer survival with a large, national hospital-based study [7]. They found that, since the VA trial, the use of NOP in laryngeal cancer has increased while the survival rates of laryngeal cancer have decreased. Laryngeal cancer was the only cancer to follow such a trend during this time frame. Chen and Halpern published a similar study in 2007 showing that stage IV laryngeal cancers have superior survival rates with TL + A than NOP [8]. These studies prompted other centers to re-examine the applicability of the two original landmark clinical trials to the population at large.

A number of other hospital and population studies noted the concurrent increase in the number of patients receiving NOP methods, decline of surgical treatment, and worsening survival trends. Retrospective analyses of the data from cancer registries in the United States [9–14], Canada [15], the Netherlands [16, 17] and Germany [18] have provided convincing evidence that the outcomes achieved in the randomized controlled trials that deemed NOP methods equivalent did not hold true on a population level (Table 11.2).

Through a German population-based study, Dyckoff found that patients with T4 cancers had significantly worse survival when treated with NOP than with TL + A; the risk of death was twofold higher in the NOP group [18]. Using the SEER database, Harris et al. found that optimal overall survival and disease-specific survival for both T3 and T4a laryngeal cancers are achieved with TL-RT [12]. Timmermans et al. used a population based cohort study to show that T3 laryngeal cancers had similar 5 year OS for all treatments; however, T4 cancers treated with TL-A had superior 5 year overall survival compared to CRT (48% versus 42%, $p < 0.001$) [16, 17]. Dziegielewski et al. conducted a population based cohort study with the Alberta Cancer Registry and also showed this pattern

Table 11.2 Summary of advanced laryngeal cancer survival studies

Study outcome	Outcome classification	Study	n	Intervention	Comparator	Type of study	Quality of evidence
No significant difference in overall survival is observed for select T3 disease treated in a well controlled system	2 year overall survival chemo-radiotherapy vs total laryngectomy with adjuvant therapy	VA Laryngeal Cancer Study Group [2]	332	CT → RT 2 year OS 68% (95% CI 60–76%)	TL + A 2 year OS 68% (95% CI 60–75%)	RCT	High
	5 year observed survival in T3N0M0 laryngeal cancer	Hoffman et al. [7]	1391	59.3% (p = .503) CRT	TL alone 63.3% (p = .503)	Observational retrospective hospital-based cohort	Low
	Overall survival in T3N0M0 patients, RT based approaches vs surgical management	Ko et al. [23]	2622	RT based approaches 5 year OS 59% (95% CI 55–62%)	TL + A 5 year OS 54% (96% CI 45–63%)	Observational retrospective hospital-based cohort	Low
	Overall survival/Disease free survival	Luo et al. [22]	400	OS: CT-RT OR 1.563 95% CI 0.55–4.44) p = 0.402 DFS: CT-RT OR 1.923 (95% CI 1.284–2.878) p = 0.001	TL + A	Meta-analysis	Moderate
	Overall survival, disease-free survival, rates of laryngeal preservation, local-regional control, toxicity of therapy, and cost	Pfister et al. [24]	Not given	All NOP methods	TL + A	Systematic review Based upon RCT, meta analysis and observational cohort studies	High

Patients with large volume T3 and T4a disease, as well as those with pretreatment laryngeal dysfunction, benefit from total laryngectomy	Survival outcomes and factors predictive of outcome for stage III and IV laryngeal cancer and T3 and T4a disease treated with total laryngectomy or nonsurgical therapy	Forastiere et al. [6]	Multiple studies reviewed	All NOP methods	TL + A	Systematic review Based upon RCT, meta analysis and observational cohort studies	Moderate
	Risk of death (stage IV laryngeal cancer)	Chen et al. [8]	4874	CT-RT HR: 1.43 $p < 0.001$	Surgical treatment: HR: 1	Retrospective population based cohort	Low
	Risk of death in T4a disease	Grover et al. [19]	969	CT-RT HR: 1.31 (95% CI 1.10–1.57 $p < 0.003$)	Surgical treatment HR: 1	Retrospective population based cohort	Low
	Overall survival in patients with stage III and IV laryngeal cancer nonsurgical vs surgical treatment	Megwalu and Sikora [13]	5394	Nonsurgical therapy HR: 1.32 (95% CI 1.22–1.43 $p < 0.001$)	Surgical treatment HR: 1	Retrospective population based cohort	Low
	Overall survival in patients with T3 and T4a laryngeal cancer nonsurgical vs surgical treatment	Dziegielewski et al. [15]	258	Nonsurgical therapy HR: 3.1 (95% CI 1.7–5.8, $p < 0.01$)	Surgical treatment HR: 1	Retrospective population based cohort	Low
	Overall survival in patients with T3 laryngeal cancer nonsurgical vs surgical treatment	Al-Gilani et al. [9]	487	Nonsurgical therapy HR: 1.3 (95% CI 1.02–1.57 $p = 0.03$)	Surgical treatment HR: 1	Retrospective population based cohort	Low
	Overall survival in patients with T4a laryngeal cancer nonsurgical vs surgical treatment	Stokes et al. [14]	3542	Nonsurgical therapy HR: 1.55 (95% CI 1.41–1.70, $p < 0.01$)	Surgical treatment HR: 1	Retrospective population based cohort	Low
	Overall survival in patients with T3 and T4a laryngeal cancer nonsurgical vs surgical treatment	Harris et al. [12]	6797	Nonsurgical therapy HR: 1.26 (95% CI 1.12–1.40 $p < 0.001$)	Surgical treatment HR: 1	Retrospective population based cohort	Low

(continued)

Table 11.2 (continued)

Study outcome	Outcome classification	Study	n	Intervention	Comparator	Type of study	Quality of evidence
	Overall survival in T4a laryngeal cancer nonsurgical vs surgical treatment	Timmermans et al. [17]	3794	Nonsurgical therapy HR: 1.27 (1.01–1.59, $p < 0.0001$)	Surgical treatment HR: 1	Retrospective population based cohort	Low
Patients should have multidisciplinary evaluation prior to initiation of treatment	Not specified	Pfister et al. [24]	Not given	Not given	Not given	Systematic review Based upon RCT, meta-analysis observational studies	Moderate
Providers should counsel and evaluate the preferences of the individual patient	Utility value of health states following treatment	Hamilton et al. [33]	122	CRT with complications Patients: 0.36 Staff: 0.49 $p = 0.026$	TL with complications Patients: 0.46 Staff: 0.51 $p > 0.05$ Lo	Time trade off analysis	Low
Quality and cost outcomes in laryngeal cancer treatment based on hospital volume	Complications and costs associated with laryngeal cancer treatment at high and low volume centers	Gourin et al. [32]	1981	Low volume hospitals LOS: 12.9 days, $p = 0.003$	High volume hospitals: 10.6 days	Retrospective regional based cohort	Low

with T3 and T4a cancers [15]. Overall and disease-free survival were significantly higher when patients were treated with TL + A. Patients treated with NOP had a 2.4–4.1 times increased risk of disease recurrence and death. Stokes et al. used the national cancer database to show that the majority of T4 laryngeal cancers have improved overall survival with TL + A versus CCRT [14]. Al-Gilani et al. published a SEER and Medicare database analysis of T3 laryngeal cancers and found that those treated with TL + A had improved survival, and those treated with NOP had a notably increased risk of a non-functional larynx [9]. Another study conducted by Grover et al. showed increased risk of death in patients with T4a disease who are treated with CRT rather than with primarily surgical management. (HR 1.43, $p < .005$) [19]. Similarly, Megwalu and Sikora showed that nonsurgical treatment in stage III and IV laryngeal cancer has poorer overall survival when compared to surgical treatment [13].

Sanabria et al. investigated the issue of generalizing the results of NOP equivalence studies. They included three categories of variability where population studies may not match those of a controlled clinical trial: patient characteristics, provision of care, and clinical trial activities [20]. With regard to patient characteristics, those selected for a clinical trial are typically less burdened with significant comorbidities and must meet stringent inclusion and exclusion criteria that are not present when the intervention is applied broadly. This suggests that better guidelines for allocation to treatment and screening of patients would help bring the general population more in line with study results. With regards to provision of care, factors such as affordability of treatment, socioeconomic issues, and intolerance of the selected treatment give rise to discrepancies between the clinical trial and the real world. This suggests that patients should be considered on an individual basis with assessment of care goals, taking into account the presence of risk factors for failing to complete treatment. The third issue is an inherent complexity bias where the treatment offered through studies could only be fully achieved in the setting of a carefully controlled trial. Protocols were in place to assess and refer patients through different departments, this is not universal or consistent in some centers and practice settings. Other issues discussed include the predominance of T3 disease with only small percentage of T4a disease in the VA trial, as well as failure to stratify the T3 disease based upon pre-treatment laryngeal function and tumor volume, which can significantly impact the outcome of preservation of function.

Looking specifically at T3 disease, A French study, GETTEC, which was comprised of almost entirely T3 disease included a large majority of patients with significant pre-treatment dysfunction due to vocal cord fixation. This randomized controlled study showed worse overall survival with chemotherapy followed by radiation when compared to TL + A [21]. Other studies comparing outcomes in T3 disease include a meta analysis by Luo et al., which showed no statistical difference in overall survival in patients treated with induction chemotherapy followed by radiation versus TL + A [22]. However, this meta-analysis was limited by few

studies with adequate design to compare the two groups and was heavily influenced by the data of the VA trial.

Additionally, there were two retrospective cohort studies specifically involving patients with T3N0M0 laryngeal cancer. Hoffman et al. found there was no statistically significant difference in 5-year overall survival in patients who underwent CRT compared to total laryngectomy alone [7]. Survival was 59.3% vs. 63.3% respectively with no statistically significant difference observed between the two ($p = .503$). Similarly, Ko et al. found that there was no statistically significant difference in 5-year overall survival between patients treated with radiation-based approaches and those treated with TL + A [23].

A systematic review conducted by the ASCO in 2006 and again in 2017 yielded a few other high and moderate-level of evidence recommendations [24]. The guidelines are based upon a small number of prospective trials, meta analyses, and a multitude of single institutional cohort and population studies. One significant recommendation from this review is that patients with pretreatment laryngeal dysfunction and/or high tumor burden would benefit from surgical treatment as opposed to NOP. It is generally accepted that patients with pre-treatment laryngeal dysfunction (i.e. severe aspiration, the need for a tracheostomy) are better served with TL + A as it is highly unlikely that the dysfunction will be reversed with CRT [12]; however, this has not been confirmed in a prospective manner. Laryngeal dysfunction tends to correlate with tumor volume [25, 26]; thus, some groups have stratified T3 disease by tumor volume to determine which patients have the best chance of functional laryngeal preservation and survival with NOP. A number of studies have shown that as laryngeal tumor volume increases, survival decreases [25–28]. Most recently, Dziegielewski et al. studied the University of Florida prospective head and neck cancer data base to determine survival in T3 glottic cancers treated with NOP based on tumor volume [29]. They found that the 5-year control rate for T3 glottic cancers with volumes <2.5 cc was 78% with NOP; the disease specific 5-year survival was 96%. Patients with tumors ≥2.5 cc on pre-treatment CT scans had a significantly worse locoregional control rate (49%) versus their lower volume counterparts (78%) [29].

Other factors have shown significance when selecting treatment modality for laryngeal cancer. Patients with poor performance status, pre-treatment aspiration, poor lung function, and comorbid conditions do not tolerate NOP well, may not finish prescribed treatment, and often eventually need a laryngectomy due to chronic aspiration. TL + A is better tolerated in these patients and provides excellent survival outcomes as well as lower feeding tube dependence [30, 31].

Treatment center characteristics also play a role in advanced laryngeal cancer outcomes [32]. In a study of patients with stage 4 disease, Chen and Halpern found that there was a significantly higher risk of death (hazard ratio 1.43) when comparing CRT to TL [8]. The study includes patients treated not only in large cancer

centers but also in smaller practice settings and postulates that the difference observed could reflect a difference in the populations studied in cancer centers when compared to those in all practice settings. Gourin et al. [32] and Nieman et al. [31] have demonstrated that survival and quality outcomes improve at high volume surgical and radiation therapy centers compared to low volumes centers. However, in reality, treatment decisions and referral patterns do not always take these factors into consideration.

An additional recommendation from the 2006 ASCO review was that all patients should receive evaluation by a multidisciplinary team prior to treatment [24]. The most recent update of this recommendation states that not only should patients be evaluated by primary treatment teams, but also by physical rehabilitation, speech and language specialists, dieticians, and dental specialists prior to treatment. This recommendation seeks to implement coordination among disciplines for optimal outcome in NOP protocols. It also serves to push towards more rigorous selection of patients, increasing the likelihood that appropriate patients will be selected for NOP.

At the outset of treatment, patients often have little understanding of anticipated treatment outcomes and their preferences often differ from providers. Studies have shown that medical professionals assigned different utility value to health states following treatment than patients faced with the same choices [33]. Providers assigned a higher value to post-treatment states than patients, and had a statistically different perception of CRT and its resulting complications; moreover, providers assigned a higher value of CRT and adjuvant treatment than patients [33]. Proper patient counseling and opportunities to review treatment goals prior to therapy may preserve autonomy and mitigate undesired health states to improve quality of life.

Lastly, functional outcomes must be examined to help differentiate treatments with equivalent survival. A study evaluating functional aspects of life after TL + A in patients with T4 disease found that overall, 82% of patients who underwent total laryngectomy had a swallowing score rated as normal to only slightly impaired [34]. The same study also demonstrated acceptable vocal ability in 80% of those who received voice prosthesis. These findings suggest that patients generally achieve good functional outcomes in the areas that they likely find important for quality of life even without a larynx [34]. Unfortunately, there is a significant late toxic effect associated with NOP. Feeding tube dependence rates, which may underestimate the true rate of dysphagia, has been estimated in various studies to be between 10–41% at 1 year and 5–22% at 5 years following organ preservation protocols [35]. Another retrospective study assessing tracheostomy and aspiration rates of NOP compared to TL + A showed 20% of induction chemotherapy followed by radiotherapy or CCRT patients were tracheostomy dependent at last contact and had an aspiration rate of 22% versus a 9% aspiration rate related to malfunctioning TEP in TL + A group [36, 37].

Advanced laryngeal cancer with poor pre-treatment function (aspiration, gastrostomy tube dependence, tracheostomy dependence) should undergo total laryngectomy with adjuvant therapy (quality of evidence moderate, strong recommendation).

T3N0 laryngeal cancer may be considered for non-surgical organ preserving therapy (quality of evidence high, conditional recommendation).

T3 glottic cancer with a tumor volume <2.5 cc may be strongly considered for non-surgical organ preserving therapy (quality of evidence low, conditional recommendation).

T4a laryngeal cancers should undergo total laryngectomy with adjuvant therapy (quality of evidence moderate, conditional recommendation).

A Personal View of the Data

The results of the VA and RTOG 91-11 trials have been broadly applied to all advanced laryngeal cancers at many institutions. However, subsequent population-based data has failed to support these results due to a number of confounding factors. While many T3 cancers can achieve maximal survival with NOP and a functional larynx post-treatment, there are still many patients who fail. T3N0 glottic cancers with pre-treatment tumor volumes <2.5 cc tend to have an excellent chance of functional laryngeal preservation and survival. Larger T3 laryngeal cancers or patients with significant aspiration or who require a pre-treatment tracheotomy are likely to have better outcomes with TL + A. Patients with T4a cancers who are cured with NOP are often left tracheostomy and/or gastrostomy tube dependent. Therefore, these patients should be recommended TL + A as per NCCN guidelines. Regardless of treatment modality, all advanced laryngeal cancers should be treated by a multidisciplinary team at a high-volume institution. Academic tertiary care centers with multidisciplinary teams have been shown to provide improved survival, functional, and quality of life outcomes for advanced laryngeal cancer as compared to low-volume private and community hospitals (Table 11.2).

Conflicts of Interest None.

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Surgery or Radiation Therapy for Early Stage Glottic Cancer

12

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Introduction

Laryngeal carcinoma is one of the most common upper aerodigestive tract malignancies. Given its early stage, high cure rate, and low concern for metastasis, early glottic carcinoma is unique in that the focus is not only on an oncologically sound method of treatment but one that also optimizes voice outcomes. Traditionally, radiation has been the most common method of treatment for these types of cancers. However, since first described by Strong and Jako in 1972, we have seen a rise in transoral laser microsurgery (TLM) [1]. Choosing between these treatment options can often be perplexing for a surgeon. This chapter will review the oncologic efficacy and voice outcomes between radiation therapy and transoral laser surgery.

Literature Search Strategy

Based on the PICO table (Table 12.1), a Pubmed search incorporating the terms "early glottic cancer" and "radiation" and "transoral laser" "laser surgery" were used to review the literature. The bibliography of applicable articles was also reviewed. The search was narrowed to focus on comparisons of radiation to TLM for T1 and T2 glottic cancers. Articles specifically describing the methods for treatment for early glottic cancer or those that included the treatment of advanced glottic cancer were excluded. Studies were included if they were published after 2000. Within this literature, there are no randomized controlled trials and preference was therefore given to meta analyses studies.

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Table 12.1 PICO table

Population	Intervention	Comparison	Outcomes
Adults with T1–T2 N0 squamous cell carcinoma of the glottis	Transoral laser microsurgery (CO_2 laser)	Radiation therapy	**Oncologic**: Laryngeal preservation rate, local control, disease specific survival, overall survival **Acoustic and aerodynamic outcomes**: Maximum, phonation time, fundamental frequency (F0), jitter, shimmer **Subjective outcomes**: GRBAS, VHI

Results

There are to date no appropriate randomized controlled trials evaluating surgery versus radiation [2]. Studies comparing TLM to radiation are confined to retrospective and prospective studies. Therefore, only meta analyses were reviewed. All meta analyses had the inclusion criteria of primary T1 glottic cancer. One meta-analysis included T2 glottic cancers. Some studies were used in multiple meta analyses.

Oncologic Outcomes

Laryngeal Preservation Rate

Four meta-analysis studies evaluated laryngeal preservation rates for T1 glottic cancers. Associated functional outcomes, including dysphagia requiring diet modification or the need for tracheostomy, were not included in these studies.

Three found superior laryngeal preservation rates with TLM over radiation therapy [3–5]. Mo et al. evaluated ten studies with significantly greater laryngeal preservation rates in TLM (OR 5.81, 95% CI 3.36–10.05, $p < 0.00$) [3]. Similar findings are seen in a meta-analysis by Huang et al. evaluating nine studies comparing TLM to radiation (OR = 3.86, 95% CI = 1.47–10.13, $p = 0.006$) [4].

Abdurehim et al. evaluated eight studies comparing TLM to radiation. However, there was high heterogeneity among studies. Therefore, studies were separated into those published before and after 2000. Once separated, heterogeneity was eliminated, and total pooled effect showed better preservation rates with TLM (OR 3.11 95% CI 1.16–8.34, $p = 0.02$) [5].

One meta-analysis showed a trend towards improved laryngeal preservation rates with TLM but there was no statistical significance (OR 0.84, 95% CI 0.36–1.95, $p = 0.68$). This analysis also included pooled single arm studies as well as comparative studies [6] (Table 12.2).

Table 12.2 Oncologic outcomes of transoral laser surgery and radiation therapy in the treatment of T1 glottic cancer—laryngeal preservation rate

	Intervention	n	Pooled OR	95% CI	P value	Type of study	Quality of evidence
Abdurehim	TLM (CO_2)	612	3.11	1.16, 8.34	0.02 Favoring TLM	Meta-analysis	Moderate
	Radiation	563					
Mo	TLM (CO_2)	666	5.81	3.36, 10.05	<0.00 Favoring TLM	Meta-analysis	Moderate
	Radiation	786					
Higgens	TLM (CO_2)	267	0.84	0.36, 1.95	0.68	Meta-analysis	Moderate
	Radiation	164					
Huang	TLM (CO_2)	618	3.86	1.47, 10.13	0.006 Favoring TLM	Meta-analysis	Moderate
	Radiation	498					

Control and Survival

Four meta-analysis studies evaluated local control outcomes of T1 cancers. No studies found significant difference in T1 local control outcome [3–6]. Abdurehim et al. evaluated ten studies, however the heterogeneity was high between studies secondary to differences in radiation dosing and type of treatment. Therefore, subgroups were created that eliminated heterogeneity with a pooled effect showing no difference between radiation and TLM (OR 0.94 95% CI 0.57–1.57, p = 0.83) [5]. Higgens evaluated both single arm studies as well as comparative studies showing no differences in 5-year local control (OR 0.84, 95% CI 0.36–1.95, p = 0.68) [6]. Mo et al. evaluated nine studies showing no differences between TLM and radiation (OR 0.98, 95% CI 0.7–1.38, p = 0.91) [3]. Huang et al. had similar findings among nine studies evaluated (OR 1.08, 95% CI 0.73–1.60, p = 0.70) [4].

One meta-analysis evaluated TLM of T1 and T2 glottic cancers in comparison to radiation therapy. They evaluated local control at 2, 3 and 5 years with no significant difference during any time period (2 years: RR = 0.55, 95% CI 0.28–1.09, p = 0.09; 3 years: RR = 0.84, 95% CI 0.48–1.47, p = 0.55; 5 years: RR = 0.90, 95% CI 0.59–1.39, p = 0.63). However, only one study of those evaluated looked at T2 so no discernable conclusions can be made concerning T2 glottic cancers [7] (Table 12.3).

Three meta-analysis evaluated disease specific survival of T1 glottic cancers. No differences were found among any of the studies in disease specific survival [4–6] (Table 12.4).

Four meta-analysis studies looked at overall survival in T1 cancers. Mo et al. evaluated nine studies finding that TLM was significantly superior to radiation in overall survival (OR = 1.35; 95% CI 1.02–1.79, p = 0.04) [3]. Higgens found a significant trend towards improved overall survival with TLM (OR 1.48, 95% CI 1.19–1.85, p < 0.004), however only single arm studies were evaluated [6]. Two meta analyses, Abdurehim et al. looking at seven studies (OR 1.22, 95% CI 0.89–1.66;

Table 12.3 Oncologic outcomes of transoral laser surgery and radiation therapy in the treatment of T1 glottic cancer—local control

	Intervention	n	Pooled OR/RR	95% CI	P value	Type of study	Quality of evidence
Abdurehim	TLM (CO_2)	765	0.94	0.57, 1.57	0.83	Meta-analysis	Moderate
	Radiation	680					
Feng	TLM (CO_2)	119 (2 years) 205 (3 years) 131 (5 years)	2 years: RR = 0.55 3 years: RR = 0.84 5 years: RR = 0.90	2 years: 0.28, 1.09 3 years: 0.48, 1.47 5 years: 0.59, 1.39	0.09 0.55 0.63	Meta-analysis	Moderate
	Radiation	106 (2 years) 223 (3 years) 186 (5 years)					
Mo	TLM (CO_2)	565	0.98	0.7, 1.38	0.91	Meta-analysis	Moderate
	Radiation	673					
Higgens	TLM (CO_2)	315	0.81	0.42, 1.55	0.52	Meta-analysis	Moderate
	Radiation	247					
Huang	TLM (CO_2)	671	1.08	0.73, 1.60	0.70	Meta-analysis	Moderate
	Radiation	546					

Table 12.4 Oncologic outcomes of transoral laser surgery and radiation therapy in the treatment of T1 glottic cancer—disease-specific survival

	Intervention	n	Pooled OR	95% CI	P value	Type of study	Quality of Evidence
Higgens	TLM (CO_2)	592	0.93	0.65, 1.32	0.68	Meta-analysis	Moderate
	Radiation	1606					
Huang	TLM (CO_2)	472	1.98	0.86, 4.54	0.11	Meta-analysis	Moderate
	Radiation	587					
Abdurehim	TLM (CO_2)	626	1.60	0.79, 3.26	0.19	Meta-analysis	Moderate
	Radiation	565					

p = 0.21) and Huang et al. evaluating nine studies (OR 1.26, 95% CI 0.9–1.76, p = 0.17), found no significant differences in overall survival [4, 5] (Table 12.5).

Voice Outcomes

Voice outcomes are difficult to evaluate as measures used in studies are not always consistent and there is often an emphasis on subjective evaluation over objective voice measures. Additionally, patient numbers in voice outcomes

Table 12.5 Oncologic outcomes of transoral laser surgery and radiation therapy in the treatment of T1 glottic cancer—overall survival

	Intervention	n	Pooled OR	95% CI	P value	Type of study	Quality of evidence
Higgens	TLM (CO_2)	1023	1.48	1.19, 1.85	0.0004 Favors TLM	Meta-analysis	Moderate
	Radiation	1081					
Huang	TLM (CO_2)	481	1.26	0.9, 1.76	0.17	Meta-analysis	Moderate
	Radiation	454					
Mo	TLM (CO_2)	554	1.35	1.02, 1.79	0.04 Favors TLM	Meta-analysis	Moderate
	Radiation	706					
Abdurehim	TLM (CO_2)	520	1.22	0.89, 1.66	0.21	Meta-analysis	Moderate
	Radiation	547					

studies are often small with poor follow up. Two meta-analyses have evaluated aerodynamic and acoustic voice outcomes in T1 glottic cancers. The first analysis found no statistically significant differences among eight studies looking at maximum phonation time and six studies looking at jitter (a measure of frequency instability) and shimmer (a measure of amplitude instability). They found significant differences among seven studies evaluating fundamental frequency (Fo) favoring radiation [5]. However all parameters evaluated had high heterogeneity among the studies evaluated. The second meta-analysis found maximum phonation time (MPT) and fundamental frequency (Fo) to favor radiation over TLM and measurements of jitter and shimmer to favor TLM over radiation. However, patient numbers were small within studies with high heterogeneity among all parameters evaluated [6].

Similar problems seen in objective voice outcome data are seen with subjective outcome data. Feng et al. attempted to evaluate six studies looking at subjective evaluations of the voice but heterogeneity was too great to perform meta-analysis [7]. Three meta-analysis studies were able to look at subjective evaluations of the voice. Two evaluated the voice handicap index (VHI) and one the GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale. The two that evaluated VHI showed no statistical significance between radiation and TLM. In both studies, heterogeneity was high [5, 8]. The one meta-analysis that looked at the GRBAS scale did find a trend towards favoring TLM ($p < 0.001$), however only two studies were evaluated with small patient numbers in each group [6].

Given superior laryngeal preservation rates and otherwise equivalent oncologic outcomes, TLM should be considered for T1 glottic cancers in medically appropriate patients able to tolerate general anesthesia (evidence quality moderate, conditional recommendation).

A Personal View of the Data

As a laryngeal surgeon, it is my preference to treat early cancers, both T1 and T2, with TLM in most patients who are surgically eligible. Radiation is a once in a lifetime treatment whereas TLM can be used multiple times in the same area. TLM also preserves the option of radiation in the future should the need arise. Radiation has a significant impact on multiple aspects of the laryngeal complex. Fibrosis of both diseased and non-diseased aspects of the glottis, destruction of glands of the saccule necessary for lubrication needed for optimal glottal vibration, long term swallowing concerns including esophageal stenosis, as well as increasing the risk for secondary cancers within the radiated field should make one appreciate the gravity of exposing a patient to radiation for such an early stage of cancer when there are equivalent oncologic outcomes in TLM. Additionally, a recent study by McNeil et al. finds that, when presented with the option of either TLM or radiation, patients prefer TLM [9]. TLM has additionally been found to be more cost effective compared to radiation [6].

With that being said, not every patient is a candidate for TLM. Patients who are not healthy enough to tolerate a general anesthetic or cannot be appropriately exposed endoscopically are not candidates for this procedure. Surgeons wanting to embark in TLM surgery should ensure they have the appropriate equipment for maximum exposure of the entire larynx including the anterior commissure.

Not thoroughly discussed in this chapter but worth noting are the different types of laser that can be used for TLM. Traditionally, CO_2 is most often used in these surgeries, however since 2006, there are been a rise in surgeons utilizing the pulsed potassium titanyl phosphate (KTP) laser. The KTP laser utilizes the principle of photoangiolysis of microcirculation in and around a lesion with the goal of ultranarrow margins as first described by Zeitels et al. [10] This differs in the wider margins obtained using the CO_2 laser and allows the opportunity for greater normal tissue preservation. While there have been large single center evaluations of KTP with equivalent oncologic and voice outcomes to those of CO_2 laser or radiation, there are to date no meta-analysis or randomized controlled trials that include use of the KTP laser [11–13]. Future evaluations of this treatment method on a larger scale will hopefully increase its use in the early glottic cancer population.

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Part IV

Thyroid/Parathyroid

How Should Well Differentiated Thyroid Cancer with Distant Metastatic Disease Be Managed?

13

Tanaz Vaghaiwalla and Peter Angelos

Introduction

Well differentiated thyroid cancer (WDTC) typically presents with cancer limited to the thyroid gland with or without spread to regional lymph nodes of the central or lateral neck [1–3]. Patients who present with distant metastatic disease have outcomes that are less favorable and associated with a higher morbidity and mortality [1–5]. Distant metastatic disease can be divided into metastatic pulmonary disease and extra-pulmonary disease, which may include primarily brain and skeletal disease. An aggressive management strategy is recommended by current national and international guidelines which includes locoregional control with surgery and postoperative radioactive iodine (RAI) therapy for [1–3]. Treatment recommendations consist of total thyroidectomy, lymphadenectomy if indicated by presence of disease in the central and/or lateral neck, and subsequent adjuvant treatment with RAI therapy with varying possible dosing regimens. Distant metastases are uncommon but reportedly occurs in 1–23% of patients with well differentiated thyroid cancer [3–5]. Although an uncommon entity, distant metastatic disease is the most frequent cause of cancer related death among these patients. Long term disease specific survival is estimated to be 23–35% in those patients diagnosed with distant metastases secondary to well differentiated thyroid carcinomas [4].

The objective of this chapter was to review the current evidence in managing patients with WDTC with distant metastatic spread and to present our practice experience.

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Table 13.1 How should well differentiated thyroid cancer with distant metastatic disease be managed?

Population	Intervention	Comparison	Outcomes
Adults with WDTC and distant metastatic disease	Radioactive iodine treatment Metastasectomy Clinical trials	No radioactive iodine treatment, surgical intervention, or clinical trial interventions	Incidence of distant metastatic disease in WDTC Survival Prognostic factors

Literature Search Strategy

Based on the PICO table (Table 13.1), Pubmed and CENTRAL searches incorporating the terms "differentiated thyroid carcinoma", "papillary", and "follicular" and "distant metastatic disease" were used to review the literature. The bibliography of articles was also reviewed, and papers were reviewed and incorporated when applicable. The search was narrowed to focus on management and outcomes of differentiated thyroid carcinoma with distant metastatic spread in primarily adults. Studies were included if they were published from 1997–2017. The majority of the data on this subject matter arises from retrospective studies and single or multi-institutional studies. Current national and international association guidelines were included. We elected to focus on pulmonary metastases and extra-pulmonary metastases, including skeletal and brain disease.

Result

Pulmonary Metastases

Distant metastatic disease can be divided into metastatic pulmonary and extra-pulmonary disease, which can include primarily skeletal and brain disease. The management of the patient with pulmonary metastases is dependent on several factors which includes the size of the nodules, macronodular or micronodular, and tumor avidity for RAI treatment [1–5]. While many dosing regimens exist, there is no current consensus. According to recent guidelines, the generally recommended dose for both macronodular or micronodular pulmonary metastases ranges from 100–200 mCi when RAI is administered empirically to patients aged <70 years old, and lower range of 100–150 mCi to patients aged ≥70 years old [2]. In order to limit RAI retention, dosimetry estimates may be employed to limit retention to 80 mCi at 48 h and 200 cGy to bone marrow and this recommendation has not changed over the last 10 years [1, 2].

Macronodular pulmonary metastases can be managed with RAI when shown to be iodine avid [1–7]. One study involving 444 patients with well differentiated thyroid cancers treated for distant metastases every 3–9 months with 100 mCi during the first 2 years and then annually until no uptake was visualized on scan.

In patients who achieved negative studies who had lung metastases only, the median cumulative activity given to patients was 220 mCi, ranging from 65 to 700 mCi [7]. The particular treatment regimen is determined by several factors such as age, response to treatment, and any evidence of disease progression between treatment administrations [2, 7]. The response to treatment of macronodular metastases may be demonstrated by following objective clinical variables in order to guide therapy such as thyroglobulin levels or change in lesion size [7]. Remission is less likely with macronodular metastases than with micronodular metastases [2]. RAI therapy is strongly recommended for the treatment of pulmonary micronodular metastases. RAI should be repeated at intervals of approximately 6–12 months while response to treatment and progression of disease is monitored [1–3]. RAI treatment was found to be more effective in younger patients (<40 years of age) and smaller pulmonary metastasis [7].

Pulmonary metastases which do not demonstrate RAI avidity are an entity that remains a therapeutic challenge for clinicians [1, 4–9]. RAI is not recommended as a treatment modality in this disease subgroup, and there are no set guidelines for the management of this disease. Interestingly, a lack of RAI avidity may not be the only predictive factor for disease progression. One retrospective study of 199 patients with follicular cell-derived thyroid cancer with lung metastases demonstrated that there was a strong correlation with overall survival and clinical progression free survival (defined as a 30% increase in longest diameter of the lesion or new lesions), which was shorter not only in RAI refractory disease, but also poorly differentiated cancers, males, older age patients >45 years old, metastases greater than 1 cm, and fluorodeoxyglucose avid lesions [8]. When these factors are taken together, they may identify a subset of patients that benefit from early discussion of other novel treatment modalities. Systemic cytotoxic chemotherapeutic agents, specifically doxorubicin, have been studied as monotherapy or used in combination with another agent. The use of chemotherapeutic options in distant metastatic disease is limited by their toxic profiles and provide little impact on survival or remission [9]. Combination of chemotherapeutic agents does not appear to add significant benefit. Several clinical trials involving anti-angiogenic agents are available for eligible patients with non-RAI avid pulmonary metastases. For patients with symptomatic disease, such as pain or bleeding secondary to pulmonary metastases, resection of metastases, ablative therapies, and external beam radiation may be used [1–4]. In RAI non-avid metastatic lesions, novel therapeutic targets such as kinase inhibitor sorafenib is a potential treatment option. In recent randomized controlled trial phase 3 study, sorafenib demonstrated improved progression free survival of 10.8 months compared to placebo 5.8 months (hazard ration 0.59; 95% CI, 0.45–0.75, $p < 0.0001$), however no overall survival difference was demonstrated [10]. Another potential therapeutic agent is lenvatinib the oral tyrosine kinase inhibitor to several targets including vascular endothelial growth factor rector, platelet derived growth factor, fibroblast growth factor receptor, and RET and KIT proto-oncogenes. In a randomized double-blind phase 3 trial, patients with RAI refractory disease who took lenvatinib

dosage 24 mg/day demonstrated improved progression free survival compared to placebo. Two treatment arms stratified patients by age (median age 56 and 71 years of age) and in both arms there was a statistically significant improvement in progression free survival with lenvatinib of 20.2 months compared to 3.2 months for those who took placebo (HR 0.27; 95% CI, 0.17–0.27; $p < 0.001$) [11].

Pulmonary micronodular metastases should be treated with radioactive iodine (RAI) therapy (quality of evidence moderate; conditional recommendation).

Pulmonary macronodular metastases should be treated with RAI therapy if shown to be RAI (quality of evidence low; conditional recommendation).

Bone Metastases

Extrapulmonary metastases include bone metastases and are associated with a worsened prognosis. Patients with resectable disease who undergo surgery experience improved survival [12]. For patients with symptomatic isolated bone metastasis, surgery is recommended [1–3]. Survival is improved in this patient population. One retrospective study of 245 differentiated thyroid cancer patients with bone metastases evaluated skeletal events, demonstrated the increased morbidity of this disease. The majority of patients presented with a skeletal event, defined as spinal cord compression, pathological fracture, requirement for external beam radiation or surgery, and malignancy related hypercalcemia, at the time of their diagnosis while the remainder presented at a median of 5 months from the time of initial diagnosis [13]. Unresectable disease may be palliated with external beam radiation therapy, RAI, or bisphosphonate infusions. Selective arterial embolization and/or external radiation may also be used; however, these modalities are not associated with improved survival [12]. Iodine-avid lesions should be treated with RAI for improved survival after resecting gross disease. One single institution study evaluating prognostic factors and treatment strategy for patients with bone metastases in 52 of 1398 patients who underwent initial thyroidectomy for WDTC demonstrated a significant 5-year survival advantage in patients who underwent RAI therapy at 59% compared to 23% for those who did not undergo RAI therapy ($p = 0.0028$) [14]. This improved prognosis appeared dependent on the dose of RAI with a cumulative RAI dose ranging from 100 to 600 mCi [14].

RAI is recommended for RAI-avid tumors metastatic to the bone (quality of evidence moderate; conditional recommendation).

Surgical resection is recommended for isolated resectable bone metastases (quality of evidence moderate; conditional recommendation).

Brain Metastases

Brain metastases associated with well differentiated thyroid cancer are rare and estimated to range from 0.5–1% of patients [1–3, 15, 16]. The treatment of brain metastases has few options and there is limited data which arises from retrospective analyses and single institution studies. Surgery is associated with improved survival for both RAI avid and non-avid disease [1]. If surgical resection is not possible, external beam radiation therapy may be employed. RAI therapy is recommended for RAI avid lesions [1, 3]. In one retrospective series of 16 patients with brain metastases treated with local therapies, resection of brain metastases was associated with a longer survival of 20.8 months (n = 13 patients, ranging, 5.2–55.3 months), compared to 2.7 months (n = 3, ranging, 0–6.4 months). Of note while the majority of the patients had either papillary or follicular carcinomas, this series included 3 of 16 patients with medullary thyroid cancer, Hurthle cell, or anaplastic carcinomas [15]. In another single institution study of 25 patients, 16 patients had metastases to the brain, while 9 patients had metastases to the skull. A total of 96% of patients (24 of 25 patients) had extracranial disease at the time of the initial diagnosis of cranial metastases. The factors associated with improved survival were the metastatic site involving only skull ($p < 0.006$), well differentiated histology ($p < 0.001$), and surgical resection ($p < 0.001$) [16].

> Surgical resection is recommended for resectable brain metastases (quality of evidence low; conditional recommendation).

A Personal View of the Data

The approach to treatment of patients with well differentiated thyroid cancer and distant metastatic disease at our institution is in keeping with the current national guidelines. Our institutional practice is to take a multidisciplinary approach to the patient's care. From a surgical standpoint, our practice is to resect all detectable disease, with total thyroidectomy and locoregional lymph node dissection of the central and lateral neck when indicated. Surgical resection of distant metastasis is recommended if the lesion is amenable to resection and when the patient's performance status is amenable for undergoing the procedure. While the recommendations for pulmonary metastases which are RAI avid are stronger and demonstrate an improved survival, particularly in younger patients (<45) with lower metastatic disease burden, there is unfortunately limited data regarding treatment of RAI non-avid metastases. It is in this patient population where significant research is needed in the form of clinical trials targeting cell cycle, angiogenesis, and signaling pathways. Overall, there is a paucity of data on how best to manage these challenging well-differentiated thyroid cancer patients with distant metastases and more data is necessary to make strong recommendations.

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14 Should Routine (Prophylactic) Central Neck Dissection Be Performed for Clinically Node Negative Well-Differentiated Thyroid Carcinoma?

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Introduction

The role of the prophylactic central neck dissection at the time of thyroidectomy (PCND) for well-differentiated thyroid carcinoma (WDTC) has been debated extensively. While there is a great deal of available literature on this topic, conclusive studies are lacking [1–7]. The primary argument supporting PCND is that the initial surgery is the least invasive and safest time to remove central neck nodes that are likely to harbor occult metastases. Naysayers argue that most occult lymph nodes are unlikely to be clinically relevant. By definition, PCND is completed in patients without clinically apparent metastatic lymphadenopathy. WDTC has an excellent prognosis, with recent guidelines recommending less extensive surgery and even observation in some cases [1]. In such cases of indolent carcinoma without obvious metastasis, can the risks of additional surgery be justified?

Herein, we will address three specific questions that all patients and surgeons must consider when deciding the role of PCND. First, does PCND improve overall survival (OS) when compared to observation of the clinically negative neck in patients with WDTC? Second, does PCND improve disease free survival (DFS) among the same population (i.e. will PCND prevent the need for further surgery or intervention)? Third, are patients more likely to suffer increased complications when PCND is completed? If PCND improves OS or DFS significantly, then perhaps an increased risk of complications can be justified. If, however, the improved OS or DFS is marginal, then risks must be very low before we can advocate routine PCND. We will conclude by reviewing these findings in the era of the 2015 ATA

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guidelines, when hemithyroidectomy is indicated for papillary microcarcinomas and permitted for all WDTC less than 4 cm.

Literature Search Strategy

Based on the PICO format detailed in Table 14.1, PubMed and Cochrane databases were electronically searched for all studies published in English in PubMed or cited by studies published in PubMed between 2000 and 2018 (search completed May 2018). The terms searched included "thyroid and central neck dissection" for the Cochran Library and "(thyroid carcinoma) AND (prophylactic central neck dissection)" was used in PubMed. The "similar articles" option in PubMed were used to broaden the search. A total of 335 articles were identified. All retrieved titles and abstracts were reviewed by two clinicians to identify studies specifically comparing outcomes of TT alone versus TT + PCND in patients with WDTC. In the instance of systematic reviews and meta-analyses, only two well performed meta-analyses were selected to avoid repeated review of the pooled data. Additionally, the reference list of each selected article was reviewed to ensure a complete assessment of the current literature. After removing duplicate entries and articles with duplicate patient cohorts, a total of 35 unique articles were reviewed for this chapter. Within the included studies, we reviewed for outcomes including overall survival (OS), disease free survival (DFS), and complications such as RLN injury and hypocalcemia.

Results

Question 1: Does PCND at the Time of TT Improve Overall Survival When Compared to Observation with Salvage?

With any oncologic intervention, the ultimate goal is to prolong overall survival (OS). Because WDTC is an indolent disease, determining a difference in OS between therapeutic decisions requires both a large number of patients and prolonged follow up. By necessity, a majority of studies examining OS in WDTC are retrospective, suggesting that the evidence will be of a low to moderate quality. Likewise, they may require pooling of several data sets, thus incorporating additional variables that are difficult to control and may lead to lower quality studies. Within those constraints, there is no single study with a high quality of evidence that demonstrates improved overall survival with PCND.

Table 14.1 PICO search strategy

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with clinical node negative well differentiated thyroid carcinoma (WDTC)	Prophylactic central neck dissection (PCND) at time of total thyroidectomy (TT)	Observation with salvage CND if necessary	Overall survival (OS), disease free survival (DFS), recurrent laryngeal nerve (RLN) paralysis (temporary vs permanent), hypocalcemia

Table 14.2 Effects of PCND on overall survival (OS)

Study	Patients	Length of follow-up	OS with PCND	OS without PCND	p-Value	Quality of evidence
Barczynski [8]	640 pts., 282 TT/358 TT + PCND	TT Median: 128.8 m Mean: 120 m TT + PCND Median: 126.4 m Mean: 120 P 0.121	5y: 97.1% 10y: 96.2	5y: 94.6% 10y: 91.5	5y: P 0.101 10y: P 0.014	Moderate
Moreno [9]	252 pts., 133 TT/119 TT + PCND	Mean: 71.5 m	5y: 98.1% 10y: 82.6%	5y: 97.4% 10y: 91.1%	P 0.93	Moderate
Costa [10]	244 pts., 118 TT/126 TT + PCND	TT = 64 m TT + PCND: 47 m	95.2%	93.2%	P 0.96	Moderate
Dobrinja [11]	186 pts., 112 TT/74 TT + PCND	TT: 76 m TT + PCND: 37 m P < 0.0001	10y: 93%	10y: 91%	P 1.00	Moderate

Abbreviations: *TT* total thyroidectomy, *TT + PCND* total thyroidectomy and prophylactic central neck dissection

Improvements in OS could occur from at least two hypothetical mechanisms: by removing metastatic disease which would directly affect mortality or by identifying metastatic disease so that patients could be more accurately triaged for adjuvant therapies such as RAI. While direct measurements of surrogate markers will be discussed later in this chapter, some of the available literature surrounding OS is summarized in Table 14.2. Among all the studies reviewed, Barczynski et al. [8] reported an increase in overall survival associated with PCND at 10 years, while other studies failed to demonstrate improved overall survival attributed solely to PCND.

Question 2: Does PCND Result in Improved DFS When Compared to Observation (i.e., Does PCND Prevent Recurrence)?

With long-term survival in the 90-percentiles years after treatment of WDTC, it can be difficult to adequately assess OS without exhaustive studies using data from thousands of patients [12]. Disease free survival is the most frequently reviewed outcome measure for the role of PCND and acts as a surrogate for measuring the survival advantage in the treatment of WDTC. As with any surrogate, assumptions must be made that DFS somehow results in either improved OS or other improvements in quality of life (QOL). There is little data that exists to support either of these assumptions. Therefore, even though some studies suggest some improvement in DFS, we must interpret the data with caution. As mentioned previously, risks must be minimal to justify improvements in an unproven surrogate outcome measure. There is some evidence to suggest that PCND may improve DFS when Chen et al. [13] pooled data from 20 studies. Others have

calculated that approximately 31 patients would need to be treated with PCND along with TT to prevent one recurrence [14]. A table summarizing the effect of PCND on DFS is detailed in Table 14.3.

Question 3. Do Complications Increase with PCND?

The answers to the first two questions have established that there is no definitive OS advantage with PCND, but that there may be some marginal benefit at improving DFS. Again, the risks associated with PCND must be minimal to justify the intervention since it may not directly result in improved survival or QOL. Injuries to the recurrent laryngeal nerve (RLN) and hypocalcemia secondary to iatrogenic hypoparathyroidism are the most commonly described complications associated with PCND. Nerve injuries are theoretically more likely during central neck dissections because of the extensive dissection over the length of the RLN. Similarly, hypocalcemia is more common because of devascularization or incidental parathyroidectomy. Evidence exists that suggest an increased rate of temporary RLN injury, temporary hypoparathyroidism, and permanent hypoparathyroidism is associated with PCND. The increased risk of these complications, temporary or permanent, make the justification for PCND difficult. The effects of PCND on rates of RLN injury and hypocalcemia are summarized in Table 14.4.

> Patients with well differentiated thyroid carcinomas should not routinely undergo prophylactic central neck dissection (quality of evidence—moderate, weak recommendation).

A Personal View of the Data

Although expanding a thyroidectomy to include a central neck dissection is relatively straightforward, consideration of the risks and benefits in clinically node negative patients is critical. While the allure of surgically sterilizing the central neck is enticing, it is clear that a majority of occult central neck metastases are not clinically relevant. Current data supports a slightly improved DFS; however, the increased risk of complications does not justify routine PCND in most patients. In such a situation, more intervention is difficult to justify. We would also add the data from long-term observational series in Japan to further justify this point [39]. If expectant management without surgical intervention of known WDTC is occasionally appropriate, then aggressive management of clinically negative nodal basins where the patient is at an increased risk of permanent complications is difficult to justify. Randomized controlled trials are unlikely to be adequately powered to answer the role of the PCND or ipsilateral PCND because these procedures are unlikely to affect OS or DFS in a meaningful way [12].

In our practice, there are some exceptions where PCND is indicated, such as T3 and T4 tumors [1, 39]. Additionally, in situations where tumors have proven to be

Table 14.3 Effect of PCND on disease free survival (DFS)

Study	Patients	Length of follow-up	Recurrence rate with PCND	Recurrence rate without PCND	p-Value	Quality of evidence
Barczynski [8]	640 pts., 282 TT/358 TT + PCND	Median TT: 128.8 m TT + PCND: 126.4 m Mean TT: 120 m TT + PCND: 120 m P 0.121	4.2% 5y: 4.3% 10y: 5.5%	13.1% 5y: 6.6% 10y: 12.4%	P < 0.001 5y: P 0.213 10y: P 0.003	Moderate
Wang [14]	1740 pts., 995 TT/745 TT + PCND	NA	4.69%	7.93%	Not significant	High (Meta-analysis)
Moo [15]	81 pts., 36 TT/45 TT + PCND	Mean: 3.1y	4.4%	16.7%	P 0.13	Moderate
Moreno [9]	252 pts., 133 TT/119 TT + PCND	Mean: 71.5 m	5y: 4.4% 10y: 11%	5y: 4.1% 10y: 5.4%	P 0.79	Moderate
Gemsenjager [16]	117 pts., 88 TT/29 TT + PCND	Mean: 8.1y Median: 6.0y	4%	2%	Not reported	Moderate
Calo [17]	285 pts., 220 TT/65 TT + PCND	Median 100 m	0.45%	0%	Not reported	Moderate
Lee [18]	257 pts., 104 TT/53 TT + PCND	Mean TT: 49.2 m TT + PCND: 55.2 m P = 0.214	3.9%	3.3%	Not significant	High (Randomized cohort study)
Calo [19]	163 pts., 103 TT/30 TT+(i) PCND/30 TT+(b)PCND	Mean TT: 56.3 m TT+(i)PCND: 74.9 m TT+(b)PCND: 67.8 m P = 0.03	(i) 0% (b) 2.1%	3.9%	Not significant	Moderate
Ywata [20]	580 pts., 478 TT/102 TT + PCND	Mean TT: 67.4 m TT + PCND: 80.2 m P < 0.001	3.9%	1.5%	Not significant	Moderate

(continued)

Table 14.3 (continued)

Study	Patients	Length of follow-up	Recurrence rate with PCND	Recurrence rate without PCND	p-Value	Quality of evidence
Raffaelli [21]	186 pts., 62 TT/62 TT+(i) PCND/62 TT+(b)PCND	Mean TT: 25.5 m TT+(i)PCND: 25.1 m TT+(b)PCND: 24.9 m P = NS	(i) 1.6% (b) 0%	0%	Not significant	Moderate
So [22]	232 pts., 113 TT/119 TT + PCND	Mean TT: 45.4 m TT + PCND: 44.7 m P = 0.687	1.7%	3.5%	P 0.436	Moderate
Choi [23]	101 pts., 53 TT/48 TT + PCND	Mean 24.4 m	2.1%	3.7%	Not reported	Moderate
Popadich [24]	606 pts., 347 TT/259 TT + PCND	Mean TT: 50 m TT + PCND: 32 m P < 0.001	4%	22%	P 0.004	Moderate
Lang [25]	185 pts., 103 TT/82 TT + PCND	Median: 26.0 m	LRR: 3.7% Distant: 0	LRR: 2.9% Distant: 1.0%	Not reported	Moderate
Costa [10]	244 pts., 118 TT/126 TT + PCND	Mean TT: 64 m TT + PCND: 47 m	10y: 6.6% Total: 6.3%	10y: 7.1% Total: 7.7%	10y: P = 0.69 Total: P = 0.83	Moderate
Kim [26]	11,569 pts., 2834 TT/8735 TT + PCND	Median: 62.6 m	Total LRR: 2.1%	Total LRR: 2.9%	No reported	Moderate
			5y: 2.3%	5y: 3.0%		
			10y: 4.3%	10y: 4.1%		
			15y: 7.0%	15y: 6.6%	P = 0.485	
Dobrinja [11]	186 pts., 112 TT/74 TT + PCND	Mean TT: 76 m TT + PCND: 37 m P < 0.0001	5.4%	3.6%	P = 0.71	Moderate

Hyun [27]	152 pts., 87 HT/65 HT + PCND	Mean: 51.31 m	1.5%	14.9%	P = 0.017	Moderate
Korkmaz [28]	243 pts., 104 TT/139 TT + PCND	Median TT: 28 m TT + PCND: 29 m Mean TT: 30.7 m TT + PCND: 30.1 m P = 0.992	0%	0%	NA	Moderate
Zhang [29]	242 pts., 108 TT/134 TT + PCND	Median TT: 66 m TT + PCND: 61 m	2.2%	8.3%	P < 0.01	Moderate
Zuniga [30]	266 pts., 130 TT/136 TT + PCND	Mean: 6.9y Median: 6.1y	19% 5y: 14.4%	14% 5y: 11.8%	p = 0.19 5y: p = 0.72	Moderate
Chen [13]	16,681 pts., 5583 TT/11,098 TT + PCND	NA	2.52%	4.59%	Odds ratio 0.65 in favor of PCND 95% CI 0.48–0.88)	High (Meta-analysis)
Said [31]	864 pts., 830 TT/34 TT + PCND	Mean: 7.9y	2.9% 10y: 3.2%	2.8% 10y: 3.6	p = 0.95 10y: P 0.80	Moderate
Conzo [32]	752 pts., 390 TT/362 TT + PCND	Mean: 9.5y	3.3%	3.8%	Not significant	Moderate

Abbreviations: *TT* total thyroidectomy, *TT + PCND* total thyroidectomy and prophylactic central neck dissection; *(i)* ipsilateral, *(b)* bilateral, *m* months, *y* years

Bold values are statistically significant or represent higher levels of evidence

Table 14.4 Effects of PCND on rates of RLN injury and hypocalcemia (the absolute increase in the rate of injury or hypocalcemia is calculated by subtracting the rate of injury in TT from the rate of injury in TT + PCND)

Study	Patients	Absolute increase in RLN injury rates with PCND (temporary/permanent)	Absolute increase in hypocalcemia rates with PNCD (temporary/permanent)	Quality of evidence
Narendra [33]	50 pts., 25 TT/25 TT + PCND	4%/0% P not reported	12%/−4% P not reported	Moderate
Barczynski [8]	640 pts., 282 TT/358 TT + PCND	0.4%/0.2% P 0.668/0.750	17.3%/1.5% P < 0.001/0.122	Moderate
Moo [15]	81 pts., 36 TT/45 TT + PCND	26%/−5% P 0.001/not reported	4%/none P not significant	Moderate
Hughes [34]	143 pts., 65 TT/78 TT + PCND	−3.1% (total) P not reported	19%/2.6 <0.01/not reported	Moderate
Sywak [35]	447 pts., 391 TT/56 TT + PCND	0.8%/−1% P 0.62/0.45	10%/1.3% P 0.02/0.27	Moderate
Calo [17]	285 pts., 220 TT/65 TT + PCND	1.71%/0 permanent injuries P 0.698/NA	13.46%/6.22 P 0.049/0.117	Moderate
Lee [18]	257 pts., 104 TT/153 TT + PCND	1.4%/1.3% P 0.245/0.211	16%/1.4% P 0.043/0.245	High
Calo [19]	163 pts., 103 TT/30 TT+(i) PCND/30 TT+(b)PCND	Temporary: (i) 3.3%/(b) −1.0% P 0.30 Permanent: None reported	Temporary: (i) 10.7%/(b) 24.1% P 0.01 Permanent (i) 1.4%/(b) 1.4% P 0.46	Moderate
Ywata [20]	580 pts., 478 TT/102 TT + PCND	5.7%/4.4% P 0.04/0.02	13.9%/9.5% P 0.004/<0.001	Moderate
Raffaelli [21]	186 pts., 62 TT/62 TT+(i) PCND/62 TT+(b)PCND	Temporary: (i) 1.6%/(b) 0% P not significant Permanent: (i) 1.6%/(b) 0% P not significant	Temporary: (i) 11%/(b) 38% P < 0.001 Permanent: (i) 1.6%/(b) 0% P not significant	Moderate
So [22]	232 pts., 113 TT/119 TT + PCND	−0.1%/−1% P 0.941/0.531	7.6%/4.1% P 0.235/0.105	Moderate
Choi [23]	101 pts., 53 TT/48 TT + PCND	2.1%/NR P 0.48/NR	5.4%/−1.9 P 0.78/NR	Moderate
Popadich [24]	606 pts., 347 TT/259 TT + PCND	−1.9/−1.4% P 0.052/0.124	5.6%/0.35% P 0.026/0.99	Moderate
Lang [25]	185 pts., 103 TT/82 TT + PCND	1.8%/0.1% P 0.324/0.443	9.6%/1.4% P 0.017/1.000	Moderate

(continued)

Table 14.4 (continued)

Study	Patients	Absolute increase in RLN injury rates with PCND (temporary/permanent)	Absolute increase in hypocalcemia rates with PNCD (temporary/permanent)	Quality of evidence
Kim [26]	3950 pts., 1975 TT/1975 TT + PCND	3.3%/0.2% P 0.037/1.0	15.9%/2% P < 0.001/0.004	Moderate
Dobrinja [11]	186 pts., 112 TT/74 TT + PCND	6.8%/3.1% P 0.009/0.303	6.9%/7.2% P 0.065/0.016	Moderate
Giordano [36]	1087 pts., 394 TT/385 TT+(i) PCND, 308 TT+(b)PCND	Temporary: (i) 0.3%/(b) 1.9% P 0.404 Permanent: (i) -0.5%/(b) 1.3% P 0.99	Temporary: (i) 8.4%/(b) 24.2% P (i) 0.014/(b) <0.001 Permanent: (i) 0.7%/(b) 9.9% P 0.818/<0.001	Moderate
Korkmaz [28]	243 pts., 104 TT/139 TT + PCND	NR/1.2% P NR/0.501	1.5%/0.1% P 0.698/0.963	Moderate
Palestini [37]	305 pts., 148 TT/93 TT + PCND	4%/−1.4% P 0.059/0.344	14.1%/−2.7% P 0.003/0.2	Moderate
Viola [38]	181 pts., 88 TT/93 TT + PCND	NR/−3.7% P NR/0.3	NR/11.4% P NR/0.02	High
Zhang [29]	242 pts., 108 TT/134 TT + PCND	0.6%/−0.2% NS/NS	21%/1.5% P <0.01/NS	Moderate
Chen [13]	Variable	1.54%/0.15% Significant/NS CI: (1.32–3.13)/(0.75–2.27)	10.92%/2.16% Significant/significant CI: (1.84–2.7)/(1.58–3.13)	High (Meta-analysis)
Conzo [32]	752 pts., 390 TT/362 TT + PCND	Unilateral: 2.3%/0.9% P 0.0385/0.49 Bilateral: 0.2%/0 P 0.29/0	7.7%/2.3% P 0.0006/0.028	Moderate

Abbreviations: *TT* total thyroidectomy, *TT + PCND* total thyroidectomy and prophylactic central neck dissection, *(i)* ipsilateral; *(b)* bilateral, *(u)* unilateral
Bold values are statistically significant or represent higher levels of evidence

aggressive with metastasis to the lateral neck, we manage these with bilateral central neck dissection given the high rate of central neck disease and recurrence in these patients.

Some have begun to advocate ipsilateral PCND when performing hemithyroidectomy for small WDTC. There is insufficient evidence to recommend for or against such an approach at this time, but we do not routinely perform PCND in this population for all of the reasons outlined above. To conclude, PCND in cases of small WDTC may be safely performed in a majority of patients, but does not result in significantly better OS or DFS. Because few studies find added benefit and there is a suggestion of increased risk, routine PCND is not advised. Table 14.5 summarizes the original research studies that are discussed in this article.

Table 14.5 Summary of original research studies reviewed

Citation	Study design	Patients	Diagnosis	Intervention	Comparator	Outcomes
Narendra [33]	Prospective cohort study	50	WDTC	25 TT + PCND	25 TT only	No increase in morbidity associated w/ PCND
Barczynski [8]	Retrospective	640	PTC	282 TT + PCND	358 TT only	Improved 10y disease specific survival and locoregional control without increase in morbidity w/ PCND
Wang [14]	Systematic review and meta-analysis	1740	PTC	745 TT + PCND	995 TT only	NNT for PCND to prevent 1 recurrence is 31. No significant difference between TT and TT + PCND for recurrence or long-term complication rates
Podnos [40]	Retrospective cohort study (SEER database)	19,918	PTC/FTC	Not reported	Not reported	Of 9904 pts. with known cervical LNs status, 82% overall survival at 14y with −LN versus 79% with +LN (P = 0.0001) Subgroup analysis shows lower survival for FTC w/ +LNs
Moo [15]	Retrospective/ cross-sectional study	81	PTC	45 TT + PCND	36 TT only	Higher dose of RAI in PCND group, higher rate of transient hypoparathyroidism, no significant difference in permanent hypoparathyroidism or recurrence rate
Moreno [9]	Retrospective/ cross-sectional study	252	PTC	119 TT + PCND	133 TT only	No significant difference in recurrence or survival
Hughes [34]	Retrospective/ cross-sectional study	143	PTC	78 TT + PCND	65 TT only	Significant increase in temporary hypoparathyroidism, significantly higher dose of RAI for PCND patients, equivalent rates of central recurrence
Roh [41]	Prospective	184	PTC	184 TT + PCND	0 TT only	Positive nodes in 43.5% No recurrences in central compartment with mean follow up of 46 mo

Sywak [35]	Retrospective cohort study	447	PTC	56 TT + PCND	391 TT only	No significant difference in central neck recurrence, increase in temporary hypoparathyroidism
Gemsenjager [16]	Retrospective review	117	PTC	29 TT + PCND	88 TT only	No significant difference in recurrence with PCND
Calo [17]	Retrospective review	285	PTC	65 TT + PCND	220 TT only	Hurthle cell- and tall cell-variants associated with high risk of lateral neck recurrence 1/285 (0.35%) patients had recurrence in the central neck compartment
Lee [18]	Prospective randomized study	257	PTC	153 TT + PCND	104 TT only	No significant difference recurrence rate, significantly higher rate of transient hypoparathyroidism in PCND group
Calo [19]	Retrospective review	258	DCT	37 TT + ipsilateral PCND 48 TT + bilateral PCND	173 TT only	No significant difference in rate of nodal recurrence. Increased risk of temporary hypoparathyroidism for CND which increases with extent of dissection (ipsilateral vs bilateral)
Ywata [20]	Retrospective cohort study	589	PTC	102 TT + PCND	487 TT only	PCND group with higher rates of hypoparathyroidism, permanent and temporary RLN injury. No decrease in local recurrence rates
Raffaelli [21]	Prospective	186	PCT	62 ipsilateral PCND 62 bilateral PCND	62 TT only	Significantly more patients in bilateral PCND group with transient hypoparathyroidism
So [22]	Retrospective review	232	microPTC	119 TT + PCND	113 TT only	Lower postop stimulated thyroglobulin level in PCND group, difference disappears after RAI. No difference in 3y locoregional control rates

(continued)

Table 14.5 (continued)

Citation	Study design	Patients	Diagnosis	Intervention	Comparator	Outcomes
Choi [23]	Retrospective review	101	microPTC	48 TT + PCND	53 TT only	Increased risk of transient hypoparathyroidism and transient RLN injury
Popadich [24]	Retrospective, multicenter cohort study	606	PTC	259 TT + PCND	347 TT only	Lower stimulated thyroglobulin levels before RAI, lower rate of reoperation in PCND group, NNT to prevent one reoperation was 20
Lang [25]	Retrospective review	185	PTC	82 TT + PCND	103 TT only	PCND group had larger tumors, more extrathyroid extension more nodal metastasis, more temporary hypoparathyroidism, lower preablative thyroglobulin, no difference at 6 m
Costa [10]	Retrospective review	244	PTC	126 TT + PCND	118 TT only	No difference in survival, but presence of metastasis on PCND was associated with recurrence
Kim [26]	Retrospective cohort	11,569	PTC	8735 TT + PCND	2834 TT only	No significant decrease in locoregional recurrence, significant increase in RLN palsy, temporary and permanent hypoparathyroidism
Dobrinja [11]	Retrospective cohort	186	PTC	74 TT + PCND	112 TT only	Higher complication rate with PCND, no improvement in recurrence or overall survival
Giordano [36]	Retrospective review	1087	PTC	385 ipsilateral PCND 308 bilateral PCND	394 TT only	Increased risk of temporary hypoparathyroidism in both PCND groups, higher rate of permanent hypoparathyroidism in bilateral PCND group
Hyun [27]	Retrospective review	152	mPTC	87 ipsilateral PCND	65 HT only	Significantly lower rate of locoregional recurrence in PCND group

Korkmaz [28]	Retrospective review	302	PTC	162 TT + PCND	140 TT only	Preablative thyroglobulin was higher in TT group, but no difference after RAI or after 1 year in group not treated with RAI
Palestini [37]	Retrospective review	305	PTC	93 TT + ipsilateral PCND	148 TT only	No increase in permanent morbidity with PCND, but found a significant number of metastases
Viola [38]	Prospective randomized controlled trial	181	PTC	93 TT + PCND	88 video-assisted TT only	TT group received more RAI, PCND group higher rate of permanent hypoparathyroidism. Otherwise similar outcomes
Zhang [29]	Retrospective cohort	242	mPTC	134 TT + PCND	108 TT only	Higher rate of temporary hypoparathyroidism in PCND group, no difference in long term complications, higher rate of recurrence and reoperation in TT group
Zuniga [30]	Retrospective cohort	266	PTC	136 TT + PCND	130 TT only	No significant effect on disease free survival
Chen [13]	Systematic review and meta-analysis	18,376	cN0 PTC	NA	NA	Significant reduction in LRR associated with PCND, OR 0.65 (CI 0.48–0.88). PCND also significantly associated with transient RLN injury and permanent and transient hypoparathyroidism
Said [31]	Retrospective review	864	Malignant thyroid neoplasm	34 TT + PCND	830 TT only	Rate of recurrence between the treatment groups was not significantly different

(continued)

Table 14.5 (continued)

Citation	Study design	Patients	Diagnosis	Intervention	Comparator	Outcomes
Shen [42]	Retrospective review	295	PTC	106 reoperative CND	189 Initial CND	No significant difference in difference in rate of recurrence, permanent RNL hoarseness, or hypoparathyroidism. Significantly lower rate of temporary hypoparathyroidism observed in the re-operative group
Yu [43]	Retrospective cohort study (SEER database)	18,445	mPTC	NA	NA	Overall survival of 94.5% and 90.7%, and disease specific survival of 99.5% and 99.3% at 10y and 15y respectively Significant risk factors for overall survival include, age >45, minority race, node metastasis, extrathyroidal invasion, and distant metastasis
Zaydfudim [44]	Retrospective cohort study (SEER database)	33,088	PTC/FTC	NA	NA	Significant increased risk of death was associated with age >45y in patients with lymph node metastasis regardless of tumor type
Conzo [32]	Retrospective review	752	DTC	363 TT + PCND	390 TT only	Similar incidences of locoregional recurrence with increased rate of permanent and temporary complications

Abbreviations: *TT* total thyroidectomy, *TT + PCND* total thyroidectomy and prophylactic central neck dissection, *HT* hemithyroidectomy, *mPTC* papillary thyroid microcarcinoma, *RAI* radioactive iodine, *RLN* recurrent laryngeal nerve

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Management of the Clinically Negative Lateral Neck in Medullary Thyroid Cancer

15

Raymon H. Grogan

Introduction

Medullary thyroid cancer arises from parafollicular c-cells found in the thyroid and makes up approximately 1–2% of all thyroid cancer diagnoses in the United States [1]. It is generally more aggressive than well-differentiated forms of thyroid cancer that arise from thyroid follicular cells. This leads to a difference in overall survival, disease-free survival, and metastatic rate which dictates a different treatment algorithm for this type of thyroid cancer. C-cells produce calcitonin, thus allowing it to be used as a tumor marker which correlates with disease burden both at the time of diagnosis as well as after surgical resection. It can denote completeness of resection as well as recurrence, thus it is a good biochemical marker of disease control. Carcinoembryonic Antigen (CEA) can also be used as a tumor marker to denote tumor burden at the time of diagnosis and detect recurrence [2].

Surgery is the first-line treatment for medullary thyroid cancer, with the primary goal being cure [3]. In addition to structural imaging showing no disease, biochemical markers (calcitonin and CEA) remain one of the mainstays of measurement of treatment success. While cure is possible, particularly in early stage disease that has not metastasized outside of the neck, due to the aggressive nature of this cancer, complete cure is often not achieved. In cases where compete cure cannot be achieved disease control serves to debulk tumor as well as prevent morbidity associated with invasion of disease into sensitive structures in the neck. As the tumor metastasizes from the thyroid to the central neck, lateral neck and then systemically, survival concurrently decreases.

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Several markers have been described to predict the likelihood of biochemical cure at the time of initial diagnosis. These include number of lymph nodes involved, location of lymph nodes, presence of systemic metastasis, calcitonin level, and CEA level. Prognosticators of survival are fewer. Only age, lymph node status, and stage at diagnosis have been shown to be independent prognostic factors for survival [4]. Calcitonin levels have been shown to approximately correlate with survival, however this is less clear. As with most cancers, none of these markers of biochemical cure or survival are exact, thus it is not entirely clear when more extensive surgery will be helpful. Designing good treatment algorithms is further complicated by the fact that current staging systems are inaccurate [5]. This remaining uncertainty has led to continued controversy over how extensive the initial operation should be for medullary thyroid cancer when there is no structural evidence of disease in the lateral neck. In general, there are two principles that are agreed upon: (1) If there is metastatic disease in the neck that is evident on preoperative imaging it should be removed/debulked with compartment-based neck dissection, and (2) If there is no structurally evident disease on imaging then prophylactic central neck dissection is warranted. What is not agreed upon is when or if a prophylactic ipsilateral or contralateral lateral neck dissection is warranted. This is because few studies address the impact on survival or biochemical cure is for prophylactic lateral neck dissections. In addition to this, the morbidity of lateral neck dissections is higher than that of thyroidectomy or central neck dissection, making the decision to move forward with a lateral neck dissection more challenging.

What continues to cause confusion in the literature is the lack of consensus on which of the biomarkers is most useful in helping to determine survival outcomes. Different studies have looked at calcitonin, CEA, lymph node location, number of nodes, and have come up with different cutoffs that seem to be useful. However, because so many markers exist, with multiple different cutoffs possibly being useful, the literature remains confusing.

Literature Search Strategy

The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma published an extensive literature review with recommendations in 2015 [1]. The ATA publication included an extensive Pubmed literature review done from January 1980 to April 2014. The relevant sections of the ATA publication were reviewed as well as the primary literature sources from that review. In addition, an expanded review of the literature was performed in Pubmed based on the terms “Medullary” AND “Thyroid” AND “Neck Dissection” between the dates of 5/1/2014 and 1/1/2018 to consider any new articles that were published after the 2015 ATA guidelines. This additional search returned a total of 72 new articles. The abstracts of this search result were reviewed by hand. Case reports, non-relevant review articles, and non-English language articles were removed. This left a total of 51 new articles which were reviewed in detail for this chapter

Table 15.1 PICO Criteria

Population	MTC with clinically negative lateral neck lymph node compartment
Intervention	Prophylactic lateral neck dissection
Comparison	Central neck dissection only
Outcome	Survival, biochemical cure

in addition to the previously described literature from the 2015 ATA guidelines (Table 15.1).

Does Complete Biochemical Cure with Calcitonin and/or CEA Levels Predict Improved Survival?

If biochemical cure is associated with improved survival then prophylactic neck dissections are a worthwhile pursuit if they lead to biochemical cure. Thus understanding the data behind whether biochemical cure predicts survival is central to answering the question of utility of prophylactic neck dissection in medullary thyroid cancer. A longitudinal French registry study of 899 medullary thyroid cancer patients from 1952 to 1996 provides the best data on this subject [6]. The study was designed as a nationwide registry follow-up of both sporadic and hereditary cancer. Because it was not a prospective trial patients were not randomized to particular types of treatment. Thirty-seven percent of patients had total thyroidectomy with bilateral radical lymph node dissection, 31.5% had total thyroidectomy with partial lymph node dissection, 22.8% had total thyroidectomy without lymph node dissection, and 8.6% had partial thyroidectomy. Survival results were not broken down by type of surgery, giving minimal insight into how the extent of surgery impacts survival other than showing that bilateral neck dissection improved survival over less extensive resections. Most importantly however, when taken in aggregate, there was a 97.7 10-year survival if biochemical cure was achieved, regardless of any other factors including extent of surgery. This is compared to a 70.3% survival rate in those not biochemically cured. Biochemical cure was defined as either normal basal or pentagastrin stimulated calcitonin levels after surgery. The fact that survival rates with complete biochemical cure are so high, and so different relative to those without biochemical cure makes these data more convincing in spite of the study being non-randomized and not controlled for confounders. The biggest confounders in this case are the extent of disease at the time of diagnosis and secondly the extent of operation. Thus based on this study alone one cannot draw conclusions about the effect of stage and surgery type, but it seems clear that if biochemical cure can be achieved there is a significant survival advantage. Other smaller series have corroborated this finding [7].

Complete biochemical cure can be used as a prognostic factor for improved survival (quality of evidence moderate, conditional recommendation).

Do Calcitonin and CEA Levels Predict Metastatic Disease Beyond the Neck?

The question being addressed currently is whether prophylactic lateral neck dissection leads to biochemical cure. In this context a lateral neck dissection cannot lead to cure if there is distant metastatic disease outside the neck, thus factors that positively predict distant metastatic disease can be used to rule out the need for prophylactic lateral neck dissection. The gold standard for confirming distant metastatic disease is biopsy proven disease. Without a biopsy there are decreasing levels of certainty of distant disease. Biopsy proven disease is followed by evidence of disease on functional imaging, i.e. somatostatin receptor and other PET tracer imaging modalities. Next would be structural disease on cross-sectional imaging in the setting of known medullary thyroid cancer, i.e. CT or MRI. Lastly are tumor intrinsic factors such as the level of biochemical disease, number of positive metastatic lymph nodes in the neck, and the number of neck lymph node compartments with metastatic disease. Lymph node status is not useful in the preoperative setting, as the true lymph node status is not known until after surgery. Realistically this means when imaging is negative for metastatic disease the only practically useful way of assessing for distant metastatic disease is through biochemical levels of the tumor markers calcitonin and/or CEA.

A study of 300 consecutive operations on medullary thyroid cancer patients in Germany is one of the largest studies in the literature to specifically address the utility of preoperative calcitonin and CEA levels in predicting both metastatic burden as well as biochemical cure [8]. This study is a retrospective analysis of a prospectively followed cohort of medullary thyroid cancer patients that include both hereditary and sporadic cases. The study suffers from a lack of standardization of surgical approach, due to its retrospective nature. However, 100% of patients underwent bilateral central neck dissection and more than 70% of patients underwent bilateral modified radical neck dissection. The results of the study show that preoperative calcitonin and CEA levels more closely correlate with tumor size than metastatic disease burden. However, both calcitonin and CEA do correlate with metastatic disease burden in spite of the confounding issue of primary tumor size. Calcitonin was shown to be a more granular predictor of metastatic disease and biochemical cure over CEA. Thus, based on this study there is value in attempting to use calcitonin and/or CEA level cutoffs to direct extent of primary surgery.

Preoperative calcitonin and CEA levels can predict (with limitations) the possibility of biochemical cure as well as metastatic disease burden, and can be used to direct extent of primary surgery (quality of evidence low, conditional recommendation).

What Cutoff Values for Calcitonin and CEA Can Be Used to Predict Complete Biochemical Cure and Thus May Justify Prophylactic Lateral Neck Dissection?

The German study cited above as well as a follow-up to that study give the best look at possible cutoff values for calcitonin and CEA and the predictive value of complete biochemical cure [2]. As is shown in Table 15.2 complete biochemical cure is as high as 80% with a calcitonin level <500. Calcitonin levels >500 are associated with only a 20% chance of complete biochemical cure. This is in the context of bilateral modified radical neck dissection in 70% of first-time surgery. The percent cure is a dramatic cutoff, and thus strongly suggests that calcitonin levels greater than 500 predict distant metastasis outside of the neck. Table 15.3 shows a similar pattern for CEA levels, although its utility seems less clear. Undetectable CEA levels <4.6 show a 95% biochemical cure rate. This drops to 51% for CEA levels less than 50, and the cure rates fall dramatically to 15% once the CEA level increases above 50.

Calcitonin >500 and CEA >50 are associated with dramatically decreased possibility of complete biochemical cure, and can guide the extent of prophylactic lateral neck surgery (quality of evidence low; conditional recommendation).

Table 15.2 Prediction of metastasis and biochemical cure by calcitonin level [8]

Calcitonin level	Metastasis site	% Biochemical cure with bilateral MRND
<20	None	100
21–50	Ipsilateral central and lateral neck	100
51–200	Contralateral central neck	89
201–500	Contralateral lateral neck	81
>500	Mediastinum or distant	27

Table 15.3 Prediction of lymph node involvement and biochemical cure by CEA level [8]

CEA level	# of positive nodes	(%) Biochemical cure with bilateral MRND
<4.6	1.1	95
4.6–10	5.2	51
10.1–50	5.1	73
50.1–100	23.2	15
100–300	20.4	8
>300	25.5	13

Does Number of Positive Lymph Nodes Predict Lateral Neck Lymph Node Metastasis and/or Distant Metastasis?

The German group has also looked at the number of lymph nodes in the neck as predictors of both lateral neck disease as well as distant metastatic disease [9–11]. One of the strengths of their findings again is that a large number of patients in their series underwent bilateral lateral neck dissections, and many of these patients had >50 lymph nodes removed at the time of dissection. These data show that the number of lymph nodes in the central neck correlate with lateral neck disease (Tables 15.4 and 15.5). In addition, the total aggregate number of lymph nodes found in the central and lateral neck correlate with distant metastasis. In addition, they found that involvement of mediastinal lymph nodes had a very high risk of distant metastasis regardless of total aggregate nodes involved.

> Number of positive lymph nodes does correlate with the risk of both lateral neck disease and distant metastatic disease (quality of evidence low, conditional recommendation).

A Personal View of the Data

There can be significant morbidity and delayed recovery associated with lateral neck dissection [12, 13]. Even without complications lateral neck dissection can impact Quality of Life, and many patients will need physical therapy [14]. The morbidity of lateral neck dissection needs to be weighed against the benefits of prophylactic lateral neck dissection. Given this it seems reasonable to accumulate as much evidence as possible prior to proceeding with prophylactic lateral neck dissections,

Table 15.4 Prediction of lateral neck metastasis based on number of positive central neck lymph nodes [9]

# of nodes	Ipsilateral lateral (%)	Contralateral lateral (%)
0	10.1	
1–3	77	
>3	98	
0		4.9
1–9		38
>9		77

Table 15.5 Prediction of distant metastasis based on number of aggregate positive neck lymph nodes [11]

# of nodes in aggregate	% Distant metastasis
1–10	4
11–20	13
>20	30
Mediastinal node involvement	46

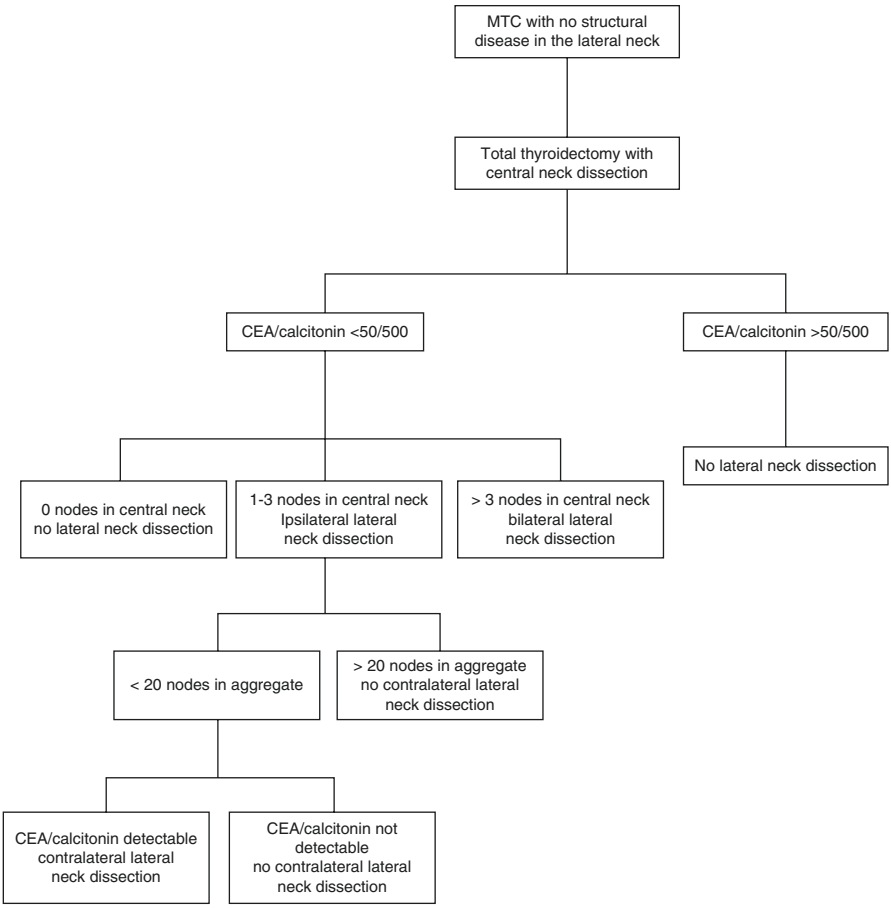

Fig. 15.1 Proposed algorithm for deciding when to perform prophylactic lateral neck dissection in medullary thyroid cancer

particularly of the contralateral neck. It seems reasonable to use both biochemical markers as well as number of lymph nodes to guide the extent of surgery. With all of the information presented above this author proposes the following algorithm for prophylactic neck dissection decision making (Fig. 15.1).

While CEA and calcitonin levels are helpful, at this time they are not definitive at predicting complete biochemical cure. This is due in part to the confounding effect of the primary tumor size. Because the number of positive lymph nodes in the neck also have value in predicting lateral neck spread as well as potential cure, it seems reasonable to use both biochemical markers as well as lymph node status to decide when to perform lateral neck dissection. At the time of diagnosis the 50/500 rule can be helpful. If CEA is greater than 50 or calcitonin is greater than 500, the likelihood that there is metastatic disease beyond the neck is very high, and the likelihood of complete biochemical cure is low, thus lateral neck dissections should

only be undertaken if structural disease is present in this situation. If the biochemical markers do not reach the 50/500 threshold (i.e. CEA <50 calcitonin <500) then prophylactic lateral neck dissection should be considered, depending on the number of positive lymph nodes that are found after prophylactic central neck dissection. If 0 nodes are found in the central neck then no lateral neck dissection is required, if 1–3 nodes are found then an ipsilateral lateral neck dissection can be considered, and if >3 central neck nodes are found then a contralateral lateral neck dissection can be considered. If an ipsilateral lateral neck dissection is performed and >20 nodes are found in aggregate, then contralateral neck dissection may not be warranted due to the high likelihood that biochemical cure will not be achieved due to likely distant metastasis.

While the data in the literature to date do provide value, they are not definitive and thus it is difficult to make strong recommendations in any regard at this time in regards to when a prophylactic lateral neck dissection should be undertaken. Some argue for undertaking prophylactic central neck dissection at the time of initial operation due to the fact that if not done at the initial operation it will require a reoperation in an already operated upon field in the central neck. However, after initial thyroidectomy and central neck dissection, the lateral neck should remain scar free, and thus a staged approach to the lateral neck does not increase morbidity in the way that a staged approach to the central neck might. Given the morbidity of lateral neck dissection and the lack of clarity based on biochemical markers alone it seems reasonable to this author to proceed with a staged approach to prophylactic lateral neck dissections taking into consideration structural imaging, biochemical markers as well as number of lymph nodes involved in the central neck at the time of the initial operation.

Finally, it is unclear what to do if biochemical markers fall below the 50/500 cutoffs after one of the neck compartments is dissected. For example, if the initial biochemical markers are >50/500, but fall below 50/500 after total thyroidectomy and central neck dissection. Again, the confusion here is in part due to the confounding effect of the primary tumor size on the biochemical marker levels. In a case where the biochemical markers fall below the 50/500 cutoff range after a compartmental lymph node dissection it seems reasonable to proceed with lateral neck dissection based on the proposed algorithm and lymph node status at that time, however there are no data for or against this recommendation.

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Part V

Soft Tissue

Should Pre-operative Embolization Be Utilized Routinely for Carotid Body Tumors Prior to Surgical Excision?

16

Chris J. Britt and Wojciech K. Mydlarz

Introduction

Carotid body tumors (CBT) are a type of paraganglioma that arise from extra-adrenal chromaffin cells at the carotid bifurcation usually deriving their blood supply from the external carotid artery [1, 2]. They represent the most common paraganglioma of the head and neck (60–78%) with an incidence of approximately 1 in 30,000 [3]. First described by von Haller in 1743, these tumors generally present as a slowly enlarging, painless neck mass. These tumors are often associated with conditions producing chronically decreased oxygen tension including chronic obstructive pulmonary disease and living at elevated altitude [4, 5]. They also tend to be more common in women given lower baseline hemoglobin levels. CBTs are almost always benign, with a malignant incidence of 2–9%; however, malignancy can only be appreciated by the presence of metastasis [3, 6].

Surgery is the gold standard and is curative for resectable CBTs. Resection is recommended in otherwise healthy patients because of the risk of local complications mostly related to tumor size and surrounding tissue involvement and a small but definite cumulative long term risk of malignancy [7]. These tumors are highly vascular, and resection can be fraught with complications including prolonged operative times, increased blood loss, cranial nerve injury, stroke and death. The use of preoperative angiography with embolization for CBT surgery was first successfully performed in 1980 by Schick et al. and sought to decrease

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intraoperative blood loss and operative time [3, 8–11]. Pre-operative embolization is typically performed 24–48 h before resection to prevent regrowth of tumor vascularity and to allow post procedural edema to resolve [12]. Although the theoretical aims of pre-operative embolization for carotid body tumor resection are clear, a careful analysis of the available literature is needed to determine its actual benefits. This chapter explores the efficacy of preoperative embolization prior to surgical resection of carotid body tumors.

Literature Search Strategy

Based on the PICO table (Table 16.1), Pubmed and CENTRAL searches incorporating the terms "Embolization" and/or "Pre-operative evaluation" and ("Carotid Body Tumor" or "Paraganglioma") were used to review the English language literature. Five hundred and two studies were identified. The bibliography of applicable articles was also reviewed. The search was narrowed to focus on articles that directly compared groups of patients who underwent embolization or no embolization of the CBT prior to resection. Non-English language articles, retrospective studies that contained three tumors or less in either group, studies without direct comparison groups were excluded. Studies were included if they were published between February 1998 and February 2018, included patients undergoing surgical intervention for cervical paragangliomas and compared the effects of preoperative versus no preoperative vascular embolization on CBT. We gave preference to meta analyses and claims-based data studies as there were no randomized control trials identified.

Results

There are no current Otolaryngology, Neurosurgery, or Vascular surgery published consensus clinical practice guidelines for pre-operative management of carotid body tumors. Since 1997, there were 21 studies that met our criteria and addressed the utility of CBT resection with and without pre-operative embolization: two meta-analyses, two claims-based data multi-institutional studies, and 17 retrospective

Table 16.1 Impact of embolization on surgical management of carotid body tumors

Population	Intervention	Comparison	Outcomes
Adults with carotid body tumors undergoing surgical intervention	Pre-operative embolization of carotid body tumor	No pre-operative embolization of carotid body tumor	Incidence of complications associated with embolization and with surgical resection of carotid body tumor including Mortality Stroke incidence Cranial nerve paralysis Adverse events

analyses. There were no randomized control trials or prospective studies identified during our literature review. When examining the primary question, it is critical to establish acceptable endpoints for comparison. In this chapter, we will examine the meta-analyses and claims-based studies and their endpoints and supplement the gaps in knowledge with the retrospective studies to help answer the question of the efficacy of pre-operative embolization in surgical management of CBTs.

Jackson et al. published the first meta-analysis on the utility of CBT pre-operative embolization [13]. They identified 22 studies which met their inclusion criteria and of those, 15 that specifically compared surgical excision of the tumor with and without preoperative embolization. Their primary analysis of these two groups looked at overall operative time and estimated blood loss (EBL). They found that 12 studies (295 tumors) included enough data to show that EBL was significantly lower in patients undergoing preoperative embolization than patients undergoing surgical excision alone (Standardized Mean Difference (SMD) = −0.52; 95% CI: −0.77, −0.28; $p < .0001$). Six of the 22 studies meeting inclusion criteria (174 tumors) showed operative time to be significantly lower in the preoperative embolization tumor group compared to surgical tumor excision alone group (SMD = −0.46; 95% CI: –0.77, −0.14; $p = .004$). Subgroup analysis of the EBL group for different embolization methods (percutaneous versus trans-arterial) and tumor size were without significant differences. No comparison analysis could be done to compare EBL for differences in Shamblin classification or length of hospital stay. Operative time could only be compared for tumor size, but there was no significant difference found in this subgroup. Complications could not be directly compared, but out of 160 embolization procedures there were only four complications and no mortalities. The authors concluded that although embolization had few complications and seemed to lower EBL and operative time, more research would be needed due to the rarity of these tumors and the lack of prospective or randomized studies.

Abu-Ghanem et al. published the second meta-analysis that contradicted the Jackson et al. results on the positive impact of pre-operative embolization in surgical management of CBTs [12]. They identified 15 studies with 470 total patients that met their inclusion criteria. The study evaluated EBL (six studies included), operative time (three studies included), cranial nerve injury (nine studies included), vascular injury (seven studies included) and length of stay (LOS) (two studies included) between pre-operative embolization and surgery only groups and saw no statistically significant differences between these two groups. They concluded that given a general paucity of quality data, the results allude to the fact that preoperative embolization likely does not confer any significant advantages during surgical resection of CBTs. While the inclusion criteria between the two meta-analyses were very similar, fewer articles were initially identified through the database review in the study by Abu-Ghanem et al. and fewer were included in the EBL and operative time analysis which may account for the lack of significant findings by Abu-Ghanem et al. Compared to Jackson et al. [12, 13].

Cobb et al. performed a claims-based database study using the Healthcare Cost and Utilization Project State Inpatient Database [14]. They included data from five heterogeneous US states between 2006 and 2013. They identified 472 patients who

underwent resection of the CBT without embolization and 75 patients who underwent embolization using International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9) codes. Primary outcomes for comparison included inpatient mortality, cranial nerve injury, EBL, and LOS using ICD-9 codes as identifiers. They found no significant differences in mortality, cranial nerve injury, or EBL between groups. They found that embolization significantly increased the odds of LOS (odds ratio 5.3, 95% confidence interval 2.1–13.3). They acknowledged that this data set was limited by the use of billing codes, making some comparisons (i.e. tumor size) impossible, and some (i.e. EBL) incomplete.

Vogel et al. performed a claims-based database study utilizing the nationwide inpatient sample from 2002–2006 [15]. They identified 2117 patients, 1686 of which underwent surgery without any need for carotid artery reconstruction, 129 who underwent excision with embolization, and 302 with tumor excision and carotid artery reconstruction. Patients, procedures, and outcomes were identified using ICD-9 codes. Primary outcomes for comparison included inpatient mortality, stroke, cranial nerve injury, EBL, LOS, cost, cardiac complications, and respiratory complications using ICD-9 codes as identifiers. When comparing the excision only group to the embolization group, there was no difference in rates of death, stroke, cranial nerve injury, LOS, EBL, or cardiac or respiratory complications. Cost was significantly greater for the embolization group versus the excision only group ($11,640 ± 9552 versus $17,748 ± 5845, p = 0.0016); however, there was no difference in cost when comparing the embolization group with the excision plus carotid artery reconstruction group ($14,256 ± 8548). The study limitations were similar to the previous study by Cobb et al. They concluded that embolization does not confer an overall higher risk of complications, and while resource utilization and cost may be higher, the procedure is significantly helpful if it helps avoid carotid artery resection and reconstruction [14].

Unfortunately, these studies provide limited answers with disagreement in their overall conclusions regarding the utility of pre-operative embolization of CBTs. One meta-analysis showed that embolization decreased EBL and operative time while the other meta-analysis did not find any statistical differences based on similar comparisons. Both database studies saw no difference in EBL between embolization and CBT excision only; however, when compared to patients who had carotid artery reconstruction, embolization did significantly decrease EBL, LOS, and chance of complications. One database study found that LOS was significantly different between groups, while the other did not. Cost was significantly greater for the embolization group compared to excision alone in the only study that measured cost. This leaves us to rely on the available retrospective studies to answer some of our questions. Retrospective studies which compare CBT resection with and without pre-operative embolization are summarized in Table 16.2. EBL, operative time, complications (embolization related and surgically related), LOS, vascular injury, and tumor size were commonly compared.

There were 17 retrospective studies in the English literature that directly compared patients undergoing surgical resection of CBTs with and without embolization and had at least three patients in each subgroup (Table 16.2). Studies either

Table 16.2 Single institution retrospective studies comparison of CBT excision only (CBTR) vs CBT with pre-operative embolization (CBTRE)

Primary author and publication year	Tumor #	Mean EBL in ml, ±sd or (95% CI range if given)	Mean operative time, h, ±sd or (95% CI range if given)	Vascular sacrifice/ injury	Tumor size, cm, ±sd	LOS, d, ±sd, or (95% CI range if given)	Cranial nerve injury	Stroke	Death
Ward et al. [16]									
CBTRE	6	396.6, ±244.6	1.75, ±1.08	1	NP	NP	0	0	0
CBTR	11	1250, ±864.8	4.2, ±1.5	1	NP	NP	4	0	0
Significance, if present									
LaMuraglia et al. [17]									
CBTRE	11	372, ±213	4.1	NP		NP	1	NP	
CBTR	8	609, ±564	4.5	NP		NP	2	NP	
Significance, if present			p = .02						
Litle et al. [11]									
CBTRE	11	1123, ±1450	5.1, ±2.5	6	5.0, ±2.1	1.5, ±0.8	5	0	0
CBTR	10	764, ±588	3.9, ±1.6	5	4.2, ±1.5	0.8, ±0.4	5	1	0
Significance, if present		NS	NS			p = .02			
Tikkakoski et al. [18]									
CBTRE	20	588 (65–1800)	3.4 (1.7–5.5)	7	3.1	NP	1	0	0
CBTR	11	1375 (250–3500)	4.7 (2.5–7)	8	3.8	NP	3	0	0
Significance, if present									
Kasper et al. [19]									
CBTRE	13	365, ±180	NP	NP	4.2	2.6	NP	0	0
CBTR	12	395, ±177	NP	NP	2.2	1.2	NP	0	0

(continued)

Table 16.2 (continued)

Primary author and publication year	Tumor #	Mean EBL in ml, ±sd or (95% CI range if given)	Mean operative time, h, ±sd or (95% CI range if given)	Vascular sacrifice/ injury	Tumor size, cm, ±sd	LOS, d, ±sd, or (95% CI range if given)	Cranial nerve injury	Stroke	Death
Significance, if present					p = .03	p = .007			
Liu et al. [20]									
CBTRE	6	238 (80–400)	NP	2	NP	NP	2	0	0
CBTR	11	600 (100–1000)	NP	7	NP	NP	6	0	0
Significance, if present									
Ozay et al. [21]									
CBTRE	14	375, ±150	NP	NP	NP	NP	NP	0	0
CBTR	9	411, ±344	NP	NP	NP	NP	NP	0	0
Significance, if present									
Arnold et al. [22]									
CBTRE	5	700	3	0	7.75	NP	0	0	0
CBTR	4	150	2.1	1	6.8	NP	2	0	0
Significance, if present		p = 0.02	p = 0.02						
Li et al. [23]									
CBTRE	36	354.8, ±334.4	2.8, ±1.25	3		8, ±2.1	1	1	0
CBTR	30	656.4, ±497.4	3.7, ±1.9	4		9.5, ±3.5	4	3	0
Significance, if present		p = .008	p = .034			p = .042	NS	NS	
Lim et al. [24]									
CBTRE	7	400 (200–1200)	6 (3–9)	NP	3.5 (2.2–5.5)	8 (4–12)	NP	NP	0

CBTR	6	550 (200–1400)	6 (3.6–8)	NP	3.9 (2–5.5)	8 (6–10)	NP	NP	0
Significance, if present									
Zeitler et al. [10]									
CBTRE	10	305 (50–1000)	NP	0	4.8 (2.9–8.3)	NP	3	NP	0
CBTR	15	265.5 (40–900)	NP	1	4.4 (2.8–7.9)	NP	2	NP	0
Significance, if present									
Avgerinos et al. [25]									
CBTRE	4	415 (230–850)	NP	NP	NP	NP	NP	NP	NP
CBTR	16	720 (350–1650)	NP	NP	NP	NP	NP	NP	NP
Significance, if present									
Power et al. [26]									
CBTRE	33	263	4.1	3	4.7 (1.7–8)	5.1 (3–18)	21	0	0
CBTR	71	599	4.4	14	4.1 (2.5–7)	4.2 (2–35)	32	1	0
significance, if present		p = .002				p = .03			
Zhang et al. [27]									
CBTRE	21	280 (50–850)	3 (2.6–3.6)	NP	4.5 (2.8–6.0)	5 (4–8)	NP	0	0
CBTR	8	450 (100–1000)	3.6 (2.8–4.3)	NP	3.9 (2.5–5.5)	8 (5–11)	NP	0	0

(continued)

Table 16.2 (continued)

Primary author and publication year	Tumor #	Mean EBL in ml, ±sd or (95% CI range if given)	Mean operative time, h, ±sd or (95% CI range if given)	Vascular sacrifice/ injury	Tumor size, cm, ±sd	LOS, d, ±sd, or (95% CI range if given)	Cranial nerve injury	Stroke	Death
Significance, if present		p = .027	p = .036			p = .045			
Bercin et al. [28]									
CBTRE	7	375 (200–1000)	2.8	4	4.6 (3–7)	NP	NP	NP	0
CBTR	6	283 (60–750)	2.6	1	4.1 (3–6.5)	NP	NP	NP	0
Significance, if present		NS	NS						
Mourad et al. [29]									
CBTRE	53	105	0.58 (0.3–0.9)	10	NP	NP	4	0	0
CBTR	43	110	0.64 (.35–1.02)	14	NP	NP	2	0	0
Significance, if present									
Law et al. [30]									
CBTRE	9	530 (40–2000)	4.4 (2–10.5)	2	3.8 (2.0–7.0)	NP	NP	2	0
CBTR	12	667 (20–1500)	4.45 (1.5–8.8)	0	3.9 (2.2–8.0)	NP	NP	0	0
Significance, if present									

LOS length of stay, *NP* not provided, *NS* not significant, *sd* standard deviation, *CI* confidence interval

specified a trans-arterial technique used for embolization or did not specify the type of technique utilized; thus, no comparison could be made between trans-arterial and percutaneous techniques. Overall, this consists of 283 CBT undergoing excision without embolization and 266 CBTs with embolization. There were no deaths reported, but there were five cerebrovascular accidents (CVA) in the CBT resection only group versus one in the pre-operative embolization surgery group. Three studies found significantly higher EBL in the CBT excision only group, while eight studies found no significant difference in EBL with one study identifying higher EBL in the embolization group. Three studies also found longer operative times in the CBT excision only group, while five studies saw no difference between these two groups. One study found longer operative times in the embolization group. Inpatient LOS was longer for the embolization group in three studies, longer for the CBT excision only group in two studies and there was no overall difference between the two groups in two studies. Finally, one study showed that embolized tumors were usually larger, while four other studies found no significant difference in tumor size.

In these studies, it was difficult to compare vascular sacrifice or injury because the definitions of vascular sacrifice and/or injury varied among the studies. Vascular sacrifice sometimes included resection of the external carotid artery, repair or patching of the carotid bulb without sacrifice, or sacrifice or reconstruction of the internal carotid artery itself. Likewise, for cranial nerve injury, most studies did not distinguish between temporary and permanent nerve paralysis. Even so, there were 56 number of vascular sacrifices or injuries reported in the resection alone group and 38 number of vascular sacrifices or injuries reported in the embolization group. Power et al. compared complications between the embolization group and surgery only group and found no difference in the complication rate between the two groups, but they did not stratify between the nature of the complications [26].

Extent of soft tissue tumor involvement was indicated in several studies comparing embolization as an absolute measurement or was otherwise defined by the Shamblin classification [31]. This classification was introduced in 1971 by Shamblin et al. to indicate the degree of carotid artery involvement [31]. Briefly, it consists of three classifications: type I being localized between the internal and external carotids and easily resectable, type II partially surrounding or adherent to the carotid arteries, and type III completely encasing at least one branches of the common carotid artery. The absolute measurement in most studies was the maximum dimension of tumor diameter measured preoperatively with imaging; however, LaMuraglia et al. used pathologic measurements to determine diameter [17]. Shamblin classification was not mentioned in Table 16.2 secondary to the subjective nature of the classification and the fact that several studies grouped classifications together [21, 24, 27]. Although the Shamblin classification is somewhat dependent on the interpretation of the radiologist or the provider, it is correlated with tumor size and tumor volume [19, 26, 32]. Several of the retrospective studies concluded that Shamblin classification size II and III or tumor size >3 cm are indications for consideration of

pre-operative embolization based on their individual experience with difficulty of operation, operative time, and blood loss [19, 23, 33–37]. However, only one study with direct comparison of surgery only to pre-operative embolization with surgery showed a significant difference in both tumor size ($p = .03$) and Shamblin classification ($p = 0.001$) while showing no difference in EBL, concluding that larger tumors deserved embolization [19]. Tumor size or Shamblin classification would seem to be obvious reasons to perform embolization, but due to a paucity and quality of data, the evidence remains unclear.

While uncommon, complications do arise from the embolization procedure itself. Pain and post embolization fever are the most common complications of embolization [38]. More serious complications such as hemorrhage, stroke or death are rare [12, 13, 39]. In one meta-analysis, Jackson et al. listed a complication rate of 2.5% (4/160) including temporary aphasia, cranial nerve XII palsy, arterial dissection and vocal fold paralysis [13]. Liu et al. reported two cases of permanent vision loss after embolization [20]. In addition, while no single institutional study compared costs between the two groups, one study did examine cost between Shamblin groups with higher costs for Shamblin III classification and insinuated that a significant amount of cost was due to use of pre-operative embolization for these more involved and larger tumors [40].

So why do surgeons embolize without specific recommendations? Surgeon preference is commonly cited as a reason for embolization [41]. Gupta et al. defines eight indications for embolization of hypervascular head and neck tumors including decreasing total operative procedural time, decreasing EBL, allowing for better visualization of the surgical field with decreased overall surgical complications, and decreasing the risk of damage to adjacent tissue (such as major arteries and nerves), all of which are discussed in this chapter [9]. Tumor size >3–5 cm, more advanced Shamblin classification, or tumors extending above C2 vertebral body are used as more objective criteria for embolization [26, 42]. Embolization criteria vary from study to study, between individual surgeons within one study, and occasionally will change with time or situationally with the same surgeon within a study, making these analyses challenging [26].

Based on the available evidence, no strong recommendation regarding the use of pre-operative embolization can be made for surgical management of CBTs. Embolization does not seem to lead to more complications than surgery alone. EBL and operative time are at least no different between surgical excision only and pre-operative embolization with surgery groups, and there is weak evidence to suggest that these are less in the embolization group. Embolization could lead to longer hospital stays and may be costlier when compared to excision alone. It is also unclear if tumor size or Shamblin classification affects EBL, operative time, overall complications or LOS compared between these two groups. Embolization could be useful in patients who potentially need carotid artery sacrifice and reconstruction; however, it is often difficult to know and predict who will need reconstruction pre-operatively. Based on all the available evidence, no recommendation can be made regarding pre-operative CBT embolization.

Surgeon preference and experience of the angiographer must guide decision making for the use of embolization.

> Routine carotid embolization should not be employed prior to the surgical excision of carotid body tumors (evidence quality—very low, weak recommendation).

A Personal View of The Data

At our institution, we consider embolization for tumors that are 5 cm or greater or approach the skull base. We generally admit patients scheduled for embolization for 24 hours pre-operatively in the intensive care unit for monitoring. We believe that LOS and cost are most likely increased in patients who undergo embolization, but operative time and EBL can be significantly decreased especially if the procedure eliminates all the identified perforating vessels to the tumor. We also believe that embolization is safe, and the risk of cerebrovascular accident is low in high volume specialty centers with interventional neuroradiology expertise.

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17 Vagal Paraganglioma and Schwannoma—Surgical or Non-surgical Management

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Vagus nerve associated Paraganglioma and Vagus nerve associated Schwannoma are entirely different in their clinical behavior, and the two are therefore being discussed separately.

Vagal Paraganglioma (Glomus Vagale)

Introduction

Vagal paragangliomas (VPGLs) are rare, highly vascular neoplasms of neuroectodermal origin arising in the neck in the vicinity of the jugular foramen. The neoplasms develop in paraganglionic tissue found alongside the ganglia of the vagus nerve, with the most common location being the ganglion nodosum or inferior ganglion [1, 2]. The tumor may be largely asymptomatic when small in size and often becomes manifest only when it grows to a size of over 5 cm so as to present as a swelling in the upper neck. Pre-surgical manifest and symptomatic vagal nerve paralysis is unusual, though careful evaluation may often pick up a subtle (and often undetected) superior laryngeal nerve involvement. The lesion is typically detected as a highly vascular mass high in the parapharyngeal space which displaces the internal carotid artery anteriorly or anteromedially (Fig. 17.1). It is differentiated from a carotid body tumor by its location (away from the carotid bulb and bifurcation; abutting or extending to the skull base and jugular foramen) and also the lack of splaying of the internal and external carotid arteries. Radio-nuclide imaging with

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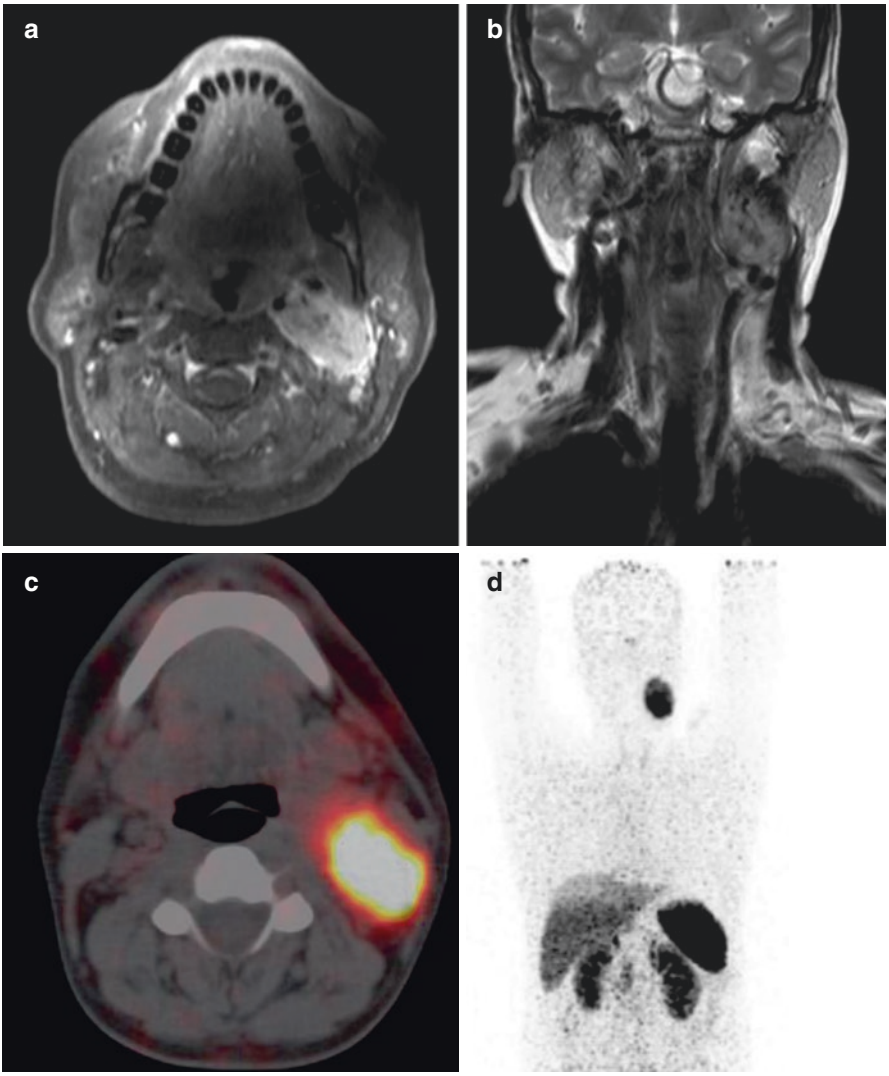

Fig. 17.1 Classical radiological images of a vagal paraganglioma demonstrating—(**a**, **b**) a higher location in the skull base in comparison to Carotid Body Tumors with anterior displacement of the Carotid Vessels; (**c**, **d**) DOTONOC images showing intense uptake within the tumor

MIBG scans or with Somatostatin receptor DOTANOC scans can further confirm the tumor as a vascular tumor of neural crest origin [3].

Though typically benign, malignant variants are noted in 16–19% of VPGLs [4]. Among the Head-neck paragangliomas (PGs), Vagal PGs have the highest malignancy rates in comparison to carotid body tumors and jugulo-tympanic PGs [4, 5]. Histological evaluation is not sensitive for detecting malignant changes and such

behavior is generally manifested only by the discovery of regional or distant metastatic lesions.

Surgical excision has been the traditional treatment. Recent years have however brought about a realization of the high risks of permanent vagal nerve injury consequent to surgery. Advances in radiology have allowed for non-invasive monitoring of the growth of tumor. Unravelling of the human genome and some insight into the genetic abnormalities predisposing to such tumors has allowed for better prognostication. Non-invasive approaches towards watchful waiting (with radiological monitoring) and radiation treatment have therefore emerged as alternate treatments.

Literature Search Strategy

The literature search was undertaken on Pubmed and CENTRAL and included the terms "Paraganglioma Head-Neck", "Vagal paraganglioma", and "Glomus Vagale". Original research articles and Review articles available in the English language literature and published from January 2000 to June 2018 were evaluated. Cross references were further evaluated as per their perceived relevance.

Most literature tends to look at head-neck PGs in conjunction and literature specifically on Glomus Vagale are fewer in number. Manuscripts were selected on the basis of their clinical relevance and scientific strength. The literature was scanned to bring forth data as per the PICO format as listed in Table 17.1.

No randomized controlled trials comparing the various treatment options were noted.

Surgery

Table 17.2 lists the evidence in the literature for surgical management. Surgery is noted as the only treatment option offering the chance of definitive and immediate cure but with significant morbidity rates. Since all data reported is as retrospective case series, a case selection bias is to be expected. Given this expected selection bias, gross tumor resection (GTR) is noted in 91–100% of reported

Table 17.1 PICO parameters as selected for the review (vagal paraganglioma)

P—Population	Vagal paraganglioma
I—Intervention	Surgical management
C—Comparison	Non-surgical managements – Observation (wait and scan) – Fractionated radiotherapy – Stereotactic radiosurgery/"Gamma-knife" radiation – Peptide receptor radiotherapy (PRRT)
O—Outcomes	Tumor control rate Incidence of complications

Table 17.2 Vagal paragangliomas managed by surgery

Publication	Study design	n	Complete excision (%)	Vagus nerve sacrifice (%)	Other CN deficits (%)	Follow up Mean (range) months	Other complications
Bradshaw and Jansen [2]	Retrospective case series	10	100	100	60	100 (12–312)	Aspiration pneumonia: 1
Paris et al. [6]	Retrospective case series	11	NA	81.8	9.1	6	–
Kollert et al. [7]	Retrospective case series	12	90.9	100	NA	65 (1–226)	–
Zanoletti and Mazzoni [8]	Retrospective case series	16	100	100	25	75 (9–156)	Cerebrovascular accident:—1 Death (cause unrelated)—1
Lozano et al. [9]	Retrospective case series	6	100	100	NA	120 (44–182)	Metastasis on follow up—1
Neskey et al. [10]	Retrospective case series	4	100	25%	25	30	100% transient Xth CN palsy 50% permanent Xth CN palsy
Shin et al. [11]	Retrospective case series	21	90.5	100	52	NA	Recurrence—1
Künzel et al. [12]	Retrospective case series	7	100	100	71.4	50 (8–119)	Percutaneous gastrostomy—2
González-Orús Álvarez-Morujo et al. [13]	Retrospective case series	11	100	100	60	36 (12–96)	Respiratory distress syndrome—1
Suárez et al. [5]	Systematic review	226	93.3	95.1	9.1–27	–	23.5%—serious complications 1.8%—deaths

cases [5]. A mortality incidence of up to (1.8%) [5], has been described, and with a near-invariable loss of the vagus nerve [2, 7, 8, 14].

Cerebrovascular accidents and stroke have been described in in 2.2%, cerebrospinal fluid (CSF) leak in 2.6%, and meningitis 0.4% of patients undergoing surgical resection [15]. Other new post-operative cranial nerve palsies involving CN IX, XI and XII (usually IX) are noted in 23–61% of the cases [5, 6, 9].

Severe aspiration as a consequence of lower cranial nerve palsies occurs in 10.2% of the cases [15]. The majority of patients needed complex rehabilitation regarding speech and swallowing [5, 15]. Partial recovery and compensation based on intact contralateral functions form the basis for renewal of aspiration free swallow. Surgical risks should be very carefully assessed in situations of multiple tumors wherein bilateral lower cranial nerves are at risk.

Surgical Rehabilitation of Cranial nerve deficits and swallowing function: The morbidity and mortality following surgery is mainly consequent to Cranial nerve dysfunction [5]. Surgical treatments to aid rehabilitation are noted to be effective [16–18]. Vocal cord medialization aims to improve glottis closure, improve the effectiveness of the cough, and thereby improve aspiration and voice. As opposed to the usual vocal fold paralysis wherein only the recurrent laryngeal nerve is involved ("low" vagal paralysis), a vagus nerve paralysis in the jugular foramen ("high" vagal paralysis) impacts on both the Superior laryngeal nerve and the Recurrent laryngeal nerve. A high vagal paralysis leads to not only an immobile and horizontally lateralized vocal fold as in low vagal paralysis, but also to additional deficits in supraglottic sensation, additional laryngeal motor deficits of cricothyroid muscle paralysis with consequent loss in vocal fold tension, bowing of the vocal fold, and a vertical mismatch in the levels of the two vocal folds, and also pharyngeal motor deficits with incoordination of the pharyngeal constrictors and the upper esophageal sphincter [17]. Medialization of the vocal fold alone is noted to be suboptimal in correcting these deficits associated with high vagal paralysis [16–18].

Surgical treatments aiming to correct not only the horizontal glottic gap, but also the vertical glottic mismatch and vocal fold sagging, have been consistently successful with invariable improvements noted in dysphagia and vocalization scores. Acceptable swallowing function enabling full nutrition was reported in all 9/9 patients by Cheesman and Kelly with a single stage procedure incorporating vocal fold medialization, arytenoidopexy to elevate the vocal fold, pyriform sinus mucosal plication, upper esophagus constrictor myotomy and laryngeal suspension [17]. Thakar et al. reported similar swallowing outcomes in 5/5 patients with a unilateral cricothyroid approximation (tensioning thyroplasty) to simulate the deficient cricothyroid muscle function, and Chirilă and Muresan reported no aspiration in 5/5 patients undergoing vocal fold medicalization and elevation with insertion of tragal cartilage and perichondrium grafts in the lateral cricoarytenoid muscle [16, 18].

Cheesman and Kelly advocated that surgical intervention be reserved for cases not showing improvement with compensation and rehabilitation strategies over 6 months [17]. However, Thakar et al. recommend an early surgical treatment, as adequate compensation cannot be expected for deficits such as loss of vocal fold tension and its vertical sagging [16].

Observation (Wait and Scan)

The cranial nerve morbidity associated with surgery, and the availability of MR for monitoring, has led to the exploration of regular observation in the quest to avoid surgery and its complications in non-growing tumors. Most literature to date on this option is based on selected cohorts of patients (Table 17.3) and while the reports are encouraging, there remain concerns on applying this data to all patients.

The recent literature is summarized in Table 17.3. While such tumors are generally noted to be very slow growing with a usual doubling time of approximately 10 years [4]. It is also acknowledged that great variability exists among tumors with regard to their rate of growth.

The best quality evidence probably comes from a retrospective cohort study from Jansen et al. in the Netherlands, wherein from a total of 258 Head-Neck Paragangliomas, 159 were routed for initial observation [21]. The exact aspects of the selection criteria for undertaking observation rather than active treatment are not elucidated, but it may be safely assumed that it was biased towards older patients (median age 65 years—range 13–90 years), and tumors deemed as relatively less aggressive on initial evaluation. 29 of the 157 patients had VPGLs. The median duration of observation was 51 months.

While on observation, 12/29 VPGLs demonstrated continued growth, and 4/29 developed new cranial nerve palsies. The mean rate of growth among growing tumors was 11 mm/year, (mean growth in volume 25 mm^3/year). New Cranial nerve palsies were as common in the non-growing tumors (3/17) as in growing tumors (1/12). Patients younger than 50 years were significantly more likely to demonstrate tumor growth as compared to older patients. Patients younger than 50 years were more likely to have genetic mutations compared to older patients. No significant difference between the rate of complications was noted as per tumor size or mutation status, or between Vagal, jugulotympanic or carotid body tumors [21].

It has been speculated that growth rates may differ among different populations. The slow growth rates in the above reported Danish cohort [21] may possibly be attributed to a homogenous genetic cohort (predominantly SDHD genotype) and to minimal hypoxic stimulation for reason of the Netherlands being a low altitude area at sea-level [5].

Reports of unselected cohorts of HNPGLs from previous years are not so well documented or well categorized, but do indicate to some concern. These reports come from the pre-CT era wherein Carotid body tumors and Vagal paragangliomas would probably be indistinguishable from each other and have the potential to be analyzed as a single patient cohort. Monro in a literature review of 223 such patients in 1950 states that in patients with no treatment or inadequate surgical treatment, mortality consequent to tumor growth occurred in 30%. However, the exact period of follow up was not mentioned [23]. Martin et al. noted metastatic spread to lymph nodes in 25% of a cohort of 28 untreated patients over an 11 year follow up time period [24]. A recent update from the Netherlands group in a specific cohort of SDH-D genotype has also noted of eventual growth in the long term, with 85% tumors showing growth over a 11 year follow up [22].

Table 17.3 Vagal paragangliomas managed by observation

Publication	Design	Selection criteria	n	Follow-up mean (range)	Complications	Control rate (%)
Bradshaw and Jansen [2]	Retrospective case series	Multiple PGL/, B/L VGPL	40	100 months (12–312)	8%—new Crnl. Nrv. palsy 5%—distant metastasis	87
Langerman et al. [19]	Retrospective case series	Patient preference, advanced age, preexisting C/L cranial nerve deficit	19	60 months (12–196)	Nil	100
Shin et al. [11]	Retrospective case series	Advanced age	1	NA	Nil	100
Álvarez-Morujo et al. [20]	Retrospective case series	Advanced age	6	36 months (12–96)	No progression	100
Jansen et al. [21]	Retrospective cohort study	Not specified (60% of total cohort of HNPgl had observation)	29	51 months (26–261)	12/29 (41%) Tumor growth 4/29 (14%) New CN palsy	86
Heesterman et al. [22]	Retrospective cohort study	SDH-D genotype	66	55 months median	–	64% growth 5% regression at 55 months median follow up 42% tumor growth at 1 year follow up 85% tumor growth at 11 year follow up

Vagal paragangliomas are noted to be most likely among the Head-Neck Paragangliomas to harbor malignancy [4, 5], with an estimated malignancy rate of 16–19% [4]. The recent availability of Somatostatin receptor DOTANOC imaging has improved our ability to pick up metastatic disease, and a recent report of Head-Neck Paragangliomas identified metastatic disease in 38% (10/26) by such imaging [25]. Metastatic disease may however remain indolent and not be rapidly progressive.

Recent advances on the molecular and genetic understanding of PGLs has indicated to germline mutation in the VHL, RET and SDH genes [5]. Genetic testing for these genes can indicate to the genetic abnormalities and the SDH mutations underlying particular syndromes. It is estimated that up to 1/3 of seemingly sporadic tumors may harbor genetic germline mutations [4]. Variations in the phenotypic expression of various SDH subtype mutations can aid in prognostication and the advisability of considering a non-surgical observation plan. The SDH-C mutation prognosticates towards benign and unifocal disease, the SDH-D mutation to multifocal tumors in the Head-Neck, and the SDH-B mutation towards a greater potential for malignant disease [4].

In patients with established pre-surgical vagal paralysis, surgical intervention is recommended over observation as operative resection could prevent further loss of cranial nerves (quality of evidence moderate; weak recommendation).

In patients with minimal pre-surgical cranial nerve deficit, treatment-induced cranial nerve deficits are far more likely following surgery, than following nonsurgical therapy. Surgery may however yet be indicated as it is the only treatment option offering a long term and definitive cure (quality of evidence high; weak recommendation).

A significant subset of VPGLs, especially in patients older than 50 years, demonstrate non-progressive or slowly progressive growth patterns, and a period of observation can help identify such tumors wherein aggressive treatment and its morbidity may be totally avoided or significantly delayed (quality of evidence moderate; weak recommendation).

Radiation Therapy (RT)

Fractionated Radiation (External Beam RT/Intensity Modulated RT/Stereotactic RT)

The effect of radiotherapy has been studied in general for head and neck PGs and isolated large studies on vagal paraganglioma are not available. Radiotherapy acts mainly by its action on the vascular and perivascular cells, but the glomus cell is noted to be radiation resistant [5, 15, 26]. Tumor control is defined as the absence of

Table 17.4 Vagal and jugular PGLs managed by fractionated radiotherapy as primary treatment

Publication	Case group/ study design	n	RT dose (Gy)	Follow up Mean (range)	Local control (no progression)	Complications/ CN palsies
Hinerman et al. [27]	VGPL Retrospective case series	10	35–45	136 months (18–180)	100%	Nil
Künzel et al. [12]	VGPL Retrospective case series	2	50–56	60 months (30–90)	100	Nil Nil
Dupin et al. [28]	VGPL Retrospective case series	18	45	50 months (6–110)	100	Nil
Cao et al. [29]	VGPL Case report	1	50.4 proton based RT	24 months	100	Nil
Suárez et al. [5]	Jugular PGL Systematic review Case selection not defined	461	–	112 months	89.1% control 3.2%—tumor related death	10.4%—major complications 2.0%—Rx related deaths

further tumor progression. The tumor may gradually regress but almost never completely disappears. Radiation may be preferred to surgical treatment because of the lesser incidence of cranial nerve palsies; or in situations wherein patients are deemed unsuitable for surgery for reason of co-morbidities or unresectable tumors; or in situations of incomplete excision/residual disease which is usually the case with Jugular paragangliomas but less likely in VPGLs.

Table 17.4 synopsizes the limited data that is available with regard to primary radiation treatment specifically for Vagal PGL A more significant experience is however available for Radiation in Jugular PGLs and this may be loosely extrapolated to VPGLs. A recent systemic review on Jugular Paragangliomas is compared in Table 17.4.

The summed-up data on radiation for Head-Neck PGLs indicates to patients in the radiation group being generally older than in the surgical groups [5]. Given the slow growing nature of many untreated PGLs, the incremental benefits of radiation have been difficult to quantify. For Head-Neck PGLs overall, the data on fractionated radiation is dominated by the Miami group [27, 30, 31]. Radiation used as primary treatment for patients with HNPGL has yielded local control rates (i.e., stable disease) of 90% or more with low-dose (45 Gray or less) radiation, even after long-term follow-up of 15 years [5, 27, 30, 31]. Other reports are however not that encouraging [4, 32, 33]. The glomus cell per se is believed to relatively radioresistant [5, 15, 26], and concerns remain of breakout growth in the long-term [4]. The systematic review by Suárez et al. [5] noted a 10.4% major complication rate, 2.0% treatment related deaths, and 3.2% death consequent to subsequent disease

progression. The complication profile for Jugular PGL included mainly osteoradionecrosis, deafness and brain necrosis.

RT may be considered as a treatment alternative for older patients or patients considered unsuitable for surgery (quality of evidence moderate; weak recommendation).

Stereotactic Radiosurgery (SRS)/Gamma Knife Treatment and Fractionated SRS

This modality of treatment is restricted to jugulo tympanic paragangliomas and is unsuitable for vagal paragangliomas.

Peptide Receptor Radiotherapy (PRRT)

PRRT using various radiolabeled somatostatin analogs like 111In-octreotide, 131I-metaiodobenzylguanidine (131I-MIBG) and 177LU-DOTATA have been used in locally advanced unresectable and metastatic paragangliomas [34, 35]. PRRT specifically for VPGL is less documented, and only a single case with partial remission has been reported [36].

A Personal View of the Data

Genetic understanding of these tumors is increasing incrementally. Such genetic profiling of the tumor is likely to become mainstream in the next decade or two and will likely become the predominant tool to prognosticate tumor behavior and accordingly to weigh the degree of risk and morbidity that is justifiable in its treatment.

Workup for these patients should include appropriate anatomical imaging (CECT/MR/MR Angiography), functional imaging (DOTA scan), assessment of serum and urinary catecholamines, and a genetic workup when feasible. Ga-68 DOTA based peptide PET/CT scan is currently the best modality to image these lesions as it is the most sensitive modality to pick up multiple and metastatic tumors. The detection of multiple or metastatic tumors has significant implications for management, and our detection of such metastasis/multiplicity has increased dramatically since the routine use of such scans [25].

Recent trends indicate to a move towards non-surgical treatment for Head-Neck PGLs [21]. Studies on the natural history of such lesions (Wait and Scan treatment) have tended to be focused on favorable situations rather than on consecutive patients. They demonstrate that about half such favorable patients will not demonstrate growth and these patients may be possibly spared needless treatment and its complications.

Patients with relatively greater age (>50 years), asymptomatic and small tumors, and tumors with no significant cranial nerve morbidity are probably best suited for observation.

Situations wherein continuing observation is unsuitable and treatment is indicated include the following:

(a) Situations wherein the aggressive nature of the tumor is already manifest by significant tumor size or cranial nerve dysfunction.
(b) Situations wherein tumor growth and morbidity is anticipated. Younger patients, and patients with a suggested genetic basis as indicated by multifocality seem more likely to have tumor growth. Younger patients also have a greater anticipated lifespan and tumor growth is therefore more likely.

    A genetic workup may specifically identify involved genes and help towards a more specific prognostication regarding growth.
(c) Concerns regarding an underlying occult malignant nature of the tumor. Among the HN PGLs such concerns are maximal with Vagal PGLs and noted at 16–19% [4]. Again, a genetic workup can better prognosticate on such risks.

    Manifest malignancy indicated by lymph node involvement or distant spread to the lungs or bones obviously merits treatment.
(d) Demonstrable growth following a period of watchful waiting as indicated by either an increase in tumor size or a new cranial nerve deficit.

Once a choice is made for active treatment then the next weighing of options is between treatment with radiation or surgery. This is based on a consideration of the perceived and likely risks of surgery in a particular situation.

For Vagal PGs the prime risk of surgery is to the Xth CN. The risk to the ICA is relatively small and can be quantified further by MRI Scanning. Loss of the Xth CN with a high vagal paralysis is however an almost invariable consequence of surgery. A unilateral high vagal paralysis can nevertheless be appropriately and consistently treated by a combination of rehabilitative and surgical procedures. In our practice, this is undertaken by an ipsilateral cricothyroid approximation (*aka* tensioning thyroplasty/Type IV thyroplasty). The technique simulates the action of the denervated cricothyroid muscle and restores vocal fold tension and vertical position in a physiologic way, and also partly corrects horizontal vocal fold position. It corrects the deficits which compensate poorly (i.e. deficits on vocal fold position and sagging) and leaves a small deficit in horizontal position which subsequently compensates excellently. The procedure is simple and safe, and reliably improves both speech and swallowing deficits [16]. In situations wherein a Xth nerve section/loss is confirmed at surgery, the corrective thyroplasty is best undertaken concurrent with the excision procedure [16].

Radiation is avoided in young patients due to its long-term risks and also due to concerns with breakout growth in the long term. It may be preferred in some situations wherein there is significant extension into the jugular foramen or significant vascular involvement with consequent increased surgical risks. Surgery may also be

avoided in the very elderly as cranial nerve deficits are less well tolerated in the older patient population.

Patient preferences are a major part of decision making. Some patients may prefer radiation to surgery due to concerns regarding the post-surgical Xth nerve deficit (despite assurances regarding its rehabilitation), and others may prefer surgery to radiation due to concerns of having a post radiation persistent and residual tumor (despite assurances regarding it being non-progressive).

PRRT is emerging as an alternative to external beam radiation. Data on local control of tumors treated by PRRT is yet unavailable. In situations with metastatic disease, treatment with PRRT is an option and temporary disease control has been noted [15, 36].

Vagal Schwannoma

Introduction

Schwannomas arising from the vagus nerve are rare. They may arise from the intracranial section or the extracranial section of the nerve.

Pure intracranial vagal schwannomas with no connection with the jugular foramen are extremely unusual with only six reported cases [37–39]. Intracranial schwannomas are typically located in the Jugular foramen and are classified into three types: Type A tumor, with primary intracranial involvement and minimal extension into the jugular foramen; Type B tumor, primary involvement of the jugular foramen with or without an intracranial component; Type C tumor, primarily extracranial with minimal extension into the jugular foramen. Most symptoms are not localized to the vagus nerve but tend to mimic those of an acoustic neuroma with decreasing hearing, vertigo and ataxia being the most common presentations. Occasionally, neurogenic hypertension consequent to hyperstimulation of the vagus nerve has been noted [37].

Extracranial Cervical Schwannoma arising from the vagus nerve presents as a benign nerve tumor in the parapharyngeal space. It typically occurs in adulthood and affects both genders equally. MR and FNAC are the evaluation methods of choice. On CT images, vagal schwannomas appear as well-defined masses, usually of higher attenuation than muscle on contrast-enhanced images. MR evaluation typically shows masses of intermediate signal on T1-weighted images and increased signal intensity on T2-weighted images with smooth, well-delineated margins and a homogeneous overall appearance (Fig. 17.2). Vagal schwannomas splay the common or internal carotid artery from the jugular vein, whereas schwannomas of the cervical sympathetic chain tend to push both the carotid artery and IJV anteriorly [40]. Glomus tumors may be reliably differentiated from Schwannomas by their vascularity, the salt and pepper appearance on MR consequent to its multiple vascular channels, and by the intense uptake on a DOTANOC Scan [25, 41–43]. Diffusion weighted MR imaging may further aid in this differentiation [7]. Current radiological sophistication can confirm the diagnosis with a fair degree of certainty and the same may be further supported by FNAC. Additionally, radiological assessment of

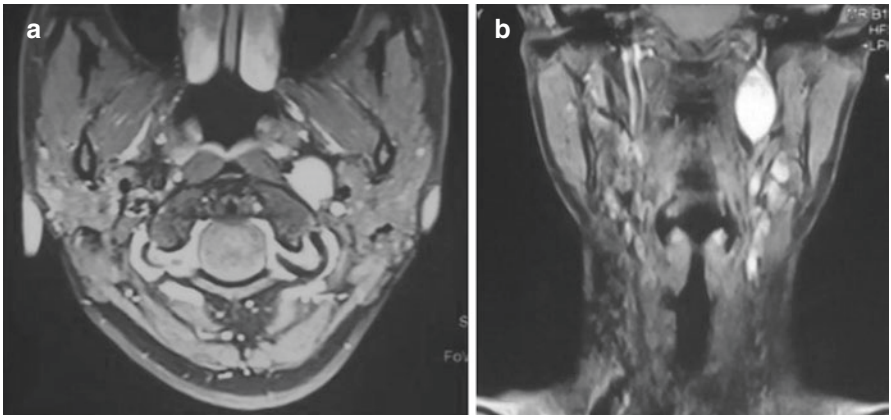

Fig. 17.2 Vagal Schwannoma—T1W Contrast MR (**a**) Axial sections, showing the hypointense lesion on left side separating the ICA and IJV. (**b**) Coronal sections, showing the same homogenous mass with fusiform tapering edges continuous with the X Cranial nerve and splaying the ICA and IJV

Table 17.5 PICO parameters as selected for the review (vagal schwannoma)

P—Population	Vagal schwannoma
I—Intervention	Surgical management
C—Comparison	Non-surgical managements – Observation (wait and scan) – Fractionated radiotherapy – Stereotactic radiosurgery/"Gamma-knife" radiation – "Cyber-knife" radiation
O—Outcomes	Tumor control rate Incidence of complications

the nerve of origin serves to prognosticate the risks of surgery. Associated malignancy or malignant transformation in Schwannomas is extremely rare.

Surgical excision has been the traditional treatment of choice. Surgical planning is often influenced by lesion size, location, vascularity, and relation to adjacent structures such as the vagus nerve, sympathetic chain, carotid artery, and jugular vein. Post-surgical paralysis of the vagus nerve is however frequent [40]. Improving radiology has allowed for both a certainty of diagnosis and also an ability for growth monitoring of the tumor. Alternative forms of non-surgical approaches towards 'wait and scan' are therefore emerging.

Literature Search Strategy

Based on the PICO table (Table 17.5), Pubmed and CENTRAL searches incorporating the terms "Schwannoma Head-Neck", "Vagal schwannoma", "Vagal Neurilemmomas" and "Jugular schwannoma", were used to review the literature. There were no randomized control trials to compare the various treatment options.

Review articles and original research articles available in the English language and published from January 2000 to June 2018 were evaluated. Manuscripts were selected on the basis of their clinical relevance and scientific strength, as per our discretion. Due to rarity of the tumor, most available literature was in the form of case reports and case series.

Surgery

Surgery is the only treatment option offering a permanent one-time cure, but has significant morbidity relating to loss of the vagus nerve. The tumor may be excised by an extracapsular complete excision, or by an intracapsular enucleation attempting to preserve the nerve fibers in the tumor periphery/capsule. Positive identification of the nerve fibers in the capsule is however typically difficult, and nerve monitoring may aid in this endeavor. A damaged cranial nerve should be appropriately rehabilitated by a vocal fold medialization or tensioning as appropriate.

Table 17.6 lists the surgical experience. The data with regard to surgical excision of X nerve Schwannoma is limited with no reports with long term follow up. This may relate to the general surgical confidence, especially so with extracapsular excision wherein complete excision is the rule and little risk of recurrence is anticipated.

A larger number of reports exist for intracapsular enucleation than for extracapsular excision, but this may relate to publication bias. It is perceived that intracapsular resection would have a greater chance of preserving nerve function, but this is not consistently noted in the literature [44, 45].

Similarly, intracapsular resection would be expected to lead to greater recurrence rates but the follow-up periods are too short for this to be reflected in the data [46, 47, 51]. Longer term series have noted that the mean time to recurrence after near-total resection ranged from 2–20-years [48–50, 52–58]. The rates of X nerve paralysis (temporary and permanent) following surgical resection range from 26–93% [44–47, 51].

> Surgical treatment of vagal schwannomas is an effective treatment but has significant risks towards loss of X nerve function.
>
> Intracapsular excision may preserve neural function but risks recurrence in the long term (quality of evidence moderate: weak recommendation).

Stereotactic Radiation (Gamma Knife/Cyber Knife)

The use of radiosurgery as a primary treatment modality or an adjunct therapy for schwannomas (intracranial and those involving jugular foramen) is a topic of debate. The literature reported for stereotactic radiosurgery is essentially for jugular foramen

Table 17.6 Vagal schwannomas managed by surgery

Publication	Case group/study design	Site	N	Surgical procedure	Pre-op vagal paralysis	Post-op vagal paralysis	Follow up (months) (mean)	Recurrence (%)
Cavallaro et al. [44]	Systematic review	Cervical	53	35 intracapsular 18 extracapsular	4	10 permanent 9 transient	9	–
Valentino et al. [45]	Case series	Cervical	6	5 intracapsular 1 extracapsular	1	2 permanent 1 transient	10	–
Zheng et al. [46]	Systematic review	Cervical	50	50 intracapsular	4	6 permanent 7 transient	14	–
Netterville et al. [47]	Retrospective cohort study	Cervical	20	16 intracapsular	–	1 permanent 2 transient	32	–
Yasumatsu et al. [48]	Case series	Cervical	10	5 intracapsular 5 extracapsular	n.r.[a]	–	n.r.	n.r.
Lahoti et al. [49]	Case series	Cervical	4	n.r.	n.r.	2 permanent	n.r.	n.r.
Liu et al. [50]	Case series	Cervical	6	n.r.	n.r.	n.r.	n.r.	n.r.
Sreevatsa et al. [40]	Case series	Cervical	3	Intracapsular	–	–	12	–
Kim et al. [51]	Case series	Cervical	6	Intracapsular	–	–	n.r.	n.r.
Kang et al. [52]	Case series	Cervical	6	Intracapsular	n.r.	–	14	–
Sanna et al. [53]	Retrospective cohort series	Jugular foramen	22	Skull base approaches	n.r.	11	n.r.	–
Bulsara et al. [54]	Retrospective cohort series	Jugular foramen	53	Skull base approaches	7+	16	101	6
Sedney et al. [55]	Retrospective cohort series	Jugular foramen	81	Skull base approaches	n.r.	29 permanent 16 transient	n.r.	9
Chibbaro et al. [56]	Case series	Jugular foramen	16	Skull base approaches	–	2 permanent 2 transient	79	–

[a]*n.r.* not recorded

Table 17.7 Jugular foramen schwannomas managed with stereotactic radiosurgery

Publication	n	Mean tumor volume (cm^3)	Mean follow up (months)	Mean C.N. deficits pre S.R.S. (no)	C.N. improvement[a] post S.R.S. (%)	C.N. worsening[a] post S.R.S. (%)	Tumor control rate (%)
Pollock et al. [59]	23	8.9	43	n.r.[b]	20	17	96
Zabel et al. [60]	13	19	33	7	30	0	100
Kano et al. [61]	92	4.1	51	28	38	4	87
Hasegawa et al. [62]	117	4.9	52	46	66	4	89

[a]Percentage of patients demonstrating improvement or worsening of lower cranial nerve function as reported
[b]*n.r.* not recorded

schwannomas rather than specifically vagal nerve schwannoma, as a clear pre-treatment radiological demarcation on the nerve of origin in this region is usually not possible. Good tumor control rates and fewer post treatment neural deficits than reported with surgery are noted (Table 17.7) [59–62]. The data however predominates with relatively small tumors and the follow up periods are also not long (Table 17.7). The slow growth rate of these tumors necessitates long-term follow-up data.

In a series including jugular foramen schwannomas that studied the effect of stereotactic radiosurgery without specifying nerve of origin, it was demonstrated that the progression-free survival (PFS) was 93% at 3 years, 87% at 5 years, and 82% at 10 years. They found that factors associated with better PFS included tumor volume <6 cm^3 ($p = 0.037$) and non-dumbbell-shaped tumors ($p = 0.015$). Preexisting cranial neuropathies improved in 27% patients [61]. In another series, 3 and 5-year progression-free survival (PFS) rates were 91% and 89%, respectively. The preexisting hoarseness and swallowing disturbances improved in 66% of the patients [62].

While intuition may favor radiosurgery over resection for high-risk patients and residual or recurrent tumor, larger studies are required before final conclusions can be drawn. Certainly, a conservative non-operative approach is a valid option for head and neck schwannomas if the diagnosis has been established and the patient is tolerating the tumor well without neurogenic deficit, mass effect or rapid progression.

Only one case to our knowledge has been reported for radiosurgical treatment (cyberknife) of extracranial vagus nerve schwannoma [63]. There were no treatment related side effects and the tumor exhibited greater than 50% diminution in volume radiographically after 19 months follow up.

Stereotactic radiosurgery is a safe and effective primary or adjuvant management approach for Jugular Foramen Schwannoma with encouraging long-term tumor control rates and stability or improvement in CN function (quality of evidence moderate: weak recommendation).

Observation/Wait and Scan

Given the relatively rare occurrence of these lesions, no clear data exists with regard to a treatment approach focused on "observation" or "Wait and Scan". Given that the tumor is almost always benign, that "Wait and Scan" is an established practice for similar schwannomas elsewhere (e.g. Vestibular Schwannoma), and that surgical treatment for most vagal Schwannomas risks X nerve damage, such a treatment strategy would be suitable for asymptomatic patients and those with minimal symptoms or deficits.

A retrospective study by Alemi et al. [64] is the only work available evaluating the growth rate of the cervical schwannomas when left alone. Thirteen such patients have been followed over a mean period of 21 months (range 1–80 months), and in six patients further treatment was avoided. The mean tumor volume at inception of treatment was 125 cm^3 (range 5–608 cm^3), the average growth rate for all tumors was 2.61 cm^3/month, and the growth rates for tumors wherein observation was persisted with was 2.75 cm^3/month. Great variation was noted in the growth rates with the maximum being 33 cm^3/month and 3/13 patients showing mild tumor regression. The authors noted that in their practice a growth rate of <5 cm^3/month predicated towards continuing observation and greater growth rates led to surgery.

No clear predictors to prognosticate the potential for growth are yet identified. It is however expected that the data on this treatment modality would build up over the next decade or so.

Another concern with keeping patients on observation is the potential for malignant transformation. Malignant change in schwannomas in the head and neck region is very rare with approximately a dozen cases reported in English literature. Malignant peripheral nerve sheath tumors, seen especially in von Recklinghausen disease, do not occur with schwannomas. However, malignant transformation from schwannoma to angiosarcoma has been postulated in a few reports [65–67]. They neither show any specific features on imaging, nor can be differentiated on FNAC. Consequently, if follow-up observation is chosen, surveillance MRI should be undertaken periodically. An initial repeat scan at 4–6 months and subsequent yearly scans seem prudent.

> Observation and wait and scan is an acceptable management strategy for asymptomatic patients and those with minimal symptoms or deficits (quality of evidence low: weak recommendation).

A Personal View on the Data

Though surgery has been the mainstay of treatment for Vagal nerve Schwannomas, it has been associated with considerable morbidity related to iatrogenic injury to the Vagus nerve. Given that the tumor is almost never malignant, and that radiology can confirm the diagnosis with a high degree of certainty, and enable periodic

observations for unexpected growth, the rationale of continuing with surgery and its morbidity as first line treatment should be reassessed.

Little data exists today with regard to the efficacy of Wait and Scan for such tumors and also the parameters which may predicate future growth. Nevertheless, for asymptomatic tumors a period of continuing observation may help select those patients wherein no ongoing growth is noted, and treatment therefore seems imprudent. Early data suggests that treatment may be deferred or significantly delayed in approximately half the patients. No clarity currently exists regarding how long these observations need to be continued.

For situations wherein surgery is undertaken, an intracapsular excision or preservation of the nerve fibers in the tumor capsule should be attempted, but nerve function is often lost nevertheless. Nerve monitoring may improve the chances of functional preservation. Any loss of X nerve function should have early rehabilitative and surgical treatment by a medialization or tensioning thyroplasty.

For tumors in the jugular foramen, surgery and stereotactic radiotherapy are both effective treatments. SRT promises good initial cranial nerve preservation rates and may be preferred for suitable situations.

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Part VI

Salivary

Parotid Malignancy with Facial Weakness: Should the Facial Nerve Be Sacrificed?

18

Luiz Paulo Kowalski, Alvaro Sanabria, and Joel Arevalo

Introduction

Carcinoma of the parotid gland accounts for 14–25% of all parotid lesions [1]. The mainstay of treatment for patients with parotid malignancies is surgery. Most patients present with a detected mass but no clinical indication of a malignancy. Some of these masses are identified as malignant tumors only after pathological examination. In these cases, the surgeon usually performs a standard parotidectomy with facial nerve preservation as if it was a benign tumor. By contrast, some patients are referred to a surgeon with a large mass that invades the skin, with concomitant lymph node enlargement and complete paralysis of the facial nerve (FN). For these patients, most surgeons perform a radical parotidectomy without concerns about FN sacrifice. However, 14–30% patients present with no clinical indications of an advanced tumor until discovery of FN weakness/paresis during the preoperative exam or a nerve invasion during surgery [2]. In these situations, the decision to preserve or resect the FN must be

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made preoperatively or intraoperatively. If preservation is selected, the risk of local recurrence must be considered. On the other hand, if sacrifice is selected, concerns about FN reconstruction, function, and quality of life (QOL) must be considered. When making this decision, surgeons are typically faced with two different scenarios: a primary tumor of the parotid gland or metastasis from a other primary tumor, such as the skin. This chapter assesses the arguments to sacrifice or preserve the FN in the context of these two scenarios.

Search Strategy

The search strategy was performed to suit the PICO format listed in Table 18.1. To identify relevant articles, a search was conducted in the PubMed and EMBASE databases with the following terms: "parotid," "cancer," "neoplasm," "parotidectomy," "sacrifice," and "preservation" from January 1966 to February 2018. The snowball strategy, a manual search through the references of these articles, was then used to identify more relevant articles. Letter to editor, case reports and narrative reviews were excluded. After reviewing the titles, only articles on surgery in treatment-naive patients with a primary parotid tumor or metastasis to the parotid gland were assessed.

Results

Previous studies have identified some risk factors related to a high probability of FN sacrifice during parotidectomy: tumors that are large, malignant, adenoid cystic, located in the deep lobe, or accompanied with preoperative nerve dysfunction [1, 3]. However, these factors were determined by studies that combined all types of surgical techniques for parotid tumors. The literature is scarce about specific risk factors for FN sacrifice in patients with malignant tumors.

It is commonly accepted that patients with preoperative total paralysis of the FN are not candidates for preservation. Additionally, in cases of weakness or selectively compromised FN branches, attempts should be made to preserve the trunk and the non-compromised branches [4]. Electrophysiological tests have

Table 18.1 PICO table for preservation of the facial nerve in patients with weakness/paralysis

Population	Intervention	Comparison	Outcomes
Adults with parotid gland tumors and preoperative weakness/paralysis of facial nerve	Nerve preservation	Nerve section	Overall survival, disease-specific survival, functional sequelae, and QOL

confirmed that preoperative FN dysfunction is a sensitive finding of nerve invasion, but its specificity is low [5].

To date, preoperative FN dysfunction is the only objective factor that has been widely explored to define FN sacrifice. Other factors are included in the "*intraoperative decision made by the surgeon*" concept and are described in the majority of studies, but they are still ill-defined. Some terms such as "encased," a circumferential involvement of the nerve, are easily understood by most surgeons. However, other terms such as "attachment" and "adherence" are not clear and their meanings vary between surgeons, making the decision to sacrifice the FN very heterogenous.

Patients with Primary Parotid Tumors

We identified five studies [1–4, 6] on surgery in treatment-naive patients with a primary parotid tumor. In these studies, 12–37% patients had preoperative FN dysfunction, and 21–48% patients had FN sacrifice (Table 18.2). Preis et al. [1] showed that even in 27% of patients without preoperative FN paralysis, a macroscopic tumor encasement was found during surgery. Huang et al. [11] found pathological invasion in 75% patients with preoperative FN paralysis and in 30% patients without this paralysis. In all cases the FN invasion was confirmed by definitive pathologic section. Frozen section analysis was not used. In the population with preoperative nerve dysfunction, Swenseid et al. [3] determined that 100% patients with a House-Brackmann (HB) score ≥2 needed complete sacrifice of the nerve in order to obtain negative margins. Iseli et al. [4] demonstrated that most sacrifices were for cancers involving the main FN trunk.

Table 18.2 Preoperative FN dysfunction and postoperative necessity of FN sacrifice in malignant parotid tumors

Study	Year	Number of patients	Preoperative FN paralysis (%)	FN sacrifice (%)
Primary parotid tumor				
Iseli et al. [4]	2008	48	37	33
Preis et al. [1]	2010	66	12	39
Terakedis et al. [2]	2014	129	17	21
Chung et al. [6]	2015	96	24	48
Swendseid et al. [3]	2017	75	26	40
Metastatic parotid tumor				
Hong et al. [7]	2005	20	10	30
Lai et al. [8]	2002	54	30	47
Shao et al. [9]	2014	160	18	34
Sweeny et al. [10]	2014	218	NR	42

FN facial nerve, *NR* not reported

Patients with Metastatic Tumors

We identified four studies [7–10] on surgery in treatment-naive patients with metastasis in the parotid gland. In these studies, 10–30% patients had preoperative FN dysfunction, but 30–47% patients had FN sacrifice (Table 18.2). Shao et al. [9] reported that sacrifice was required in 16% of the patients without preoperative FN paralysis.

These data demonstrate that in most cases preoperative FN paralysis correlates with tumor invasion and the need for FN sacrifice. In at least a third of patients without preoperative FN paralysis, an intraoperative finding obligated the sacrifice of the FN.

> Preoperative facial nerve paralysis correlates with tumor invasion and the need for facial nerve sacrifice during parotidectomy (evidence quality low, weak recommendation).

Function and QOL

The primary argument that favors FN preservation is related to functional and aesthetic sequelae after sacrifice. Chung et al. [6] assessed 39 patients after FN sacrifice and found postoperative FN function in 36% patients with a HB score of I–II, in 33% of those with a HB score of III–IV, and in 31% of those with a the HB score V. This study observed better outcomes in terms of FN function in patients with a nerve graft. Iseli et al. [4], found 25% patients with a HB score of III–IV after FN resection. These findings indicate that 25–33% patients have moderately functional sequelae even after FN sacrifice. Wang et al. [12] compared QOL using the Functional Assessment of Cancer Therapy—Head and Neck questionnaire and The Facial Disability Index between patients with or without FN sacrifice and found no differences in measurement parameters involving physical and social well-being related to appearance.

Reconstruction after FN resection is another decision that the surgeon must make intraoperatively. Because the discovery of invasion often occurs intraoperatively, the surgeon must decide whether an immediate reconstruction is feasible and recommended. Results from retrospective studies have shown that an intraoperative free nerve graft offers a good alternative, with 40–78% patients experiencing partial or total recovery (HB score <4) after 2 years of follow-up, especially in those with reconstruction of the superior branch [13, 14]. However, the belief that postoperative radiotherapy can impair the functional effects of an immediate FN free graft reconstruction is not supported by current evidence [15–17]. Although FN sacrifice is necessary in most patients with preoperative FN dysfunction, its effects on function and QOL measured with the Functional Assessment of Cancer Therapy—Head and Neck questionnaire and The Facial Disability Index are moderate in almost

30% patients. An immediate reconstruction with nerve free graft improves functional recovery and should be performed.

Although FN sacrifice can be necessary in most cases of preoperative FN dysfunction, effects on function and QOL are moderate (evidence quality low, weak recommendation).

Survival and Recurrence

Some authors have found no differences in overall or disease-specific survival between FN preservation and FN sacrifice [6, 18, 19]. However, patients with FN sacrifice clearly have more advanced tumors with worse prognoses [9, 20–23]. In cases of preoperative paralysis, there is always a concern about preserving the FN due to the risk of not reaching a tumor-free margin resection, which is a statistically significant risk factor for recurrence [20–22]. Iyer et al. [24] compared local failure rates of patients with positive microscopic margins around the nerve and those with close/negative margins (78% vs 94%) for metastatic squamous cell carcinoma to the parotid gland and found no statistically significant differences in overall or disease-specific survival. Additionally, Iseli et al. [4] conducted a similar comparison in patients with adenoid cystic tumors (79% vs 100%) and found no statistically significant differences in overall or disease-specific survival. None of the studies reported the rate of preoperative FN paralysis. Studying 134 patients, Carinci et al. [23] found that FN preservation offered an advantage in survival for patients with T1–2 tumors but not for those with T3–4 tumors. However, the number of cases was low and the rates for local failure were clearly different (78–79% vs 94–100%), so the study was underpowered to detect statistically significant differences.

From the point of view of recurrence and survival, there is no evidence to support FN preservation in cases of preoperative FN dysfunction or macroscopic invasion of the nerve, when considering that oncologic control should take precedence over aesthetic considerations. We believe that the above-mentioned differences in survival rates are relevant and must be taken into account by the oncologic surgeon. According to GRADE criteria, the evidence for these conclusions remains low quality for the following reasons: the absence of randomized controlled trials, the observational nature of studies, a high risk of selection and verification bias, high inconsistency and indirectness between studies due to intrinsic differences of studied population, differential interventions and the lack of specific criteria to define interventions as sacrifice or preservation, and high imprecision due to small sample sizes and the difficulties of adjusting for confounding variables. However, because salivary gland malignancies remain infrequent, designing an RCT is almost impossible. Furthermore, most decisions occur intraoperatively, which are liable to many factors that are hard to standardize.

Facial nerve preservation should not be performed in cases of preoperative FN dysfunction or macroscopic invasion of the nerve (evidence quality low, weak recommendation).

A Personal View of the Data

Preoperative FN dysfunction is clearly a marker of a more aggressive disease, with consequently worse prognosis. Therefore, the decision to sacrifice or preserve the FN should be adapted to the severity of the disease and the location of the tumor and not to functional outcomes. In presence of a malignant or suspicious parotid tumor, the most common deciding factor for FN sacrifice is the macroscopic invasion of the nerve identified intraoperatively. We cannot imagine a scenario where a FN should be preserved in the presence of an invading advanced tumor. Regarding the extension of the FN resection, it should be defined by the goal of cancer-free margins. Sacrifice of a branch or the main trunk of the FN depends on the preoperative clinical findings and the possibility of achieving a complete tumor resection. Complete FN paralysis is almost always an indication of main trunk involvement. In cases of weakness and paralysis of a specific branch of the FN, the surgeon must intraoperatively evaluate the compromise of the trunk in order to decide whether to preserve or sacrifice it.

Because surgical findings do not always correspond with malignancy, preoperative biopsy by fine-needle aspiration (or intraoperative confirmation with frozen section in doubtful cases) is advised, especially when lymphoma is clinically suspected [25]. Patients with a sacrificed FN experience significantly lower QOL due to loss of nerve function. However, the primary concern of patients with parotid malignancies is favorable survival outcomes, including reducing risk of recurrence. Therefore, the surgeon must attempt to preserve the nerve but without compromising oncological results [26]. The belief that postoperative radiotherapy can control positive microscopic margins in cases of FN preservation is not supported by existing evidence [2]. The additional protective effects of postoperative radiotherapy are heavily dependent of complete resection of the tumor. If FN sacrifice is necessary, immediate reconstruction with a free nerve graft is recommended to improve chances of functional recovery [13].

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Adjuvant Management of Advanced High-Risk Salivary Gland Malignancy

19

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Introduction

Salivary gland malignancies (SGM) are a rare and morphologically diverse group of head and neck cancers. They represent only 3% of all head and neck cancers; yet, World Health Organization (WHO) identifies 24 different subtypes [1, 2]. The natural history and prognosis for each subtype varies. Surgery remains the definitive treatment of choice in patients with SGM. However, in a subset of patients with specific high risk features, treatment failures occur not only locoregionally but also at sites of distant metastasis, and often in a delayed manner [3]. For instance, histologic grade has been shown to correlate with prognosis, with a 5-year survival of 40% in patients with high grade malignancies compared to 85–90% of those with low and intermediate grade tumors [4].

This pattern of failure and poor prognosis invites consideration of whether there is any benefit in employing treatment strategies that include both surgical resection and adjuvant locoregional radiation therapy (RT), systemic therapy, or both. Below, we review the literature surrounding the effectiveness of the different modalities of adjuvant therapy following surgical resection in the treatment of high risk SGM.

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Table 19.1 Population, Intervention, Comparison and Outcomes (PICO) table for adjuvant management of advanced high risk salivary gland malignancy

Population	Intervention	Comparison	Outcomes
Patients with high risk salivary gland malignancies treated with surgical resection	Adjuvant therapy with either radiation therapy or chemoradiation therapy	Surgical resection alone	Survival Locoregional control Recurrence Treatment toxicities

Search Strategy

In conjunction with a medical librarian, we performed two searches in PubMed to help us answer the question delineated in our PICO table (Table 19.1). The first search was performed using the Medical Subject Headings (MeSH) terms. The two MeSH terms used were (1) Salivary Gland Neoplasm and (2) Combined Modality Therapy.

We also performed a second free text-based PubMed search to identify new literature that had not yet been indexed to appear in our MeSH term search. The terms used in this the free text search included salivary gland, parotid gland, neoplasm, malignancy, cancer, high grade, high risk, advanced, chemotherapy, radiation therapy, chemoradiation, and systemic therapy. We also searched specifically for high grade adenocarcinoma, high grade mucoepidermoid, and high-grade salivary duct carcinoma (SDC), as these three subtypes are the most common and well-studied amongst the high grade salivary gland malignancies.

We narrowed our results to include only those studies conducted in adult patients, those that were conducted in the last 20 years from 1998–2017, and those that specifically stated the use of adjuvant therapy after oncologic surgical resection. Articles that were older than 20 years were only included if they represented landmark findings. We preferentially included data from prospective randomized controlled trials whenever possible, and if these studies were not available, data from larger retrospective series and national registry database studies were prioritized. We excluded studies related to palliative therapy, lymphoma, distant metastatic disease, case reports, or small single institution studies, though exceptions were made at times due to the overall limited data available.

Adjuvant Therapies

Adjuvant Radiation Therapy

Several studies have attempted to describe the rationale and indications for adjuvant radiation therapy. A 2004 multi-institute retrospective series of 565 patients published by The Dutch Head and Neck Oncology Cooperative Group (NWHHT) identified T stage, N stage, and facial paralysis as risk factors associated with worse locoregional recurrence (LRR) [5]. Similarly, in 2007, Chen et al. retrospectively

analyzed a data on 207 patients from a single institute with carcinoma of the major salivary glands who were treated with surgical resection without postoperative radiation therapy (PORT) in an effort to identify variables that predict LRR [6]. In this study, the clinicopathologic predictors of worse LRR included T3–4 disease, positive surgical margins, high grade histology, and lymph node metastases, with 10-year LRR rates ranging from 37–63% with surgery alone.

A follow-up multi-institute retrospective review of 538 patients published by NWHHT in 2005 found that PORT significantly improved the 10-year local control rate compared with surgery alone in patients with T3–4 tumors (84% vs. 18%), close margins (95% vs. 55%), incomplete resection (82% vs. 44%), bone invasion (86% vs. 54%), and perineural invasion (88% vs. 60%) [7]. In this study, tumor histology was not an independent factor predictive of local control. These studies conclude that PORT be routinely offered to patients with these high-risk features to improve locoregional control (LRC). Two other smaller retrospective studies have demonstrated similar benefits of PORT on LRC (Table 19.2) [8, 9].

The impact of PORT on overall survival (OS) is more challenging to interpret, as the existing data, which are largely retrospective series and database studies, are conflicting. The previously mentioned studies have historically have failed to demonstrate a statistically significant survival benefit for patients with high risk SGM who receive PORT (Table 19.3) [8–10]. However, more recent studies on large population-based cancer registries suggest otherwise.

Several studies published on the National Cancer Database (NCDB) have found survival benefit of PORT for patients with certain adverse features. The NCDB is one of the world's largest clinical cancer registries and is estimated to capture more than 70% of all cancers diagnosed in the USA. The first study by Bakst et al. analyzed 8234 patients with SGM without distant metastasis who underwent primary partial or total surgical resection with histologies of adenocarcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinar cell carcinoma, epithelial-myoepithelial carcinoma, and carcinoma ex pleomorphic adenoma from 2004–2013 [11]. They then stratified patients into three groups: (1) a high risk group, for those with extracapsular extension (ECE) and/or positive resection margin, (2) an intermediate risk group, for patients with pT3–T4 disease, pN+ disease, lymphovascular

Table 19.2 Impact of postoperative radiation therapy (PORT) on local or locoregional control in patients with advanced high-risk salivary gland malignancy

Author	n	Outcomes	Type of study	Quality of evidence
Terhaard et al. [7]	538	10-Year local control rates of 76% and 91% for surgery only vs. surgery plus PORT (p = 0.0005)	Multi-institute retrospective analysis	Low
Renehan et al. [8]	103	Locoregional recurrence rates of 43% and 15% for surgery only vs. surgery plus PORT (p = 0.002)	Single institute retrospective analysis	Very low
Pohar et al. [9]	163	Locoregional recurrence rates of 37%, 11% and 15% for surgery only, surgery plus PORT, vs. RT only (p = 0.001)	Multi-institute retrospective analysis	Low

Table 19.3 Impact of postoperative radiation therapy on overall survival in patients with advanced high-risk salivary gland malignancy

Author	n	Hazard ratio	95% CI	P value	Type of study	Quality of evidence
Renehan et al. [8]	103	Not reported	Not reported	Insignificant	Single institute retrospective analysis	Very low
Pohar et al. [9]	163	1.31	0.85–2.01	0.216	Multi-institute retrospective analysis	Low
Bhattacharyya et al. [10]	903	0.78	0.61–0.99[a]	0.090	National registry database analysis	Low
Bakst et al. [11]	8234	0.76	0.64–0.91	<0.002	National registry database analysis	Low
Safdieh et al. [12]	4069	0.84	0.74–0.95	0.006	National registry database analysis	Low
Cheraghlou et al. [13]	8580	0.744[b]	–	0.004	National registry database analysis	Low
		0.688[c]	–	<0.001		
Mahmood [14]	2170	0.76	0.65–0.89	<0.001	National registry database analysis	Very low

[a]90% confidence interval (CI)
[b]Stage I–II disease with adverse features
[c]Stage III–IV disease with adverse features

invasion, adenoid cystic histology, and/or grade 2–3 disease, and (3) a low risk group, for patients who did not meet criteria for either the high or intermediate risk groups. Patients were excluded if they had received neo-adjuvant chemotherapy or radiation, palliative doses of RT (<50 Gy or >70 Gy), brachytherapy, or if RT was initiated after 90 days. The authors found a statistically significant hazard ratio (HR) for overall survival of 0.76 (95% confidence interval [CI], 0.64–0.91; $p < 0.002$) for patients in the high-risk group who received PORT after adjusting for sex, race, ethnicity, insurance type, chemotherapy, and Charlson-Deyo score for comorbidities. No statistically significant HR was found in the intermediate and low risk groups.

The second NCDB study by Safdieh et al. examined the records of 4068 patients who underwent partial or total primary surgical resection for SGM [12]. They included only those with pT1-4Nx-1M0 high-grade disease or pT3-4Nx-0M0 or pT1-4N1M0 low-grade disease. Patients were excluded if they received palliative doses of RT (<50 Gy or >70 Gy) or survived <6 months from diagnosis to prevent immortal time bias. In a subset analysis of 2808 patients, after excluding patients with squamous cell carcinoma (SCC) histology, PORT was significantly associated with improved OS with a HR of 0.84 (95% CI, 0.74–0.95; $p = 0.006$). It was noted that patients receiving PORT tended to be younger and were more likely to have positive nodal status, high-grade disease, and positive margins.

Finally, a more recent NCDB study of 8580 patients published by Cheraghlou et al. in 2018 produced similar results showing that PORT offered survival benefit to patients with stage I–II (HR 0.744; $p = 0.004$) disease and stage III-IV (HR 0.688;

$p < 0.001$) with adverse features (adenoid cystic histology, intermediate or high grade, and positive surgical margins) [13].

The results of these three large NCDB studies have been mirrored in a similar study using the Surveillance, Epidemiology, and End Results Program (SEER) database. In 2011 Mahmood identified 2170 patients over the age of 20 with high-grade and/or locally advanced SGM, defined as T3/4 disease or with positive nodal disease, who underwent definitive surgical resection [14]. On multivariable analysis, the authors demonstrated a survival benefit for patients that received PORT with a HR of 0.76 (95% CI, 0.65–0.89; $p < 0.001$). On a subset analysis, the survival benefit was most striking in patients with both high grade and locally advanced disease (HR 0.63; 95% CI, 0.51–0.79; $p < 0.001$). There was no statistical significance for patients with high grade disease that was not locally advanced or locally advanced disease that was not high grade. However, when analyzing by histologic subtype, the survival benefit with the use of PORT was only observed in patients with SCC while the survival benefit did not reach significance in patients with adenocarcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, or the other primary salivary gland histologies. The authors state that there were limited numbers of analyzable patients in these histological subgroups to make any definitive conclusions.

The findings based on these large population-based cancer registry studies argue for the role of adjuvant RT in patients with SGM with high risk features to improve LRC and possibly OS. High risk features highlighted include high histologic grade, close or positive surgical margins, extracapsular extension, bony invasion, advanced stage (T3/T4), positive nodal status, and perineural invasion. Nevertheless, the results of these studies must be interpreted with caution, as these retrospective registry database studies are subject to inherent limitations and bias [15]. These limitations include inconsistencies in staging due to the lack of central pathology review board, data entry/coding errors, and the lack of specific data (i.e. reasons for mortality, detailed pathologic information, such as perineural invasion or close margin distance, patterns of recurrence, and treatment toxicity/quality of life data). The database also only includes data on patients treated at cancer programs accredited by the American College of Surgeons Commission on Cancer. Despite the absence of high level, prospective clinical evidence, based on the limited but overall consistent retrospective series, PORT is still considered part of the standard of care for patients with high risk features.

Patients with surgically resected SGM with high risk features (close or positive margins, advanced T stage, high grade histology, nodal metastasis, bone invasion, perineural invasion, and extracapsular spread) should receive adjuvant radiation therapy, as there is a consistent pattern of evidence from retrospective series and large database studies demonstrating improved locoregional control and possible survival benefit (quality of evidence: weak, conditional recommendation).

Adjuvant Chemoradiation Therapy

While PORT may offer improved local control and possible survival benefit, patients with primary SGM treated with surgery and radiation therapy are subject to distant failure. For instance, in a retrospective review spanning 1995–2010 at a single cancer institution, distant metastasis were found to be the most common cause of treatment failure and cancer-related mortality among 186 patients with primary parotid carcinoma treated with surgery and PORT [16]. This pattern of failure is the rationale behind the role of adjuvant chemotherapy in addition to PORT as a way to intensify treatment for a specific subset of patients with high risk SGM.

Unfortunately, the data on the use of adjuvant chemotherapy in patients with SGM is sparse, and the limited data that is available is difficult to interpret given the diversity in histologic types, the heterogeneity in chemotherapy agents used, and the lack of well-powered, prospective, randomized controlled trials. Landmark studies regarding the treatment of locoregionally advanced or high risk squamous cell carcinoma in other regions of the head and neck have demonstrated that concurrent postoperative chemoradiation therapy (POCRT) with cisplatin to offer an improvement in LRC, progression free survival (PFS), and OS [17, 18]. Cisplatin, the agent used in these studies, is thought to act as a radiosensitizing agent that effectively adds approximately 9–10 Gy to radiation therapy [19, 20]. As an extrapolation from these studies, cisplatin has been the main chemotherapy agent used in the setting of POCRT for SGM in majority of published studies and the agent of choice in the ongoing Radiation Oncology Therapy Group (RTOG) 1008 clinical trial, which will be discussed later.

There are three large database studies that have shown no survival benefit to the addition of chemotherapy to postoperative radiation therapy for salivary gland malignancies. In 2005, Tanvetyanon et al. published a study which included 741 older patients, age 66 and higher, from the SEER-Medicare database (1992–2009), 100 of whom received POCRT [21]. Inclusion criteria included non-metastatic, T3–T4 major and minor salivary gland malignancies that were treated with surgery within 4 months of diagnosis and with radiation within 6 months of diagnosis. POCRT was defined as chemotherapy and radiation Medicare claims within 6 months of diagnosis. On both multivariate and propensity-score adjusted analyses, POCRT showed increased mortality with a HR of 1.39 (95% CI, 1.07–1.79; $p = 0.012$) and a HR of 1.49 (95% CI, 1.14–1.94), respectively. They found no increase in OS but, instead, an increase in the rate of treatment-related toxicity in the POCRT group compared to PORT only group (72.0% vs. 27.3%, $p < 0.001$). The study concluded that "for adjuvant therapy of older patients with locally advanced salivary gland carcinoma, CRT, as observed in this study, is associated with an increased risk of death and toxicity when compared to radiotherapy alone [21].

The second study published in 2016 by Amini et al. included 2210 patients, 368 of whom received POCRT, using the NCDB database from 1998–2011 [22]. Their analysis included only those patients who had primary surgical resection of their SGM within 120 days of diagnosis and received radiation therapy within 180 days of diagnosis. Their analysis was further limited to those patients with acinic cell

carcinoma, SDC, adenoid cystic carcinoma, or adenocarcinoma, grade 2–3 disease, no distant metastatic disease, and those with high risk features, which they defined as T3–4, n > 0, or positive surgical margins. The authors found worse OS with POCRT on multivariate (HR, 1.22; 95% CI, 1.03–1.44; p = 0.02) and propensity score-matched analysis (HR, 1.20; 95% CI, 0.98–1.47; p = 0.08). Subgroup analysis based on age, comorbidity score, primary site, histologic type, grade, T stage, N stage, margin status, and chemotherapy (single agent vs. multi-agent) demonstrated equivalent or shorter OS with the addition of chemotherapy to PORT.

Another NCDB based study of 8580 patients published by Cheraghlou et al. in 2018 produced similar results showing that while PORT offered survival benefit, POCRT offered no overall survival benefit to patients with stage III–IV disease with adverse features (adenoid cystic histology, intermediate or high-grade, positive surgical margins and presence of pathological lymph nodes) (HR 1.028; p = 0.705) [13].

The limitations of database studies have been discussed previously in this chapter. Additional limitations for these studies include lack of information regarding the parameters of the chemotherapy agents used and presumed heterogeneity in the chemotherapy treatment regimens. As these studies are not randomized controlled trials, the decisions for whether adjuvant systemic therapy should be given and the specific therapy are prone to selection bias. In addition, various histological subtypes respond differently to POCRT. Another limitation is that the NCDB has limited outcomes on treatment toxicities while the SEER-Medicare database has some limited data that can be inferred.

Smaller single institution studies have demonstrated similar findings. In 2016, Mifsud et al. published their retrospective series of 140 patients with SGM treated with PORT, 37 of whom received POCRT [23]. One of the strengths of this study is that all but one patient received platinum-based chemotherapy and 89% of those receiving chemotherapy received a single platinum containing chemotherapy. Their study demonstrated worse overall survival for POCRT with a 3-year OS rates of 52.2% vs. 78.1% (p = 0.004) for the POCRT and PORT groups, respectively. Reduced LRC of 79% vs. 91% (p = 0.0031) for POCRT vs. PORT, respectively, were also reported. These results should be interpreted with caution, given the small sample size and the noted selection bias for the cohort who received POCRT who had worse prognostic features. When they attempted to account for this on multivariate analysis of PFS, they saw no improvement in PFS in the POCRT cohort when compared to the PORT alone cohort (HR of 0.783; 95% CI, 0.396–1.549; p = 0.482).

The results of the study by Mifsud et al. were echoed in another single institute retrospective study by Gebhardt et al. published in 2017 [24]. The study by Gebhardt et al. included 128 patients who received PORT, 31 of whom received POCRT. On multivariate analysis, the use of chemotherapy was neither beneficial nor detrimental to any clinical outcomes, including rate of distant metastasis, PFS, or OS, even in a subset analysis of patients with high risk features. An interesting sub-analysis on treatment toxicities showed that there was no statistically significant difference in grade 3 or higher toxicities, which resulted in their conclusion that although POCRT was well tolerated, it offered no improvement in survival.

While these studies have found no survival benefit from POCRT, a small case-control retrospective series of 24 patients with high risk features from a single institute found statistically significant survival benefit for the 12 patients treated with POCRT compared to the other 12 treated with PORT [25]. This study by Tanvetyanon et al. included patients with high risk features, defined by stage III or IV disease (excluding one patient), perineural invasion, close or positive surgical margins, facial nerve involvement, high-grade histology, and/or extra-glandular disease. They reported 3-year survival rates of 83% in the POCRT and 44% in the PORT group ($p = 0.05$). While interesting, the small sample size, retrospective nature of the study design, short duration of follow up, and heterogeneity in the patient characteristics in the two groups make extrapolation of their results into clinical practice difficult.

Another study that suggests that POCRT can offer some benefit was conducted by Hsieh et al. in 2016 [26]. Their study of 91 patients with salivary gland adenoid cystic carcinoma, 33 of whom received POCRT, demonstrated improved LRC in the group receiving POCRT but no improvement in OS. This study was unique, as it performed propensity score matching to account for bias inherent to retrospective analysis. They had 33 pairs and showed that patients receiving POCRT had improved 5 and 8-year LRC when compared to those receiving PORT alone (97% vs. 79% at 5 years and 97% vs. 67% at 8 years; $p = 0.017$). This improvement in LRC was demonstrated on subgroup analysis of patients with stage III–IV disease, positive surgical margins, and perineural invasion.

Table 19.4 Impact of postoperative chemoradiation therapy (POCRT) on clinical outcomes in patients with advanced high-risk salivary gland malignancy

Author	n	Outcomes	Type of study	Quality of evidence
Tanvetyanon et al. [21]	741	POCRT OS HR 1.39; 95% CI, 1.07–1.79 (multivariate analysis) and HR 1.49; 95% CI, 1.14–1.94 (propensity score-adjusted analysis) Treatment related toxicity rates 72% vs. 27.3% for POCRT vs. PORT respectively; $p < 0.001$	National registry database analysis	Low
Amini et al. [22]	2210	POCRT 5-year OS HR 1.51; 95% CI, 1.29–1.76; $p < 0.001$	National registry database analysis	Low
Cheraghlou et al. [13]	8580	POCRT OS HR 1.028; $p = 0.705$	National registry database analysis	Low
Mifsud et al. [23]	140	3-Year PFS for POCRT vs. PORT HR 0.783; 95% CI, 0.396–1.549; $p = 0.482$	Single institute retrospective analysis	Very low
Gebhardt et al. [24]	128	POCRT offered no improvement or harm in comparison to PORT on multivariate analysis	Single institute retrospective analysis	Very low
Tanvetyanon et al. [25]	24	3-Year OS rates for POCRT vs. PORT 83% vs. 44%, respectively; $p = 0.05$	Single institute retrospective analysis	Very low
Hsieh et al. [26]	91	No statistically significant difference observed for OS when comparing POCRT vs. PORT	Single institute retrospective analysis	Very low

HR hazard ratio, *CI* confidence interval, *PORT* postoperative radiation therapy, *PFS* progression-free survival, *OS* overall survival, *LRC* locoregional control

Although the role of POCRT in patients with high risk SGM is inconclusive based on the sparse data (Table 19.4), patients with surgically resected, high risk SGM still represent a group of patients with potential for improving clinical outcomes with treatment escalation with multimodality adjuvant therapy. A phase II/III clinical trial (RTOG 1008), which is a multi-center randomized trial to determine the efficacy of postoperative radiation therapy with or without the addition of weekly cisplatin for the treatment of high-risk malignant salivary gland tumors, is currently underway [27]. The results of this study will help further elucidate the role of adjuvant systemic therapy in these patients with high risk SGM.

Postoperative chemoradiation therapy has not been shown to offer any benefit, including improved survival, for patients with high risk SGM. Therefore, routine POCRT is not recommended (quality of evidence: weak, weak recommendation).

A Personal View of the Data

The data surrounding adjuvant therapy for the treatment of high-risk salivary gland malignancies is still nascent and populated by retrospective series. Despite the absence of high level, prospective evidence, based on the limited but overall consistent retrospective series, postoperative radiotherapy is still considered part of the standard of care following surgical resection of salivary gland malignancies with high risk features to improve locoregional control and possibly overall survival.

The role for systemic therapy in the adjuvant setting in patients with high risk salivary gland malignancies is still inconclusive based on the sparse data, although it is clear that patients with surgically resected high risk SGM still represent a group of patients with potential for improving clinical outcomes with treatment intensification. While the data is limited to guide decision making for the optimal use of systemic chemotherapy, the relative rarity of salivary gland malignancies coupled with the clinical and biological heterogeneity of these diseases make prospective, randomized trials challenging to conduct. Thus, multi-institutional, prospective clinical trials in setting of a cooperative group is ideal to study the potential role for adjuvant chemoradiation therapy in this patient population. Thus, we eagerly await the completion and the analysis of the RTOG 1008 study.

Regardless of the specific treatment regimen employed, patients with these rare salivary gland malignancies should be evaluated and treated within a multidisciplinary setting with head and neck surgical oncologists, radiation oncologists, medical oncologists, neuroradiologists, pathologists, reconstructive surgeons, and ancillary support teams who have expertise treating these patients. Each treatment plan should be tailored to the individual patient, taking into account their unique disease, patient-related

factors, goals of care, and the overall needs of the patient and their caregivers. Furthermore, most curative intent multimodality treatment regimen is associated with significant acute and late toxicities, and the clinicians should have open, frank discussions with the patient and their caregivers about the potential benefits, risks, and complications of the surgical and adjuvant interventions as well as the potential outcomes and prognosis.

At our institution, all patients with surgically resected SGM are discussed at our multidisciplinary tumor board conference to discuss the role of adjuvant therapy. Patients with high-risk features are often considered for adjuvant radiation while adjuvant chemotherapy is rarely recommended. For instance, a 39 year-old male with T1N0M0 high-grade mucoepidermoid carcinoma of the soft palate s/p surgical excision with wide margins without any other high-risk features would not receive PORT. On the contrary, a 33 year-old female with T2N0M0 high-grade mucoepidermoid carcinoma of the hard palate with perineural invasion, lymphovascular invasion, and close margins would receive PORT. One rare example of the use of POCRT was in the treatment of a 31 year-old female with T2N0M0 high-grade mucoepidermoid carcinoma of the larynx, initially treated with transoral endoscopic surgery with PORT, who rapidly recurred multiple times (r1 T3N0M0 s/p supracricoid laryngectomy, r2 T4aN0M0 s/p total laryngectomy, both with negative margins), since surgical salvage options are very limited after the treatment of the second recurrent cancer.

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Part VII

Cutaneous

Management of the Parotid Gland in Cutaneous External Auditory Canal Skin Cancer

20

Sobia Khaja

Introduction

Squamous cell carcinoma (SCC) of the temporal bone is a rare tumor, occurring at a rate of approximately 1 in a million per year [1]. Typically, patients present with otalgia, otorrhea, and hearing loss, with less common symptoms including bleeding, persistent granulation tissue, and facial palsy [1–4]. The etiology of cutaneous malignancies of the external auditory canal (EAC) is often unknown, with proposed causes including radiation (XRT) history and chronic infections [1, 2]. Because of the association of these tumors with chronic infections and drainage, diagnosis can be challenging and may be delayed [5].

Unlike other cutaneous malignancies, the AJCC does not reliably incorporate malignancies of the EAC and temporal bone. An alternative staging system was proposed by Arriaga in 1990 then revised by Moody in 2000, commonly referred to as the modified Pittsburgh staging system (Table 20.1) [1, 6, 7]. Staging for nodal disease is identical to the AJCC staging of neck disease in other head and neck cancers. Unique to temporal bone malignancies, however, is that any nodal disease automatically places the patient in stage IV [1, 6].

Patients are worked up with standard imaging techniques including CT and MRI, which while complimentary, are at risk for both over and underestimating disease burden [1, 4, 8]. The classically accepted treatment for EAC cutaneous malignancies is with en bloc resection using a sleeve resection for limited disease, lateral temporal bone resection (LTBR), or a subtotal temporal bone resection (SBTR) for more extensive disease [4]. Indications for postoperative XRT include T2 disease and above, positive margins, nodal disease, perineural invasion, or recurrent disease [1].

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Table 20.1 Modified Pittsburgh staging for tumors of the external auditory canal

T stage	Description
T1	Limited to the EAC without bony erosion or soft tissue involvement
T2	Limited to the EAC with bone erosion (not full thickness) or limited soft tissue involvement (<0.5 cm)
T3	Erosion through the osseous EAC (full thickness), with limited soft tissue involvement (<0.5 cm) or tumor involvement in the middle ear or mastoid
T4	Erosion of the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura, with extensive soft tissue involvement (>0.5 cm, such as involvement of TMJ or styloid process), or evidence of facial paresis

Table 20.2 PICO search strategy

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with clinical node negative cutaneous external auditory canal skin malignancy	Elective parotidectomy	Observation	Survival, disease control

While the management of the primary tumor is well defined, the management of the nodal basin remains controversial. The primary echelon of nodal drainage from the EAC is the parotid gland, followed by the upper neck [1, 4, 8]. Additionally, the Sylvian fissures allow for the potential tumor spread from the EAC directly into the parotid [1, 9]. Here we aim to review the literature to further evaluate the role of parotidectomy in the management of cutaneous malignancies of the EAC.

Search Strategy

An Ovid MEDLINE search was performed using the PICO table (Table 20.2), comparing a parotidectomy with observation for patients with cutaneous malignancies of the EAC. Search terms included “ear canal” or “temporal bone” or “auricular or ear canal or external auditory or temporal bone”, and “skin neoplasms” or “skull base neoplasms” or “carcinoma or cutaneous malignancy or skin cancer or skin neoplasm or skin tumor”, and “parotidectomy”, prior to January 2018. A PubMed search was also performed using similar search terms. Articles not in English were excluded. The abstracts and articles were reviewed, with exclusion of articles on non-cutaneous primary tumors (with adenoid cystic carcinoma being the most common) along with articles for non-ear canal primaries (the most common being parotid). Melanoma was also excluded due to the differences in its overall management. Articles including patients with both ear canal and primaries outside the ear canal were included for further review. Articles not addressing the management of the parotid gland were excluded. Because of the rare nature of the tumor there were no randomized controlled trials, and results were largely limited to retrospective chart reviews.

Results

All the studies identified are considered low quality evidence, limited in their strength by the fact that they are non-randomized observational trials with limited numbers of patients included, largely secondary to the rare nature of the disease process. There were limited studies that directly compared outcomes with parotidectomy to observation for EAC cancers, resulting in indirectness in the conclusions. Because of the single institution nature of the studies, it was not uncommon for all patients within a study to receive a parotidectomy as part of the general management strategy for the malignancies. If there was variable management of the parotid within a single study, it was often in regards to a parotidectomy being performed for direct tumor extension rather than nodal management. Many of the studies spanned multiple decades and therefore captured changes in imaging modality quality and changes in surgical techniques.

One of the few combined retrospective and prospective studies included a retrospective review of 17 patients from 1960 to 1980 and prospectively examined 34 patients from 1980 to 1989 [10]. Patients typically underwent a parotidectomy as part of the overall treatment strategy. Staging was based on level of invasion, rather than using the Pittsburgh staging. Eleven patients had parotid or neck metastases at presentation. There was a pathologic rate of metastasis (not separated as parotid or neck) of 29.4%, which was greater than in the literature at the time (12–16%) with the argument made that a higher rate may have been observed due to the inclusion of the parotid, and a lower rate may be observed if only surgically addressing the temporal bone.

In a study from South Korea performed by Choi et al. [9], 21 patients had malignancy of the temporal bone from 1989 to 1996, with 11 patients having SCC and 10 with adenoid cystic carcinoma. None of the patients had clinical evidence of parotid nodal metastasis. A total parotidectomy was performed for patients with direct tumor extension of the primary tumor into the parotid, otherwise a superficial parotidectomy was performed. On pathologic assessment of the parotidectomy specimens, two patients had subclinical parotid nodal metastasis (all stage III and IV disease) and three patients had direct invasion, all in patients with advanced stage SCC. Four of the patients with SCC had recurrence, none of which occurred within the parotid. This study advocated the use of parotidectomy for patients with advanced stage disease rather than for all patients presenting with a malignancy of the temporal bone. No survival data was presented.

As a comparison, Kunst et al. [11] reviewed 28 patients who underwent management of temporal bone SCC with no parotidectomy or neck dissection in the Netherlands from 1981 and 2004. The Kaplan-Meier survival curve showed an 85% survival at 2 years for early stage tumors and 64% for late stage tumors. The 5–10 year survival was 85% for early stage tumors and 46% for late stage tumors (Table 20.3). Regional recurrence within the parotid was not specified; in 4 of the 14 patients with T3 or T4 disease, there was nodal involvement at time of recurrence, 3 of which were able to be salvaged, and only 1 of these patients survived through the period of follow-up.

A study by Lobo et al. [2] captured 19 patients from 1990 to 2006 in Spain, with 3 patients undergoing a superficial parotidectomy and 6 patients a total parotidectomy; patients underwent a parotidectomy if the tumor was involving the anterior wall of the ear canal (typically T3 and T4 disease). The 5-year DFS was 37%. While not directly reporting the rate of parotid nodal disease, there were 6 patients with pathologically positive nodes (16% metastatic rate); with 5-year survival of 61% in N0 patients and 0% in N+ patients.

Cristalli et al. [5] performed a retrospective review of a smaller sample of 17 patients from 2002 to 2007 in Italy. A total parotidectomy and lateral neck dissection were performed in all patients. Unique to this study was the administration of intraoperative radiation for a total of 12 Gy. Within this study, 6 of 17 patients had parotid involvement and 6 of 17 patients had positive nodes (all T3 disease). Overall survival at 3 years was 76.6%.

In another Italian study by Zanoletti and Danesi [12] included 51 patients from 1983 to 2004, with 47 undergoing surgical resection including parotidectomy, and 45 patients had a neck dissection. Negative parotid nodal disease was present in 37 patients; positive cervical nodal disease was present in 8/45 patients (18%), with a micrometastatic rate of 7.5% (3/40). Overall 5-year survival was 47% and 5-year DSS was 60%. The study specifically examined disease free rate by cervical nodal involvement, with worse outcomes when nodal disease was present; the nodal disease was not the cause of recurrence, but rather appeared to be an indication of tumor aggressiveness and was a potential negative prognostic indicator.

The largest study included to date was performed at MD Anderson by Gidley et al. [3], reviewing 124 patients with temporal bone SCC between 1945 and 2005, with 71 patients having primary SCC, and 53 patients with persistent or recurrent disease. Patients tended to present with T1 or T4 disease and without metastatic disease. In this study, they discussed that LTBR became the standard of care around the 1980s, therefore capturing changes in practice in the data, in addition to changes in imaging techniques, skull base surgery, and microvascular reconstruction. A superficial parotidectomy was performed in 18 patients and total parotidectomy in 9 patients, 5 with direct tumor involvement into the parotid. The 5-year overall survival was 38% and 5-year DFS was 60%. Twenty-two patients had recurrence within a year, 12 of which had local recurrence. This study did not report the rate of pathologic disease within the parotid or differences in survival by parotid disease.

One of the few studies that clearly separated parotid nodal involvement was performed by Lassig et al. [7] from 1995 to 2007, which retrospectively reviewed 30 patients with SCC involving the temporal bone, 16 of which had a primary tumor of the EAC. Most patients underwent surgical management of the parotid. This study staged parotid disease separately from neck disease (P1: 3 cm node, P2: node 3–6 cm or multiple nodes, P3: >6 cm or involving facial nerve). Eight patients (27%) had pathologically verified nodal disease (not specified as cervical or parotid nodes). Breakdown by stage for primary tumors of the EAC included four patients with T1/P1, three patients with T2/P2, two with patients T3/P3, and seven patients with T4 disease. Overall DFS was 70%, with T4 disease having worse DSS at 43%, and all other T/P stages having 100% DSS. Nodal positivity did not significantly

affect DFS on univariate analysis. The patients who died of temporal bone SCC generally did so within 24 months.

Mazzoni et al. retrospectively reviewed 44 patients with temporal bone malignancies between 1983 and 2008 in Italy [13]. A superficial parotidectomy was prophylactically performed in patients with T1 or T2 disease and a total parotidectomy was performed if there was evidence of tumor extension beyond the anterior wall. Preoperative imaging was used to assess erosion of the anterior wall of the EAC and used as an indicator for potential parotid extension. A total of 37 patients had a parotidectomy; 4 patients due to age or advanced tumor status did not undergo surgical management of the parotid. The incidence of parotid nodal metastasis was not specified; a metastatic nodal metastasis rate in the neck of 17% (5/29) was identified in the clinically negative neck. All 16 patients who had failures experienced local recurrence. The overall DFS was 49% and DSS was 61%. This study found differences in survival within T4 disease, with a DFS of 62.5% and DSS of 75% in patients with anterior extension of the tumor through the canal, while spread of the disease posteriorly had a DFS of 0% and DSS of 15%, perhaps related to easier management of the anterior spread.

In another study from Italy by the same group, and likely capturing an overlapping patient population, 41 patients were treated for SCC of the temporal bone from 1980 to 2008, with 37 patients undergoing a parotidectomy [14]. The facial nerve was sacrificed in 15 of 41 patients. Nine patients had nodal disease, not defined as cervical or parotid nodes. Eighteen patients had local recurrence. When lymph node status was independently examined, there was a significant difference in DFS, however in multivariate analysis, involvement of the neck and parotid were removed. Recurrence rate, DFS and DSS were not correlated with the treatment algorithm, including the parotidectomy, neck dissection, or postoperative XRT.

Another large single institution study by Gidley et al. from MD Anderson reviewed 157 patients with cancer within the temporal bone of various pathologies and primary sites from 1999 to 2009 [15]. This study overlapped with their previous study by 6 years. A total of 121 patients underwent parotidectomy with 80 patients having a total parotidectomy; 10.8% of all patients had invasion into the salivary gland. Pathologically positive periparotid nodes were present in 11.2% of patients, but this was not differentiated based on site of primary tumor. There was a pathologic cervical nodal metastatic rate of 22.2% in patients with EAC primary tumors. The 5-year overall survival for primary tumors of the ear canal was 82.3% and 5-year DFS was 77.3%, with temporal bone primaries having rates of 58.0% and 38.1% respectively. The authors did not include analysis of survival based on the performance of parotidectomy.

In a large study performed by Morris et al., 72 patients had malignancies of the EAC of varying pathologies from 1994 to 2010, with 31 patients having SCC of the EAC [6]. Parotidectomies were performed for cT2–T4 tumors; 16 of 18 (89.9%) in patients with SCC of the EAC. In the 31 patients with SCC primary, patients who had a parotidectomy had pathologic direct tumor extension in 5 of 20 (25%) cases and nodal parotid disease was present in 6 of 14 (42.9%) cases. Among all patients with SCC, there was a 5-year DSS of 80.8% in node negative (parotid or cervical) disease

and 18.8% in node positive disease ($p < 0.0001$). Additionally, margin status (which may include need for parotidectomy) strongly predicted 5-year DSS: 90.5% vs 29.4% ($p = 0.001$). When examining survival outcomes (OS, DSS, recurrence-free survival), pathologic parotid invasion impacted all three measures, and on multivariate analysis, presence of extratemporal disease (including parotid metastasis or direct extension into parotid) was among the predictors of survival and recurrence for all tumors.

In a study from China by Zhang et al. [8], 43 patients with stage I and II disease of various pathologies of the temporal bone were included from 1993 to 2011. Twenty-six patients had a canal resection and 17 patients underwent a LTBR with parotidectomy. There was infiltration of the parotid through the EAC in 2/6 patients with T1 tumors and 5/11 with T2 tumors. They found there could be direct invasion of the parotid without radiologic findings present. For patients who underwent a canal resection, there was a recurrence rate of 46.2%, potentially contributed to by difficulty obtaining negative margins as evidenced by 53.8% of patients having positive margins; all the patients who underwent LTBR had negative margins and survived without recurrence.

The only meta-analysis identified, performed by Oya et al., published in 2017 included 20 articles and 170 patients with early stage malignancies [16]. Management of the parotid was not reported. Overall survival rate ranged from 33% to 100%, with a pooled survival of 77.3%.

A review article summarizing general recommendations for management of patients with SCC of the temporal bone was published by Gidley at MD Anderson due to the large patient series from this institution [1]. In this review, he advocates for not only an elective parotidectomy but also a neck dissection of levels II and III. The inclusion of the parotid allows for management of the first echelon of nodal drainage but also disease from direct extension through the fissures of Santorini. He reviews many of the articles described previously. While the rate of nodal disease may be relatively low, the argument for inclusion of the parotid and neck is that it assists with complete staging and provides information on prognosis due to node positive patients having significantly decreased survival.

The United Kingdom has established clinical guidelines for the management of temporal bone SCC [4]. The guidelines establish the recommendation for a superficial parotidectomy for all patients with temporal bone SCC and a total parotidectomy for patients with T3 and T4 disease. This is similarly based on management of both metastatic primary echelon disease as well as management of direct tumor involvement. The parotidectomy may also need to be performed for management of the facial nerve, which when involved by tumor is a negative prognostic indicator; nerve grafting should be performed at the time of primary resection. The overall survival, disease free survival, and disease specific survival from the various studies are summarized in Table 20.3.

Elective parotidectomy should be performed for cutaneous external auditory canal malignancy for prognostic data and to address regional metastatic disease (quality of evidence—low, weak recommendation).

Table 20.3 Overall survival, disease free survival, disease specific survival for the various studies

	Overall survival	Disease free survival	Disease specific survival
Cristalli et al. [5]	76.6% (3 years)		
Gidley et al. [3]	38%	60%	
Gidley et al. [15]	EAC: 82.3% Temporal bone: 58.0%	EAC: 77.3% Temporal bone: 38.1%	
Kunst et al. [11]	Early stage: 85% (at 2 years) Late stage: 64% (at 2 years) Early stage: 85% (at 5–10 years) Late stage: 46% (5–10 years)		
Lassig et al. [7]		Overall: 70% T1/P1: 100% T2/P2: 100% T3/P3: 100% T4: 43%	
Lobo et al. [2]		37%	
Mazzoni et al. [13]		Overall: 49% T1: 50% T2: 83.3% T3: 75% T4: 29.3%	Overall: 61% T1: 100% T2: 83.3% T3: 75% T4: 38%
Morris et al. [6]	63.2%	53.5%	67.7%
Oya et al. [16]	33–100% Pooled: 77.3%		
Zanoletti and Danesi [12]	47%		60%
Zanoletti et al. [14]		pT1: 90.6 ± 63.7 months pT2: 117.0 ± 76.4 months pT3: 92.2 ± 65.2 months pT4: 30.6 ± 43.7 months	pT1: 100% pT2: 83.3% pT3: 50.0% pT4: 38.1%

A Personal View of the Data

The literature regarding the management of the parotid in cutaneous EAC malignancies is limited, largely secondary to the rarity of the disease. There are no randomized trials, and any conclusions depend on review of cases series with limited case numbers, performed over an extended period and therefore capturing changes in imaging and surgical techniques. Conclusions are often difficult to make as the nodal involvement in studies was often not specifically defined as neck or parotid nodal disease and did not directly compare survival outcomes. Additionally, involvement of the parotid can include both nodal involvement or direct extension from the primary tumor, further complicating interpretation of the literature.

Nodal disease has been repeatedly demonstrated to be a negative prognostic indicator and as the primary echelon of lymphatic drainage, a superficial parotidectomy should be considered, though may not change survival outcomes. Numerous studies have shown metastatic disease within the parotid, particularly in advanced stage

disease. A parotidectomy may also be required if there is direct extension of the primary tumor through the anterior EAC, allowing for complete en-bloc removal with negative margins. If there is facial nerve involvement, patients should undergo nerve grafting at the time of primary resection, thereby further necessitating parotidectomy to allow better control and access of the nerve.

While the data may be limited, there are valid arguments in performing the parotidectomy to provide additional information on staging and therefore prognosis, provide an adequate tissue margin to the primary tumor, as well as allow improved control of the facial nerve with limited increase in morbidity.

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What Is the Ideal Resection Margin in Head and Neck Merkel Cell Carcinoma?

21

Cheryl C. Nocon and Mihir K. Bhayani

Introduction

Merkel cell carcinoma (MCC) is a rare neurocutaneous malignancy, with approximately 50% of cases occurring in the head and neck [1]. It often manifests as a painless, rapidly growing nodule, with a predilection for sun-exposed skin in the elderly and the immunosuppressed, as well as those infected with the Merkel cell polyomavirus. It is an aggressive malignancy, with a high tendency for locoregional recurrence and distant spread [2]. The prognosis is worse for MCC arising from the head and neck compared to other sites [3].

Because of its rarity and rapid progression, multidisciplinary management is essential. Depending on clinical stage, definitive treatment of the primary tumor most often consists of surgical excision. Clearance of the disease with wide margins is particularly important for a disease in which satellite and in-transit metastases are a prominent cause for locoregional recurrences [4]. The management of head and neck MCC, however, provides a unique challenge due to the complex anatomy and the functional and cosmetic implications of treatment. The appropriate margin size for the surgical excision of head and neck MCC is a current topic of debate and the focus of this chapter.

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Table 21.1 Surgical margin size in Merkel cell carcinoma of the head and neck

Patients	Intervention	Comparison	Outcomes
Patients with Merkel cell carcinoma of the head and neck	Surgical excision: large margin, >2 cm	Surgical excision: small margin, <2 cm	Disease control, survival

Search Strategy

Based on the PICO table (Table 21.1), Pubmed searches incorporating the terms "Merkel cell carcinoma," "treatment" and "head and neck" were used to review the literature. The bibliography of applicable articles was also reviewed. The search was narrowed to focus on the surgical treatment of Merkel cell carcinoma, although studies on adjuvant treatment were included if they evaluated the impact of surgical margin status on outcomes. Studies evaluating the use of Mohs micrographic surgery were excluded, as the focus of this chapter is on the ideal margin size with traditional surgical resection. Studies published in English within the last 20 years were included. Because of the paucity of high level evidence, organizational guidelines, consensus statements and review articles are also cited.

Results

Surgery is the primary modality of treatment for head and neck Merkel cell carcinoma (HN MCC), with wide local excision and the obtainment of negative margins when possible. However, strong evidence for surgical margin recommendations are lacking because of the rarity of the disease in general, and the anatomic constraints of the head and neck further limit margin distance. There is no level 1 or 2 evidence, randomized controlled trials or prospective studies comparing different margin sizes in the resection of HN MCC. This lack of data is acknowledged in the available guidelines, which seek to provide some guidance for clinicians tasked with managing this rare disease.

The National Comprehensive Cancer Network (NCCN) 2015 guidelines recommend a 1–2 cm margin in the head and neck when possible, given the functional and cosmetic constraints [5]. The same recommendation is echoed in a 2015 European consensus-based interdisciplinary guideline [6]. The 2014 guidelines on the surgical principles of cutaneous head and neck malignancies, published by the French Society of Otorhinolaryngology, recommend at least a 1 cm margin if approved by a multidisciplinary team meeting [7].

Such recommendations are based on limited data from retrospective studies (Table 21.2). A 2001 study by Gillenwater et al. [8] evaluated 18 patients from a single institution who were grouped by margin size: <1 cm, 1–2 cm, ≥2 cm. In this small patient population, no significant difference was detected in local, regional or distant disease control among the three groups. If the patients were divided into two groups (margins <1 cm vs ≥1 cm, or <2 cm vs ≥2 cm), significant differences in

Table 21.2 Studies evaluating surgical margin size/status and disease control outcomes

Author	No. of patients (site)	Study type	Surgical margin data	Adjuvant treatment included	Outcome	Association between margin and outcome	Evidence quality
Gillenwater	18 (HN)	Retrospective	Size: <1, 1–2, ≥2 cm	No	Recurrence, overall survival	No	Low
Morand	17 (HN)	Retrospective	Size: 2 cm, 1 cm and <1 cm	No	Recurrence-free survival	No	Low
Allen	251 (all sites)	Retrospective	Size: Mean 1.1 cm	No	Local recurrence	No	Low
Fields	500 (all sites)	Retrospective	Size: Median 1 cm	No	Overall survival, disease-specific death	No	Low
Perez	240 (all sites)	Retrospective	Size: 1 cm, 1.1–1.9 cm, ≥2 cm	No	Local recurrence, disease-specific survival, overall survival	No	Low
Finnigan	88 (all sites)	Retrospective	Margin status: Negative or positive/residual disease	Yes	Locoregional recurrence	No	Low
Strom	113 (HN)	Retrospective	Margin status: Negative or positive	Yes	Local recurrence	No	Low
Bishop	106 (HN)	Retrospective	Margin status: Negative or positive	Yes	Local recurrence	No	Low
Lok	48 (HN)	Retrospective	Margin status: Negative or close/positive margin	Yes	Locoregional recurrence, disease-specific death	No	Low
Clark	110 (HN)	Retrospective	Margin status: Negative or positive	Yes	Disease-specific survival	No	Low
Chen	4815 (HN)	Retrospective	Margin status: Negative or positive	Yes	Overall survival	Yes: positive margin and decreased survival No: when adjuvant therapy given	Low

disease control could still not be detected. Furthermore, there was no detectable trend in larger primary lesions having larger margins. While acknowledging the limitations of their study, the authors conclude that the size of surgical margins does not have a major impact on recurrence or survival rates.

In 2013, Morand et al. [9] studied 17 HN MCC patients, 15 of whom underwent surgical excision and 8 of whom had known margin information from the initial surgery. Margin sizes were grouped into 2 cm, 1 cm and <1 cm, and there was no relation between surgical margins and recurrence-free survival ($p = 0.47$). Nine out of ten patients—comprised of patients treated initially at an outside facility and those with planned margins <1 cm—had to undergo a second surgery to obtain negative margins. Based on these findings, the authors recommend margins of 1 cm, or if necessary a two-step procedure to achieve both good oncologic and cosmetic results.

Two large retrospective reviews of a prospectively maintained database of MCC from all anatomic sites supports the use of smaller surgical margins. A 2005 study by Allen et al. [10] included 251 patients from Memorial Sloan Kettering Cancer Center with an average margin size of 1.1 cm. Negative margins were achieved in 94% of patients, which yielded an overall local recurrence rate of 8%. The use of adjuvant radiotherapy (RT) to the surgical bed was not associated with local recurrence in the overall population ($p = 0.76$), and in the subgroup of patients with negative margins ($p = 0.45$). Furthermore, obtaining a margin less than 1 cm was not associated with increased local recurrence (9% recurrence for <1 cm vs 10% recurrence for ≥1 cm, $p = 0.83$). Expansion of the series in 2011 yielded 500 patients with MCC from all sites with a median margin size of 1 cm (mean margin size not available) [11]. Moreover, there was no association with overall survival (HR 0.9; 95% CI 0.7–1.1; $p = 0.26$) or disease-specific survival (HR 0.9; 95% CI 0.8–1.1; $p = 0.88$) for every 1 cm increase in margin width. The most recently published study included in this review had 240 patients and did not demonstrate differences in local recurrence (2.9% for 1 cm margin, 2.8% for 1.1–1.9 cm margin, 5.2% for ≥2 cm margin; $p = 0.80$), 5-year disease-specific survival (80.5%, 66.2%, 91.8% respectively; $p = 0.66$), or 5-year overall survival (63.6%, 59.7%, 70.7% respectively; $p = 0.28$) based on margin size [12]. Not surprisingly, it showed that more patients required a flap or a graft for wound closure with increasing margin size (43.5%, 50%, 65.9% respectively; $p = 0.006$). These studies provide interesting data from which further investigation can be conducted, but they are limited by small sample sizes, lack of randomization and other confounding factors, such as anatomic site, in their analyses.

Although the NCCN guidelines recommend a 1–2 cm margin when feasible, they note that negative margin resection should not be pursued to the degree of significantly delaying adjuvant RT because of data that indicates that margin status may not have significant impact in high-risk MCC receiving radiation. A 2012 study by Finnigan et al. [13] pooled data from three prospective trials and included 88 patients with MCC from all sites. Although surgical margin size was not defined, 9 patients had microscopic positive margins and 26 had macroscopic residual disease, all of whom were treated with RT. They found that neither positive margins (HR 0.9; 95% CI 0.21–3.90; $p = 0.89$) nor gross disease (HR 1.55; 95% CI 0.56–3.69; $p = 0.32$) was associated with locoregional failure. Similarly, in their 2016 study

examining the benefit of adjuvant RT in HN MCC, Strom et al. [14] studied 113 patients who underwent surgical excision with a minimum margin of 1–2 cm. Negative margins were achieved in 85.8% of patients, and there were no significant patient, tumor or treatment characteristics between patients treated with and without adjuvant RT. Margin status was not found to be significantly associated with local control on multivariate analysis.

Similar conclusions were gleaned from another retrospective single institution review of HN MCC by Bishop et al. [15]. In their study of 106 patients who received adjuvant RT to the primary site, the 5-year local recurrence rate was only 4%. They contend that their cohort was a high risk population, given the positive margin rate of 17% and inclusion of only head and neck sites [3, 16]. Nonetheless, their 4% local recurrence rate is lower than that found in comparable studies in which early stage MCC from all sites were treated with surgery alone. Such findings suggest that the benefit of adjuvant RT may overcome the recurrence risk of positive margins, and that larger margins may not provide additional benefit when post-operative RT is administered.

Another single institution retrospective review of 48 HN MCC patients treated with adjuvant RT did not specifically define margin size, but it found a high rate of 29% for close or positive margins [17]. It found no association between close or positive margins and locoregional recurrence ($p = 0.87$) or disease-specific death ($p = 0.42$) in a univariate analysis. Similarly, a multi-institutional study of 110 HN MCC patients mostly treated with surgery and adjuvant RT found a high positive margin rate of 32% [18]. It also did not define margin size, and it also did not find an association between margin status and disease-specific survival in a univariate analysis ($p = n/a$).

In contrast, a 2015 multivariate analysis of 4815 HN MCC patients from the National Cancer Database found that positive margins were independently associated with a decreased overall survival (HR 1.52; 95% CI 1.25–1.85) [19]. Unsurprisingly, surgery followed by adjuvant RT (HR 0.80; 95% CI 0.70–0.92) or chemoradiation (CRT, HR 0.62; 95% CI 0.47–0.81) was associated with improved overall survival versus surgery alone, although no significant difference was found between improved survival and RT versus CRT. However, in a subanalysis of 457 high-risk patients with positive margins, adjuvant CRT was associated with improved survival over adjuvant RT alone (HR 0.48; 95% CI 0.25–0.93; $p = 0.03$). These results ostensibly support the argument that margin status—and thus the need for large surgical margins—may not be as impactful when adjuvant treatment is administered.

For Merkel cell carcinoma of the head and neck, where cosmetic and functional considerations may compete with oncologic priorities, a surgical resection margin of up to 1–2 cm may be considered adequate without compromising disease control. While obtaining negative margins is an objective in oncologic surgery, it should not be pursued if there will be significant delays to adjuvant therapy, as margin status may not have an impact on disease control in patients receiving adjuvant therapy (evidence quality low; weak recommendation).

A Personal View of the Data

As per NCCN guidelines, surgical resection of HN MCC should aim for margins measuring 1–2 cm when possible without compromising the functional and cosmetic priorities of the patient. Despite the lack of strong evidence, the current data do not seem to suggest a major impact of large margin size on disease control, especially when adjuvant RT is part of the treatment plan. It should also be noted that Mohs surgery is an alternative to traditional surgical excision if indicated by anatomic factors. There is unresolved debate surrounding the potential for satellite or in-transit metastases with the use of Mohs surgery, but there is emerging data supporting its use that is outside the scope of this chapter. Mohs surgery is recognized as an alternative procedure by NCCN guidelines if tissue sparing is critical, and provided it does not interfere with sentinel lymph node biopsy when indicated. Any recommendations certainly must be accompanied by a thorough multidisciplinary team review in order to ensure proper staging and management of the neck, which, of course, impacts overall prognosis and disease control. Consultation with a facial plastics or reconstructive surgeon is also important to better understand the potential aesthetic outcomes associated with different margin sizes.

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22 Does Recurrent Cutaneous Squamous Cell Carcinoma of the Head and Neck Warrant Adjuvant Treatment After Surgical Resection?

Theresa Guo and Ana Ponce Kiess

Introduction

The head and neck is the most common region of invasive cutaneous squamous cell carcinoma (SCC), given its sun exposed location [1]. Unfortunately, there is limited evidence guiding treatment of cutaneous squamous cell carcinoma of the head and neck (SCCHN). While there is good evidence that surgical resection of disease can offer improved outcomes [1], the role of adjuvant radiation and chemotherapy is less clear. Which patients will benefit from additional treatments and truly have a reduction in rates of recurrence or improvement in rates of survival? In which patients do the risks of adjuvant therapy outweigh small or minimal benefit?

Due to limited evidence, decision making regarding adjuvant therapy is partly predicated on identifying which patients are at higher risk for recurrence, and therefore may experience increased benefit from radiation or chemotherapy following resection. In this chapter, we will discuss recurrent cutaneous SCC of the head and neck within the context of current treatment guidelines, evidence behind defining risk for recurrent disease or disease related mortality, and evidence underlying adjuvant radiation and chemotherapy for these patients.

The 2018 NCCN guidelines notes that "the value of adjuvant radiation therapy is widely debated due to lack of prospective randomized clinical trial data" [2]. Within

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the guidelines, high risk factors are identified for local recurrence including size, location, presentation, and pathology. The head and neck location itself categorizes many lesions into the high-risk category, given a greater challenge for achieving negative margins. While generally cutaneous SCC is high risk for lesions >20 mm, for lesions on the cheek, forehead, scalp, and neck, smaller lesions (>10 mm) are considered high risk. In addition, any size lesions in the "mask areas" of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular, post auricular, temple and ear) are at higher risk for recurrence given the challenges of achieving negative margins in these anatomically limited regions.

Recurrence is also considered a risk factor, as recurrent disease predicts higher risk for further recurrence. Additional evidence underlying recurrence as a risk factor will be discussed below. Other clinical features that predict higher risk for recurrence include immunosuppression, rapidly growing tumors, tumors presenting with neurologic symptoms such as numbness, and lesions arising from areas of prior radiation exposure. Pathologic features that portend high risk include perineural invasion, lymphovascular invasion, poorly defined borders, poorly differentiated tumors, and depth of invasion ≥2 mm.

Literature Search Strategy

A review of the literature was performed to evaluate the evidence for adjuvant treatment for recurrent cutaneous squamous cell carcinoma of the head and neck. Based on the PICO table (Table 22.1), a structured review of available pertinent databases (Pubmed, Embase, Scopus, Cochrane Database of Systemic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and Clinicaltrials.gov) was performed. Search terms included all permutations of relevant keywords including "cutaneous, head and neck, squamous cell carcinoma, adjuvant radiation, adjuvant chemotherapy, recurrent disease, nodal metastasis, perineural invasion". Included studies for analysis of oncologic results and survival for surgical resection with and without adjuvant therapy for cutaneous head and neck squamous cell carcinoma. Studies were excluded if they reported on outcomes of other histology besides cutaneous squamous cell carcinoma of the head and neck (primarily basal cell or mucosal squamous cell), previously treated patients, those with metastatic disease on presentation, or patients not treated with curative intent.

Table 22.1 PICO table: Outcomes for treatment of cutaneous SCCHN with adjuvant therapy

Population	Intervention	Comparison	Outcomes
Adults with cutaneous SCCHN ± adverse features (including recurrence, nodal metastasis, perineural invasion, or locally advanced disease)	Adjuvant RT or Adjuvant CRT	Surgery alone or Surgery with RT	Disease free survival (DFS) Overall survival (OS)

SCCHN squamous cell of the head and neck, *RT* radiation therapy, *CRT* concurrent chemoradiation therapy

Additionally, only studies reporting outcomes between patients with and without adjuvant therapy were included. Due to lack of studies directly evaluating patients with recurrent cutaneous SCC of the head and neck, studies evaluating patients with other risk factors (including nodal metastasis, perineural invasion, locally advanced disease) were included.

Adjuvant Treatment Recommendations in the Primary Setting

For high risk lesions, at initial presentation, NCCN guidelines recommend wider margins or Mohs resection for complete resection, while low risk lesions may be amenable to smaller margins or curettage. With positive margins, re-resection is always recommended if possible. Adjuvant radiation is then recommended for patients with final positive margins or extensive perineural invasion (diffuse or within a large nerve). Primary radiation is also a treatment option, and is generally reserved for non-surgical candidates.

In addition, adjuvant radiation is often recommended for patients with nodal disease. For patients with limited nodal disease (single node <3 cm and no extranodal extension), adjuvant radiation or observation are both options for treatment. Patients with multiple involved nodes and/or nodes >3 cm are recommended for adjuvant radiation, and patients with extranodal extension may be considered for concurrent chemotherapy.

Evidence for Defining Risk Factors for Recurrence

There are few studies that specifically investigate the indications for adjuvant treatment for recurrent cutaneous squamous cell carcinoma of the head and neck. Therefore, understanding factors that increase risk for recurrence can provide indirect evidence as to which patients may benefit most from adjuvant therapy.

Recurrence as a Risk Factor

For cutaneous SCC, local recurrence has long been recognized as a risk factor for future recurrence and worse prognosis [3]. Recurrent lesions also show more aggressive pathology including increased incidence of lymphovascular invasion, perineural invasion, soft tissue invasion and nodal metastasis [4]. In a recent review by Harris et al. of 212 patients with head and neck cutaneous SCC, more than half of enrolled patients had a history of previously treated disease, and these patients with recurrent disease had more than twofold higher risk (HR 2.21, $p = 0.041$ in multivariate cox analysis) for subsequent recurrence after wide local excision with negative margins [5]. Another study included both immunocompetent and immunosuppressed patients, primarily due to organ transplantation or hematologic malignancy, who received both surgery and post-operative

radiation. In this study, recurrent disease was an independent risk factor for locoregional recurrence with a similar hazard ratio for recurrence of 2.67 (CI 1.49–4.79) in multivariate analysis [6].

Other studies have provided conflicting evidence as to whether recurrent disease is a risk factor for nodal metastasis. In the study by Harris et al. of head and neck cutaneous SCC, no relationship was identified between recurrent disease and risk for nodal metastasis in multivariate analysis [5]. However, other studies have shown that nodal metastasis is more frequent in patients with recurrent cutaneous SCC in general, and specifically in the head and neck region [4, 7–10]. Furthermore, patients with nodal metastases in the head and neck region experienced worse outcomes with decreased disease free and overall survival [4, 8].

Other Risk Factors for Recurrence

Several other factors have been identified as risk factors for recurrence within this patient population. Tumor stage is significantly related to risk of recurrence, with increasing tumor depth associated with higher risk of recurrence (either >4 mm depth of invasion or Clark's level IV or V) [1]. Patients with nodal metastases also have significantly higher rates of recurrence [4]. Several pathologic and histologic factors have also been associated with recurrence including perineural invasion [1, 3, 5, 11], poor tumor differentiation [1, 5], and extranodal extension [12]. Additionally, positive margins are significantly associated with risk of recurrence [12]. Lastly, immunosuppressed patients, such as transplant patients, have up to 65 times higher risk of development of cutaneous SCC [13] and also have higher risk for recurrence [6, 12]. SCC in immunosuppressed patients has shown more aggressive disease biology in multiple studies [14–16].

Evidence for Adjuvant Radiation in Cutaneous SCC

In patients with high risk cutaneous SCC of the head and neck, the role of adjuvant radiation has been studied to a limited extent, primarily in the setting of nodal disease and perineural invasion. However, studies that directly compare surgery and surgery with adjuvant radiation primarily consist of retrospective reviews (Table 22.2) [22]. While the previously discussed high risk factors have been shown to be associated with increased risk of recurrence, the role of adjuvant radiation has not been clearly studied for all factors. With respect to recurrent SCC, one retrospective series of 67 patients with recurrent cutaneous SCC of the head and neck reported that those with adjuvant RT had improved disease free survival (78% vs. 30%, $p = 0.02$) and overall survival (79% vs. 46%, $p = 0.05$) [20].

Table 22.2 Adjuvant radiation

Study	Cohort	Comparison	Relative effect	Number of participants	Quality of evidence	Comments
Veness et al. [17]	Patients with cutaneous SCCHN with nodal metastasis	Surgery vs. surgery with adjuvant RT	DFS HR 0.10 (0.10–0.65, p = 0.004) in favor of surgery with adjuvant RT	167 (146 receiving surgery with adjuvant RT)	Retrospective clinical review	No variables (including treatment) were significantly associated with overall survival
Oddone et al. [12]	Patients with cutaneous SCCHN with nodal metastasis	Surgery vs. surgery with adjuvant RT	OS HR 0.32 (0.16–0.66, p = 0.002) in favor of surgery with adjuvant RT	250 (222 receiving surgery with adjuvant RT)	Prospective cohort study	Surgery only had higher rate of regional recurrence (48% vs. 23%) 73% of patients with regional recurrence died of disease
Givi et al. [18]	Patients with cutaneous SCCHN with nodal metastasis	Surgery vs. surgery with adjuvant RT	OS HR 0.18 (0.06–0.54, p = 0.002) in favor of surgery with adjuvant RT	51 (40 receiving surgery with adjuvant RT)	Retrospective clinical review	Four patients had unknown adjuvant treatment status; recurrent disease was also associated with worse OS in multivariate analysis
Sapir et al. [19]	Patients with cutaneous SCCHN with PNI	Surgery vs. surgery with adjuvant RT	DFS; Microscopic *extensive* PNI (MEPNI) HR 0.32 (0.10–0.99, p = 0.05) in favor of surgery with adjuvant RT; Microscopic *focal* PNI (MFPNI) HR 0.61 (0.12, 2.91, p = 0.525) in favor of surgery with adjuvant RT	102 (35 gross PNI with 100% receiving RT; 30 MEPNI with 63% receiving RT; 37 MFPNI with 27% receiving RT)	Retrospective clinical review	No significant differences in OS were identified in any group with adjuvant RT Overall DFS for gross PNI (all treated with adjuvant RT) was 55% at 2 years
Strassen et al. [20]	Patients with **recurrent** cutaneous SCCHN	Surgery vs. surgery with adjuvant RT	5 year DFS 30% vs. 78% (with adjuvant RT) p = 0.02; 5 year OS 46% vs. 79% (with adjuvant RT) p = 0.05	67 (30 receiving surgery with adjuvant RT)	Retrospective clinical review	Analysis was limited to univariate survival analysis. Patients with adjuvant RT were more likely to have higher N stage and lower T stage
Coombs et al. [21]	Patients with cutaneous SCCHN with parotid metastasis	Surgery vs. surgery with adjuvant RT	5 year DFS 48% vs. 84% (with adjuvant RT) p = 0.008	63 (51 receiving surgery with adjuvant RT)	Retrospective clinical review	No difference in locoregional recurrence was seen between treatment groups

SCCHN squamous cell of the head and neck

For patients with nodal metastases from cutaneous SCC of the head and neck, some evidence suggests that adjuvant radiation may reduce risk of locoregional recurrence and improve overall survival [12, 17–19, 21]. While the overall metastatic rate of cutaneous SCC is 4% [23], lesions of the head and neck occur in several high risk regions that increase risk for nodal metastasis, including face, ear, pre and post auricular regions, lips and temple [24]. Rates of nodal metastasis in these patients may be as high as 20% [4]. In a cohort of 250 prospectively studied patients with nodal metastasis from cutaneous SCC of the head and neck, treatment with adjuvant radiation was significantly associated with improved survival in multivariate analysis (HR 0.32, 95% CI 0.16–0.66) [12]. Notably, within this study, a 73% of patients who experienced regional relapse after treatment died of disease. Another retrospective review of 167 patients with nodal metastasis showed that patients treated with adjuvant radiation experienced decreased regional recurrence (20% vs. 43%) and improved 5-year disease free survival (73% vs. 54%) compared to those treated only with surgery [17]. Several other retrospective studies also suggest the potential benefit of adjuvant radiation in the setting of nodal metastasis [25, 26]. It should be noted that in all of these studies the vast majority of patients were treated with surgery and adjuvant radiation (84–100%), and factors determining treatment choice may introduce selection bias. However, based on the reported benefits of adjuvant radiation in this setting, randomized studies would not be possible due to lack of equipoise.

Additional studies have evaluated the impact of adjuvant radiation on patients with perineural invasion (PNI). In reviews of cutaneous SCC with perineural invasion that are not specific for the head and neck, adjuvant radiation has not been shown to have a significant impact on outcomes [22, 27]. However, a study focusing on cutaneous SCC of the head and neck evaluated the role of adjuvant radiation in patients with perineural invasion. In this study, perineural invasion was categorized for 102 patients as gross cranial nerve invasion, microscopic extensive PNI, and microscopic focal PNI [19]. All patients with gross cranial nerve invasion received radiation. For the remaining patients, radiation improved recurrence free survival in nerves (94% vs. 25%, $p = 0.01$) and overall disease-free survival for patients with extensive PNI (73% vs. 40%, $p = 0.05$), but no significant benefit was seen in patients with focal PNI. Several retrospective studies demonstrate a high risk of recurrence for patients with clinical PNI even after surgery and adjuvant radiation [28, 29]. In patients with recurrent cutaneous SCC of the head and neck, one case series of ten patients showed that re-irradiation of patients with gross perineural invasion resulted in a high rate (70%) of out of field locoregional recurrences, some in previously uninvolved cranial nerves [30].

We recommend adjuvant radiotherapy for high-risk cutaneous SCC of the head and neck in the setting of extensive perineural invasion or nodal metastases (evidence quality low; weak recommendation).

Evidence for Adjuvant Chemotherapy

There is fairly limited evidence for the addition of adjuvant chemotherapy for the treatment of cutaneous head and neck SCC. Previous practice had extrapolated from evidence gathered from mucosal head and neck SCC in selecting patients that might benefit from adjuvant chemotherapy. As such, current guidelines suggest that concurrent chemotherapy may be considered with adjuvant radiation for patients with extranodal extension or select patients with positive margins [2]. A smaller retrospective series of 61 patients of patients with high risk cutaneous SCC of the head and neck (stage III and IV, with high risk features including ≥2 positive lymph nodes, positive margins or ECS) were treated with either adjuvant radiation or concurrent adjuvant chemoradiation with platinum agents. Patients receiving adjuvant chemoradiation had improved recurrence free survival (HR 0.31, CI 0.13–0.78, p = 0.01), but no difference in overall survival was found (p = 0.24) [31].

However, recent data has shown limited benefit of adding chemotherapy to the adjuvant treatment of these patients (Table 22.3). A recent randomized clinical trial by the TransTasman Radiation Oncology Group (TROG) randomized 238 patients with high risk cutaneous SCC of the head and neck to adjuvant radiation with or without weekly carboplatin [33]. Extranodal extension was present in 59% of patients. No significant differences were found between chemoradiation and radiation groups in freedom from locoregional disease (HR 0.84, CI 0.46–1.55, p = 0.58), disease free survival (HR 0.85, CI 0.55–1.29, p = 0.44), or overall survival (HR 0.95, CI 0.58–1.57, p = 0.86). Freedom from locoregional recurrence was 83% in the RT group vs. 87% in the CRT group at 5 years. Notably, locoregional recurrence was the most common site of failure, and the rate of distant failure was the same (7%) in both groups. This shows both the importance of locoregional treatment and the lack of efficacy of chemotherapy in preventing distant disease.

A retrospective study of 32 patients with head and neck cutaneous SCC receiving adjuvant radiation with and without chemotherapy also showed no benefit of chemotherapy for preventing locoregional or distant recurrence [32]. Furthermore, receipt of chemotherapy was associated with a significant reduction in overall survival. It should be noted that this small retrospective study did not perform multivariate adjustment and included heterogeneous chemotherapy regimens (cisplatin, carboplatin, cetuximab, carboplatin with paclitaxel, and cisplatin with 5FU).

In light of recent data, we generally do not recommend adjuvant chemotherapy for high-risk cutaneous SCC (evidence quality moderate; weak recommendation).

Table 22.3 Adjuvant chemotherapy

Study	Cohort	Comparison	Relative effect	Number of participants	Quality of evidence	Comments
Tenvetyanon et al. [31]	Patients with stage III and IV cutaneous SCCHN with high risk features	Surgery with adjuvant RT vs. adjuvant CRT (cisplatin or carboplatin)	DFS HR 0.31 (0.13–0.78, p = 0.01); OS HR 0.58 (0.23–1.45, p = 0.24) in favor of CRT	61 (34 receiving adjuvant CRT)	Retrospective clinical review	In multivariate analysis, adjuvant CRT improved DFS but there was no difference in OS
Goyal et al. [32]	Patients with locally advanced cutaneous SCCHN	Surgery with adjuvant RT vs. adjuvant CRT (cisplatin, carboplatin, cetuximab, carbo/taxol, cis/5FU)	DFS HR 0.57 (0.11–2.8, p = 0.49) in favor of CRT OS HR 3.5 (1.04–11.6, p = 0.04) in favor of RT alone	32 (14 receiving adjuvant CRT)	Retrospective clinical review	Data limited to unadjusted univariate analysis in a heterogeneous retrospectively studied group
Porceddu et al. [33]	Patients with high risk cutaneous SCCHN	Surgery with randomized to adjuvant RT vs. adjuvant CRT with weekly carboplatin	Disease free survival HR 0.84 (0.46–1.55, p = 0.58) in favor of CRT	238 (153 receiving adjuvant CRT)	Randomized clinical trial	TROG 05.01 Phase III No significant differences in DFS or OS

Applying Evidence to Patients with Recurrent Disease

With regard to adjuvant radiation treatment for patients with recurrent cutaneous SCC of the head and neck, few studies directly evaluate this topic. As noted above, one retrospective series of 67 patients with recurrent cutaneous SCC reported that those with adjuvant RT had improved disease free survival (78% vs. 30%, p = 0.02) and overall survival (79% vs. 46%, p = 0.05) [20]. However, most studies evaluating adjuvant therapy included some patients with recurrent disease within the pooled analysis, but the benefit in this subset of patients was not specifically reported.

Another consideration is whether recurrent cutaneous tumors have occurred due to suboptimal resection or due to biologically aggressive disease. These cases should be differentiated, as adjuvant therapy should be reserved for the latter. For high risk cutaneous SCC, which includes many lesions in the head and neck, either resection with wide margins (6 mm) [34] or Mohs resection are

indicated [7]. Furthermore, any positive margins should be re-excised whenever possible. Some initial treating physicians may not feel comfortable with wide resection in the anatomically complex region of the head and neck, resulting in close or positive margins and subsequent recurrence. In these cases, if wider margins are able to be achieved with re-excision, adjuvant radiotherapy may not be indicated. However, when lesions recur despite adequately wide and negative margins, then aggressive tumor behavior may warrant adjuvant radiation in certain settings.

A Personal View of the Data

As per NCCN guidelines, we categorize recurrent cutaneous SCC of the head and neck as high-risk. We routinely recommend adjuvant radiotherapy for those patients with extensive perineural invasion. For patients with high-risk cutaneous SCC and positive margins, we often favor re-resection if possible, especially in cases of prior standard excision or Mohs microsurgery. If patients have final positive margins reflective of extensive subclinical spread or aggressive disease biology, we recommend adjuvant radiotherapy. Furthermore, we consider immunosuppression to be a very important risk factor, and we are more likely to recommend adjuvant radiotherapy for immunosuppressed patients even if margins are negative and PNI is not extensive. If lymph node metastases are present, we generally recommend adjuvant radiotherapy, and we also consider elective nodal irradiation in clinically node-negative patients with multiple high-risk factors. For patients with extensive PNI we often extend the radiation field to include proximal nerve pathways, which can be very challenging along cranial nerves V1, V2 and/or VII due to nearby optic and acoustic structures. We generally do not recommend adjuvant chemotherapy for cutaneous SCC based on recent data.

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23 Management of the Parotid/Neck Following a Positive Sentinel Node Biopsy in Patients with Cutaneous Melanoma of the Head and Neck

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Introduction

The pathologic status of the sentinel node is the most important prognostic determinant of disease recurrence and death from melanoma for intermediate-thickness (Breslow thickness 1.2–3.5 mm) cutaneous melanoma. Sentinel node biopsy (SNB) also increases disease-free survival (DFS), distant disease-free survival, and melanoma-specific survival (MSS) of intermediate-thickness SN-positive melanoma patients. These prognostic and survival benefits were demonstrated by the final results of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I), published in 2014 [1]. The role of completion lymph node dissection (CLND) in patients with a positive SNB has, until relatively recently, been less well defined. Any potential benefits of CLND have to be weighed against the inevitable adverse effects of surgery.

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Literature Search Strategy

To complete the PICO table (Table 23.1), a Pubmed literature search using the terms "cutaneous melanoma", "positive sentinel node" and "completion lymphadenectomy" or "completion lymph node dissection" was performed for the period 2000–2018.

We chose to focus on the results and subsequent reviews of the second Multicenter Selective Lymphadenectomy Trial (MSLT-II) [1]. We also reviewed several studies that pre-dated MSLT-II, including the Dermatologic Cooperative Oncologic Group Selective Lymphadenectomy Trial (DeCOG-SLT) and studies by van der Ploeg et al., Satzger et al., Smith et al., Wong et al. and Kingham et al. A summary of the key findings is presented in Table 23.2.

Table 23.1 Management of the neck following a positive sentinel node biopsy in patients with cutaneous melanoma of the head and neck

Population	Intervention	Comparison	Outcomes
Patients with positive sentinel node biopsy in head and neck cutaneous melanoma	Superficial parotidectomy/neck dissection	Observation with regular ultrasound and therapeutic neck dissection if required	Survival and complications

Table 23.2 Summary of studies comparing observation versus completion lymph node dissection

Study	Study description	Proportion head and neck patients	Conclusion
MSLT-II	Prospective randomized clinical trial comparing CLND vs observation in SN-positive patients	13.7% Total patients treated as per protocol 1755	No significant difference in MSS (86 ± 1.3 vs 86 ± 1.2%, p = 0.42)
Van der Ploeg et al.	Retrospective analysis of patients with SN-positive undergoing CLND vs observation	13.5% CLND vs 10% no-CLND Total patients 1174	CLND has no effect on MSS (HR 0.86, CI 0.46–1.61, p = 0.64)
Satzger et al.	Retrospective analysis of patients with SN-positive undergoing CLND vs observation	10% Total patients 305	No significant difference in OS and DFS, p = 0.844 and p = 0.765, respectively
Smith et al.	Retrospective analysis of effect of CLND in patients with cutaneous melanoma of the head and neck using data obtained from SEER	100% 350 patients underwent CLND vs 140 SNB alone	MSS not improved with CLND (p > 0.20)
Wong et al.	Retrospective analysis of patients who did not undergo CLND vs matched group who did	12% 134 patients did not undergo CLND vs 164 who did	No difference in MSS (p = 0.65)
Kingham et al.	Retrospective analysis of SN-positive patients who underwent CLND vs observation	8% CLND vs 17% no-CLND Total patients 313	Similar rates of DFS (p = 0.63) and MSS (p = 0.26)

MSLT-II Multicenter Selective Lymphadenectomy Trial, *CLND* completion lymph node dissection, *SN* sentinel node, *MSS* melanoma specific survival, *HR* hazard ratio, *OS* overall survival, *DFS* disease-free survival, *SEER* Surveillance, Epidemiology and End Results

Results

In MSLT-II patients with a positive SNB were randomized to receive completion lymphadenectomy or clinical observation with regular ultrasonography of the nodal basins, assessing both 1934 intention-to-treat patients and 1755 patients treated per protocol, the primary end point being MSS and secondary endpoints DFS and cumulative rate of non-SN metastasis. Head and neck patients made up 13.7% of each arm. In the per-protocol analysis, MSS at 3 years (with a median follow-up of 43 months) was very similar in the dissection and observation groups at 86 ± 1.3% and 86 ± 1.2%, respectively, (p = 0.42). DFS at 3 years was significantly higher in the dissection group (68 ± 1.7% vs. 63 ± 1.7%, p = 0.05) due to significantly better regional control. Non-SN metastasis, identified in 11.5% of patients in the dissection group, was a strong independent prognostic factor for recurrence (hazard ratio = 1.78, p = 0.005). This rate increased to 17.9% at 3 years, and 19.9% at 5 years. This contrasted with non-SN metastasis detected by physical examination or ultrasound in the observation group of 22.9% at 3 years, and 26.1% at 5 years (p = 0.02 and p = 0.05, respectively). Subgroup analysis did not reveal SN tumour burden to affect MSS. It is important to note that 66% of the SN metastases were <1.01 mm in diameter [2].

The design of DeCOG-SLT was similar to that of MSLT-II, although it was much smaller (473 intention-to-treat and 434 patients treated per protocol), and melanomas in the head and neck region were excluded. The primary endpoint was distant disease-free survival. It was ultimately underpowered, and closed prematurely due to accrual problems. After a median follow-up of 35 months, the 3-year distant disease-free survival rates for the CLND and observation groups were 75% and 78%, respectively, (p = 0.92) in the per protocol population [3].

Van der Ploeg et al. published the largest retrospective analysis of patients with SN-positive melanoma, comparing those who underwent CLND (n = 1113) with those who did not (n = 61), treated between 1993 and 2008 at ten centres from the European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group. Head and neck melanomas comprised 13.5% and 10% of the CLND and no-CLND groups, respectively. To account for prognostic imbalance in baseline factors between the two groups, multivariate as well as matched-pair analysis (matched for age, Breslow thickness, tumor ulceration and SN tumour burden in two groups of 61 patients) were carried out. CLND had no significant effect on MSS (HR 0.86, confidence interval = 0.46–1.61, p = 0.64) [4].

Satzger et al. retrospectively analyzed outcomes for 305 SN-positive melanoma patients, treated between April 2000 and December 2009 at a single institution, who had (n = 247) and had not (n = 58) undergone CLND. Matched-pair analysis was performed on 58 patients in each group to control for Breslow thickness, ulceration, and specifically SN parameters including diameter of largest tumor deposit, tumor penetrative depth and capsular involvement in the SN. Head and neck melanomas comprised 10% and 2% of the matched-pair CLND and no-CLND groups, respectively. They found that CLND, in contrary to ulceration of the primary melanoma, largest size of SN metastatic deposit and age, was not a prognostic factor on

multivariate analysis. In matched-pair analysis, OS and DFS did not differ between the two groups, p = 0.844 and p = 0.765, respectively [5].

Smith et al. studied the effect of CLND in patients with cutaneous melanoma of the head and neck using data obtained from the Surveillance, Epidemiology and End Results (SEER) program. They showed that among 350 patients with cutaneous melanoma of the head and neck, CLND (n = 210) as compared with SNB alone (n = 140) did not significantly improve MSS in the study cohort overall (p > 0.20). However, subgroup analysis identified those under 60 years of age with a non-ulcerated primary melanoma ≤2 mm in Breslow thickness as having a significantly improved MSS with CLND (p = 0.003). This finding is counter-intuitive. The authors suggested that there might be a narrow timeframe during which regional micrometastases were sufficiently contained so that CLND prevented further dissemination to distant sites. There were significant limitations of the study, some inherent to a population-based registry, including presumption of SN and non-SN status, and lack of data on extent of surgery and disease recurrence [6].

Wong et al. carried out a multi-institutional study with 16 centers contributing data of 134 SN-positive patients who for various reasons did not follow through with CLND. The primary melanoma was located in the extremities (45%), trunk (43%), and head/neck (12%). These patients were compared with 164 contemporary patients who proceeded with CLND following a positive SNB at Memorial Sloan Kettering Cancer Center. After median follow-up periods of 20 and 36 months for the no-CLND and CLND groups, respectively, multivariate analysis revealed similar nodal recurrence-free survival (p = 0.07) and MSS (p = 0.65) between the two groups [7].

Kingham et al. evaluated 313 SN-positive melanoma patients treated from 1992–2008, segregating them into those who did (n = 271) and did not (n = 42) undergo CLND. Head and neck primary melanomas made up 8% and 17% of the two groups, respectively. The CLND group had a median follow-up of 43 months as compared with that of the no-CLND group which was 32 months. Median times to first recurrence were 13 and 14 months, respectively, in the two groups. They observed similar rates (54% vs. 48%, p > 0.05) and patterns of recurrence, median DFS (36 vs. 35 months, p = 0.63) and median MSS (73 months vs. median not reached, p = 0.26) between the two groups [8].

We note that the EORTC MiniTub study, a prospective registry of melanoma patients with low SN disease burden managed with CLND or serial nodal observation, based on the management decisions made by patients (in consultation with their clinicians), is ongoing and not due to be completed until 2023.

For a new diagnosis of SN micrometastasis, and in the absence of symptoms, staging CT, MRI and PET/CT have not been found to be of staging value or to significantly alter patient management [9–11].

The Sunbelt Melanoma Trial was a multi-center prospective study that compared surgical complications for melanoma patients having SNB-only, or SNB followed by CLND. 1676 patients were enrolled in the SNB-only group, and 444 in the SNB followed by CLND group, to which head and neck patients contributed 11.1% and 9%, respectively. The most common complications were lymphedema (11.7%),

wound infection (7.0%), hematoma/seroma formation (5.9%), and sensory nerve injury (1.8%). Although lymphedema was irrelevant for head and neck patients, the complication rate was still significantly higher in the CLND subgroup (2.4% after SNB only vs. 10% after CLND, $p = 0.008$). Of the 40 patients who underwent parallel SNB and the 6 who subsequently had a superficial parotidectomy, no facial nerve injury or paresis was encountered [12].

Immediate CLND following a positive SNB in the head and neck results in improved regional control, leading to significantly better DFS, but does not offer a MSS benefit over observation followed by subsequent salvage CLND if required (strength of recommendation—strong, quality of evidence—high). The morbidity that occurs in CLND patients is generally minor, and substantially less significant in the head and neck patient population than in patients who have a CLND of the axilla or groin (quality of evidence: high, strong recommendation).

A Personal View of the Data

CLND following a positive SNB in melanoma should no longer be routine. It is appropriate to reason that the majority of melanoma patients who are going to benefit from lymph node removal would have derived the benefit from removal of the sentinel node(s), since around 80% have no additional metastatic disease found in non-SNs when CLND is performed. The 20% who do have non-SN metastases probably have biologically more aggressive disease, which is more prone to systemic metastasis, and will not benefit from CLND except in terms of more adequate regional control. The follow-up regime employed in MSLTII for the observation group was 4-monthly for the first 2 years, 6-monthly for years 3-5, and yearly thereafter. Each clinical follow-up assessment for the first 5 years included surveillance ultrasonography of the nodal basin. There is no evidence to guide surveillance imaging beyond regular ultrasound at present although this topic is currently under investigation at our institution. Improved survival outcomes reported with adjuvant targeted therapy and immunotherapy in patients with resected stage III melanoma will likely increase postoperative uptake of adjuvant therapy following therapeutic parotidectomy/neck dissection in future, and this lends further support to the approach of careful observation rather than immediate CLND in SN-positive patients [13, 14]. Extrapolating from these results, at present postoperative adjuvant nivolumab for 12 months has become the standard of care following a positive sentinel node biopsy at our institution. However, in the presence of high risk features, especially those excluded from MSLTII, i.e., patients with extranodal extension, concomitant microsatellitosis of the primary tumor, more than two involved nodal basins, and immunosuppression, an argument can be made for recommending CLND. Failure of regional control in the parotid/neck nodal basins can result in

debilitating sequelae, including airway compromise, catastrophic bleeding and cranial nerve palsy. Another important consideration is that the risk of major and long-lasting complications is much lower for CLND of the neck as compared with the axilla and groin.

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Part VIII

Reconstruction

Is Routine Anticoagulation Warranted Following Free Flap Reconstruction?

24

Shannon Rudy and Vasu Divi

Introduction

Microvascular free tissue transfer has become the mainstay of reconstruction of complex head and neck defects since the introduction of this technique over four decades ago [1]. Current success rates of microvascular free tissue transfer are generally reported in the literature as over 95% [2–4]. While rare, flap loss is a dreaded complication that can result in significant increased morbidity for patients, including treatment delays, decreased functional and cosmetic results, as well as increased hospitalization costs [5]. Among the most common causes for flap failure are venous and arterial thrombus formation at the microvascular anastomosis [6, 7]. As such, significant importance is placed on the prevention of thrombosis formation.

Perioperative anticoagulation has long been considered a critical aspect of postoperative free flap care [8, 9]. A survey done by Spiegel and Polat found that the vast majority of otolaryngologists who perform free tissue transfer use some form of postoperative anticoagulation, with 76.5% reporting use of aspirin, 35.3% using dextran, and 26.5% using low molecular weight heparin [10]. Despite these high rates of use of anticoagulation agents postoperatively, no single regimen has been demonstrated to be superior for patients undergoing head and neck free flap reconstruction [10]. As such, there is no consensus on what—if any—postoperative anticoagulation protocol should be used in the postoperative setting following head and neck free flap reconstruction [8, 11].

The purpose of this chapter is to review the literature on postoperative anticoagulation in head and neck microvascular surgery in order to better determine efficacy and safety of various agents.

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Table 24.1 Anticoagulation following head and neck free flap reconstruction

Population	Intervention	Comparison	Outcomes
Adults after head and neck free flap reconstruction	Medical anticoagulation	No medical anticoagulation	Incidence of free flap failure. Incidence of free flap complications (hematoma, seroma, partial flap failure)

Literature Search Strategy

Based on the PICO table (Table 24.1), Pubmed and Medline searches incorporating the terms: ("free flap" OR "free tissue transfer") AND ("head and neck") AND ("anticoagulation," "aspirin," "dextran," "heparin," "low molecular weight heparin") were used to review the literature. The bibliography of applicable articles was also reviewed. The search was narrowed to focus on postoperative pharmacologic anticoagulation. Studies were included if they were published in the last 25 years. Preference was given to randomized controlled trials, as well as meta-analyses and prospective studies, though retrospective studies were included for completeness and given the lack of prospective, randomized trials and meta-analyses on this subject.

We chose to focus on postoperative aspirin, heparin (including both unfractionated and low molecular weight heparin), and dextran, as these are the most commonly used chemoprophylactic agents used following free flap reconstruction, and because these have been most widely reported in the literature [10].

Anticoagulation Agents

Aspirin

Aspirin acts as an irreversible inhibitor of cyclooxygenase (COX), which in turn decreases the formation of arachidonic acid metabolites, which include thromboxane A_2, prostaglandins and prostacyclins, thereby decreasing platelet aggregation and thrombus formation. According to the survey by Spiegel and Polat discussed above, aspirin is the most commonly used anticoagulant used following head and neck free flap reconstruction, with use reported by over 75% of head and neck free flap surgeons [10].

No prospective studies, including randomized controlled trials, were identified in our literature search. Two meta-analyses analyzing the effect of aspirin on postoperative free flap loss and bleeding complications were identified however. The first, by Lee and Mun, analyzed two articles that together represented 756 cases [12]. In the pooled analysis, there was no significant difference in free flap loss between the aspirin group and control group (relative risk 0.99, 95% CI 0.47–2.08), though the aspirin group did show twice as high of a hematoma risk as the control group (relative risk 1.91, 95% CI 1.05–3.47).

A second meta-analysis, by Swartz et al. analyzed four studies on 759 radial forearm free flap (RFFF) procedures in which some form of anticoagulation was used in the postoperative period, with aspirin being used in 12% of cases [13]. The main outcome of this analysis was flap failure, and flap complications (including

bleeding, seroma, infection, and partial flap failure) were also analyzed. Pooled analysis found initial flap failure in 90 patients, or 12% of cases, of which 74 patients underwent revision surgery with 50 successful cases. Forty of 758 patients (5.3%) had final flap failure. In the pooled cohort analysis, aspirin use was not associated with a difference in flap failure (OR 1.295, 95% CI 0.317–5.293, p = 0.719). Similarly, no significant difference was found in flap complication rate between patients who received aspirin versus those who received no postoperative anticoagulation (OR 0.4, 95% CI 0.1–1.7).

A retrospective analysis by Lighthall et al. analyzed 390 patients who underwent free tissue transfer [1]. Of these, 184 patients received no postoperative anticoagulation, 142 patients received aspirin, 48 received low molecular weight heparin (LMWH) or a combination of agents, and 16 received a heparin drip. There was no significant difference in flap failure between the group who received aspirin and that who received no anticoagulation (p = 0.839). There was a significantly higher overall rate of complication in the aspirin group versus controls (p = 0.02), though no significant difference in bleeding complications (p = 0.192).

Finally, a retrospective study by Ashjian et al. analyzed the effect of aspirin versus LMWH following free flap reconstruction [14]. In this study, 260 patients received postoperative aspirin (325 mg daily) and 245 received postoperative LMWH (5000 units daily). There was no statistically significant difference in flap failure found between the two groups (p = 0.61), nor was there a difference in complications, including hematoma (p = 0.78), bleeding (p = 0.2), or death (p = 0.2). Of note, this study did not include a control group who received no postoperative anticoagulation.

There is insufficient evidence to recommend the use of aspirin postoperatively following head and neck free flap tissue transfer. There is some evidence to suggest that postoperative aspirin increases the risk of postoperative bleeding complications, including bleeding-related complications (quality of evidence moderate, conditional recommendation).

Heparin

Heparin is an anticoagulation that binds to and activates antithrombin III (AT III), an enzyme inhibitor. Activation of AT III results in the inactivation of thrombin and factor Xa, both of which are critical components of the coagulation cascade. Low molecular weight heparins (LMWHs) take advantage of the size-dependent activity of heparin against thrombin; specifically, LMWHs preferentially inhibit factor Xa over thrombin, and are associated with reduced side effects, including heparin induced thrombocytopenia (HIT) [15].

Similar to aspirin, no prospective studies on the use of heparin (either LMWH or unfractionated heparin) versus no anticoagulation following free flap reconstruction were identified in our literature search. Three meta-analyses were identified, however, that analyzed the efficacy and safety of postoperative unfractionated heparin and/or LMWH use in head and neck free flap patients.

The first meta-analysis, by Swartz et al. (also discussed above under the aspirin section) included five studies totaling 759 radial forearm free flaps, in which unfractionated heparin was used in 28.1% of cases and LMWH was used in 49% of cases [13]. As stated above, final flap failure was seen in 5.3% of 758 cases. Pooled unadjusted analysis found an increased risk of flap failure associated with heparin (OR 3.99, 95% CI 1.579–10.082, p = 0.003) and LMWH (OR 5.429, 95% CI 1.671–17.640, p = 0.005), thus favoring the control group over the heparin and LMWH groups. Furthermore, in a univariate analysis of factors associated with flap failure, patients who received unfractionated heparin or LMWH were again found to have a higher rate of flap failure (OR 3.1, 95% CI 1.7–5.9, p < 0.05), though this statistically significant difference was not seen in a multivariate analysis. The authors surmised that this difference between the univariate and multivariate analyses may reflect the fact that patients were more likely to receive postoperative heparin if they were deemed higher risk by their surgeon (such as the need for anastomotic revision during the primary surgery). Finally, this meta-analysis found no difference in complication rate between patients who received heparin/LMWH versus those who received no postoperative anticoagulation (OR 1.5, 95% CI 0.3–7.7).

A second meta-analysis by Lee and Mun (also discussed above in the aspirin section) analyzed 12 articles representing 4984 cases [12]. Of these, 1796 cases from four articles analyzing heparin use (two on unfractionated heparin, one on LMWH, and one on both) were analyzed. Meta-analysis of these articles analyzed unfractionated and low molecular weight heparin together. Pooled analysis of these cases found a trend toward a 35% decreased flap loss in the heparin/LMWH group as compared to patients who received no anticoagulation, though this result was not statistically significant (relative risk 0.65, 95% CI 0.25–1.69). This meta-analysis also found an increased risk of postoperative hematoma in the unfractionated heparin group as compared to the control group, though this result also did not reach significance (RR 4.15, 95% CI 0.99–17.36). There were not enough data to determine hematoma risk in the LMWH group.

It should be noted that postoperative heparin is frequently given to patients following large surgeries, such as head and neck free flap reconstruction, for venous thromboembolism (VTE) prophylaxis. Various risk assessment models, such as the Caprini model, are routinely used to developed to determine a patient's risk of perioperative risk of VTE [16, 17]. Based on this model, almost all patients undergoing head and neck free flap tissue transfer require chemoprophylaxis, such as LMWH perioperatively (VTE risk factors include malignancy, prolonged surgery, advanced age, and immobility, among others). Thus, while LMWH or unfractionated heparin have not been shown to have a significant benefit on flap outcome, these agents should still be considered for VTE prophylaxis based on an individual patient's risk factors.

There is insufficient evidence to recommend the use of heparin (unfractionated or LMWH) postoperatively following head and neck free flap tissue transfer for improving flap survival. There is some evidence to suggest that postoperative heparin increases the risk of postoperative hematoma (quality of evidence moderate, conditional recommendation).

Dextran

Dextran derivatives are a group of synthetic polysaccharides that have anticoagulative properties through their inhibition of thrombin [18]. Dextrans vary by molecular weight and it has previously been found that increased anticoagulative activity is associated with decreased molecular weight [19]. Dextran has previously been one of the most widely used anticoagulation agents following free flap reconstruction [20]. The previously mentioned survey by Spiegel and Polat found that 35.3% of head and neck reconstructive surgeons used dextran postoperatively [10]. However, serious complications have been associated with dextran use, including bleeding, pulmonary edema, osmotic complications, anaphylaxis and death [20–23].

Our literature search identified two meta-analyses and one prospective, randomized controlled trial that analyzed the effectiveness and safety of dextran following head and neck free flap reconstruction. The randomized controlled trial, by Disa et al., examined efficacy and complication rates in 100 patients who underwent head and neck free flap reconstruction by a single surgeon [20]. Patients were randomized to one of three groups: low-molecular weight dextran for 48 h (dextran 48), low-molecular weight dextran for 120 h (dextran 120), and aspirin 325 mg once daily for 5 days. Of note, there was no group who received no postoperative anticoagulation. The authors found two cases of flap loss (one in the dextran 48 group and one in the dextran 120 group). The incidence of systemic complications—which included congestive heart failure, myocardial infarction, pulmonary edema, pleural effusion, and pneumonia—was significantly higher in the dextran 48 and dextran 120 groups (29% and 51%, respectively) as compared to the aspirin group (7%). This represented a relative risk of 3.9 for the dextran 48 group as compared to the aspirin group, and a relative risk of 7.2 for the dextran 120 group versus the aspirin group ($p < 0.05$ and $p < 0.02$, respectively). There was one death in the study, in a patient in the dextran 120 group who died of myocardial infarction at postoperative day 28. In light of these results, the authors of this study argued against the use of dextran as a postoperative anticoagulative agent.

The meta-analysis discussed above by Lee and Mun included four studies totaling 1595 cases in which dextran were used [12]. The authors found a 2.27-fold increased risk of total flap loss in patients who received postoperative dextran as compared to those who did not (95% CI 0.66–7.76), though the difference was not statistically significant. The pooled analysis found a trend toward higher hematoma risk in patients who received dextran, though this result was not significant (relative risk 1.22, 95% CI 0.60–2.48). This meta-analysis did not analyze the relative risk of systemic complications associated with postoperative dextran administration.

A second meta-analysis, by Swartz et al., which was also discussed above, found that dextran was used in 18.3% of the 759 radial forearm free flaps included in the study [13]. In pooled analysis, the authors found no difference in rates of flap loss in patients who received dextran as compared to those who received no anticoagulation (OR 0.838, 95% CI 0.206–3.406, $p = 0.805$). This study also did not comment on differences in rates of systemic complications in patients who received dextran versus those who did not.

Finally, a retrospective analysis of 1351 free flaps performed on 1233 patients compared 283 patients who received dextran 40 postoperatively to 836 patients who

received no postoperative anticoagulation (as well as to 283 patients who received prostaglandin-E1, though this pharmacologic agent is outside the scope of this study) [24]. The authors found no significant difference in flap failure among the three groups ($p = 0.734$) or flap thrombosis ($p = 0.922$). However, there was a significantly increased flap loss rate in diabetic and hypertensive patients who received dextran and diabetic and hypertensive patients who did not ($p = 0.006$ and 0.003, respectively).

Dextran is ineffective in reducing the rate of postoperative free flap failure and has been found to cause serious systemic side effects. As such, recommend against use of this agent following head and neck free flap reconstruction (quality of evidence moderate, strong recommendation).

A Personal View of the Data

Herein we have reviewed three of the most commonly used anticoagulants, aspirin, heparin (unfractionated and LMWH), and dextran (Table 24.2). While high quality evidence in the form of prospective randomized controlled trials is largely lacking, meta-analyses of retrospective studies do allow several conclusions to be drawn, including relatively strong evidence against the use of Dextran based on lack of evidence of flap benefit and risk of severe, systemic effect (Table 24.3). Many surgeons likely follow the prophylaxis plan used in their fellowship training, possibly cautiously deescalating over time while they are in practice.

Table 24.2 Agents considered for postoperative free flap anticoagulation

	Aspirin	Unfractionated heparin	Low molecular weight heparin	Dextran
Effective in preventing flap loss?	Unlikely	Unlikely	Unlikely	No
Benefits	Favorable side effect profile Cardioprotective effect	Decreases venous thromboembolism risk	Decreases venous thromboembolism risk Generally well tolerated with favorable side effect profile	None demonstrated
Drawbacks	Possible increased risk of hematoma	Risk of heparin induced thrombocytopenia (HIT) Possible increased risk of bleeding or hematoma	Low, though theoretical, risk of HIT Possible increased risk of hematoma or bleeding	Risk of severe, systemic effects

Table 24.3 Summary of evidence for anticoagulants in head and neck free flap reconstruction

	Intervention	n	OR or RR	95% CI	P value	Type of study	Quality of evidence
Lee and Mun [12]	Aspirin vs no anticoagulation	756	RR free flap loss = 0.99	0.47–2.08	Not given	Meta analysis	Moderate
			RR hematoma = 1.91	1.05–3.47	Not given		
	Heparin vs no anticoagulation	1796	RR free flap loss = 0.65	0.25–1.69	Not given		
			RR hematoma = 4.15	0.99–17.36	Not given		
	Dextran vs no anticoagulation	1595	RR free flap loss = 2.27	0.66–7.76	Not given		
			RR hematoma = 1.22	0.60–2.48	Not given		
Swartz et al. [13]	Aspirin vs no anticoagulation	91	OR free flap failure = 1.295	0.317–5.293	0.719	Meta analysis	Moderate
	Unfractionated heparin vs no anticoagulation	218	OR free flap failure = 3.99	1.579–10.082	0.003		
	LMWH vs no anticoagulation	49	OR free flap failure = 5.429	1.671–17.640	0.005		
	Dextran vs no anticoagulation	139	OR free flap failure = 0.838	0.206–3.406	0.805		
Lighthall et al. [1]	Aspirin (no control group)	142	Not given	Not given	0.839	Case series	Low
Ashjian et al. [14]	Aspirin vs LMWH	260	Not given	Not given	0.61 (flap failure) 0.78 (hematoma)	Retrospective controlled cohort study	Low
Disa et al. [20]	Dextran (48 and 120 h) vs Aspirin	35 (D48)	RR systemic complications	Not given		RCT	High
		32 (D120)	3.9 (D48)		<0.05		
		27 (aspirin)	7.2 (D120)		<0.02		
Riva et al. [24]	Dextran vs No anticoagulation	283	Not given	Not given	0.734 (flap loss) 0.922 (thrombosis)	Retrospective controlled cohort study	Low

OR odds ratio, *RR* relative risk, *RCT* randomized controlled trial

The evidence for or against the use of heparin (including unfractionated and LMWH) and aspirin remains less clear. However, as discussed above, given the role of LMWH on VTE prophylaxis, and the elevated risk of VTE that most head and neck free tissue transfer patients represent, the senior author routinely uses LMWH perioperatively at doses recommended for VTE prophylaxis on this patient population when not otherwise contraindicated. Most hospitals consider VTE prophylaxis as a quality measure and rates are reported to Centers for Medicare & Medicaid Services and the Joint Commission. Similarly, aspirin is well known to have cardioprotective effects [25]. Given the overall well tolerated nature of aspirin, with limited systemic side effects, as well as its cardioprotective effects in a patient population with high rates of cardiac comorbidities, the senior author also routinely uses aspirin following head and neck reconstruction when not otherwise contraindicated. Although there is potential for increased rates of bleeding following surgery with these two agents, in the author's experience, most post-operative bleeding is secondary to vessels that should have been clipped or tied as opposed to cauterized, and this can be avoided with changes in surgical technique.

Given that flap success is not the only important factor in successful head and neck free flap reconstruction, future studies that determine the benefit of various anticoagulants could include other metrics, including perioperative VTE rates and cardiovascular complications, in order to better elucidate the risks and benefits of these agents and to determine what, if any, optimal regimen exists.

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Does Two Venous Anastomoses Lead to Better Outcomes in Free Flap Reconstruction of the Head and Neck?

25

Cedric Hunter and David W. Chang

Introduction

Complex three-dimensional head and neck defects often require free tissue transfer for appropriate reconstruction after resection or trauma. The nuances of free flap head and neck reconstruction extend beyond technical aspects of flap harvest and inset, and require key decision making including appropriately selecting target vessels on the ipsilateral or contralateral side and the number of anastomoses to perform. Vascular thrombosis is a major complication of free flap surgery, with the largest problem being venous thrombosis [1]. Literature support for multiple venous anastomoses is mixed. Some suggest that additional venous anastomoses lowers velocity through each vein increasing thrombosis risks, while others suggest that an additional anastomosis is protective and provides outflow when there is a thrombosis in single vein [2, 3]. This chapter reviews indications, complications, and effectiveness of performing two venous anastomoses compared to single venous anastomosis in free flap reconstruction of the head and neck.

Literature Search Strategy

Based on the PICO table (Table 25.1), Pubmed and CENTRAL searches incorporating the terms "head and neck", "microsurgical", "free flap", "venous anastomosis", and ("two venous anastomoses" or "multiple venous anastomoses") were used to review the literature. The bibliography of applicable articles was also reviewed. The

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Z. Gooi, N. Agrawal (eds.), *Difficult Decisions in Head and Neck Oncologic Surgery*, Difficult Decisions in Surgery: An Evidence-Based Approach,
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Table 25.1 One versus two venous anastomoses in head and neck free flap reconstruction

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients who underwent head and neck reconstruction with free microvascular flaps	Single venous anastomosis	Two venous anastomoses	Flap survival, venous thrombosis, venous insufficiency, flap revisions

search included some relevant articles of multiple venous anastomoses that were not in the head and neck region for completeness; however, the focus was on head and neck reconstruction. Articles published before the year 2000 were excluded to focus on more recent data with the exception of three historically significant articles key to detailing the history of the topic. Articles that did not discuss performing multiple venous anastomoses were excluded. Given the limited data consensus statements and review articles were included.

Results

Evidence in Support

Venous congestion continues to be the most common cause of flap failure and while its absolute cause is multifactorial (extrinsic pressure, intrinsic intima damage, etc.) it is ultimately related to Virchow's triad of low flow state, intimal injury, and hypercoagulability [2]. To overcome the risk of venous thrombosis that can lead to flap failure some advocate the use of multiple venous anastomoses. Particularly as most of the common flaps have multiple veins from either venae comitantes or available veins from adjacent vascular territories that can drain all or part of the flap. There is evidence that supports the use of two venous anastomoses over a single venous anastomosis.

A 2008 study by Ross et al. retrospectively examined the 10-year experience of a single senior surgeon, Peter Neligan, in head and neck reconstruction. There were a total of 492 free flaps included in the study. Three hundred and forty-five flaps utilized a single venous anastomosis, while 147 flaps utilized two venous anastomoses. The overall flap survival rate was 95%. There was successful free flap reconstruction in 145 of 147 (98.6%) of patients with two venous anastomoses compared to successful free flap reconstruction in 323 of 345 (93.6%) of patients with a single venous anastomosis ($p < 0.05$). Per the article it was routine practice for the senior surgeon to perform two venous anastomoses unless the second venous anastomosis would compromise the patency of either the first venous anastomosis or the arterial anastomosis, or if extensive additional dissection was needed for the second recipient vein. The anatomical site for reconstruction varied within the head and neck region, as did the type of free flap chosen for reconstruction in these cases. They did note that the availability of two recipient veins varied depending on the anatomical recipient site, and that only a single anastomosis was possible in the majority of the skull base, hypopharyngeal, and paranasal defect reconstructions. At the same time they noted that free flap reconstructions at these sites are particularly difficult to monitor and decreased monitoring may have contributed to the higher failure rates in this study. However, there is no mention of

statistical significance for these conclusions. This study suggests performing two venous anastomoses in head and neck reconstruction when possible [4].

A retrospective review of 310 radial forearm free flaps by Ichinose et al. compared single versus two venous anastomoses in both the superficial and deep drainage systems. All free flaps in this study were for head and neck reconstruction. They reported a lower incidence of venous insufficiency with dual venous anastomosis of both the superficial and deep venous systems compared to a single venous anastomosis of either the superficial or deep venous system (0.7% versus 7.5%, $p < 0.05$). However, they also noted that performing two anastomosis of a single system (superficial or deep) showed no significant difference in the incidence of venous insufficiency compared to a single anastomosis (11.5% versus 7.5%, $p = 0.48$). This article suggests not only performing two anastomoses, but anastomoses of both the superficial and deep venous system decreases the risk of venous insufficiency and thus flap failure. The dual venous anastomoses of both systems can provide compensation or protection in the event of a thrombosis in one system, whereas two venous of a single system influence each other with no additional protection. This study was particularly notable, as they not only focused on single versus dual venous anastomosis, but the selection of which systems the surgeon should drain [5].

A systematic review and meta-analysis performed by Riot et al. in 2015 included 27 articles for a total of 6842 flaps where single venous anastomosis was performed in 4591 flaps versus two venous anastomoses was performed in 2251 flaps. They noted a statistically significant difference in flap failure rates at 3.1% for single anastomosis versus 1.3% for double anastomosis, with thrombosis rates of 3.1% versus 2.3%, respectively. This review examined breast reconstruction flaps, and flaps for trauma coverage in addition to head and neck reconstruction. These authors argued that it was not the presence of one or two anastomosis that decreases thrombosis, but when there is venous thrombosis due to intrinsic (poor technique, intima injury, etc.) or extrinsic factors (hematoma, etc.) that an additional venous outflow could provide adequate drainage [6].

In a recent published article, Khaja et al. retrospectively compared rates of re-exploration and flap failure in patients with one or two venous anastomoses in 300 patients who underwent free flap head and neck reconstruction. A venous coupler was used for all venous anastomosis. They noted that the one venous anastomosis group had significantly more re-explorations compared to the two-venous anastomosis group (15.7% vs. 5.6%, $p = 0.028$). This finding remained significant when controlling for flap type in a multiple logistic regression analysis. However, the number of venous anastomosis did not have any effect on flap failure or survival [7]. While prior reports have noted a concern for increased operative time and increased risk of thrombosis due to venous stasis, in this study two venous anastomoses did not increase the risk for vascular compromise [2, 8]. Instead they noted that two vein anastomosis may reduce the risk of postoperative return to the operating room compared to one vein anastomosis.

A meta-analysis in 2015 examined the benefit of two venous anastomoses in head and neck free flap reconstruction where they included 16 articles and 3684 flaps for analysis. There was no statistically significant difference in free flap failure rates. However, they identified a statistically significant difference in the venous thrombosis

rate with a 2.74% rate in the two venous anastomoses group versus a 4.54% rate in the group with a single venous anastomosis ($p = 0.009$). They also noted a statistically significant difference in surgical revision with 6.04% revisions in the two venous anastomoses group versus 11.87% revision rate in the single venous anastomosis group where surgical revision is return to the operating room or revision of the microvascular anastomosis. Their findings supported that performing dual venous anastomoses was protective against venous thrombosis and surgical revision [9].

Evidence Against

In 2010 in lieu of direct comparison of free flap survival, Hanasono et al. compared venous blood velocity in free flaps in which one venous anastomosis was performed to free flaps where two venous anastomoses were performed. Using a 20-MHz Doppler ultrasound probe they measured blood velocity in the artery and vein of free flaps both before pedicle division and 20 min after microvascular anastomosis. In this study when only one venous anastomosis was performed the larger of the two venae comitantes was used for the anastomosis. They looked at 81 free flaps of various types (anterolateral thigh, radial forearm, fibula osteocutaneous, etc.) for head and neck reconstruction in addition to breast reconstruction. One venous anastomosis was performed in 69 free flaps with two venous anastomoses in 12 free flaps. They noted an increase in peak arterial blood velocity after the anastomosis compared to before pedicle division (41.3 cm/s vs. 31.0 cm/s, $p = 0.00042$). While the flap remained in situ they measured the peak venous blood velocity of each venae comitans, the mean peak blood velocity was 6.3 ± 4.8 cm/s. They then occluded each vena comitans independently and measured the peak venous velocity in the other open vena comitans. With this maneuver they noted that the mean peak venous blood velocity increased to 19.5 ± 17.3 cm/s ($p < 0.00001$). In free flaps with two venous anastomoses they noted that the mean peak venous blood velocity between the two venae comitantes were not significantly different and the mean peak venous blood velocity measured in both venae comitantes was 7.5 ± 4.3 cm/s which was significantly slower than the mean peak venous blood velocity of 13.1 ± 7.4 cm/s seen in flaps with only one venous anastomosis ($p = 0.001$). To further demonstrate that blood velocity increases in one vena comitans in response to clamping the other, the authors measured the mean peak venous blood velocity in each venae comitantes after dual venous anastomosis (7.5 ± 4.3 cm/s). They then temporarily clamped one of the vena comitans and measured the mean peak venous blood velocity in the open vena comitans and noted an increase to 17.0 ± 13.8 cm/s ($p = 0.003$) [3]. Based on prior data that suggests that flap loss is associated w/ a low velocity state and a slow intrinsic transit time, defined as the time it takes blood to flow from the arterial anastomosis to the venous anastomosis, they theorize that low blood velocity is therefore correlated with a higher risk of thrombosis [3, 10]. They used several types of free flaps in this study; however, the arterial and venous blood velocities before and after anastomoses were not significantly different between flap types by analysis of variance, which is consistent with prior studies [3, 11, 12]. Their findings of higher blood velocity with anastomosis of a single vena comitans as opposed to two venous anastomosis was also consistent between flap types.

Hanasono et al. argue strongly against routinely performing two venous anastomoses in free flap surgery.

In a 2013 study Han et al. retrospectively reviewed 201 osteocutaneous free flaps for mandible reconstruction. A single venous anastomosis was performed in 112 flaps and two venous anastomoses were performed in the remaining 89 free flaps. They noted a success rate of 98.5% overall. There were 2 of 89 cases of venous thrombosis and 1 of 89 cases of arterial thrombosis in the two venous anastomoses group, with 3 of 112 cases of venous thrombosis in the single venous anastomosis group ($p = 0.59$). They identified no significant difference in flap success rates between performing a single vs. dual venous anastomoses in free fibula osteocutaneous flap mandible reconstruction. As a result they note that single venous anastomosis reduces the operative time and allows for easier inset of the vascular pedicle [13].

The classically referenced article by Futran and Stack includes a retrospective review of patient data and a meta-analysis of radial forearm free flap reconstruction of head and neck defects. They noted no flap loss in 43 radial forearm flaps after performing two venous anastomoses in 16 patients and single venous anastomosis in 27 patients. They did note that a single venous anastomosis shortened the operative time by 21–36 min. For the meta-analysis they detected no significant difference ($p = 0.99$) with respect to flap survival in single versus dual venous anastomosis. They concluded that while two venous anastomosis may provide a more fail-safe mechanism for flap drainage, a single venous anastomosis was adequate and provided reduced operative time in an already lengthy case [2]. Their findings have been confirmed by a 2015 meta-analysis by Bai et al. who found that while there was a tendency of dual anastomosis of the deep and superficial venous system to decrease the risk of venous thrombosis, this tendency was no statistically significant [14].

Theory and Physiology

It is well known that flap failure is often secondary to microvascular complications including thrombosis, and that venous thrombosis is more common than arterial thrombosis [15].

One critical component of the discussion of one versus two venous anastomoses is operative time. Anastomosing an additional vein requires not only the time it takes to perform the anastomosis, but also a time investment for identification and preparation of the second recipient vessel and preparing the second vein of the flap. Available data has suggested that these maneuvers can add around 20–40 min of additional operative time [2, 8]. In a vessel depleted neck, an additional vein for a second venous anastomosis may not be available or it may require a vein graft to reach a second recipient vein. In addition, performing a second venous anastomosis may create an unfavorable lie of the pedicle create kinks or twists increasing the risks of thrombosis.

While adding venous anastomoses in theory may provide protection against flap congestion and failure, the additional venous anastomoses could actually be placing the flap at increased risk as high venous flow is thought to be protective against venous anastomotic thrombosis. Additional venous anastomoses decrease the venous pressure in the flap thereby decreasing the venous flow and increasing the

potential for venous thrombosis [2]. Rodbard notes that increased resistance to venous flow results in venous distension thereby increasing venous flow [16]. One can theorize here that, at least according to this theory, the increased resistance and flow through a single venous anastomosis acts as a makeshift stent. While this physiologic data may show that blood flow is slower in two venous anastomosis flaps which some suggest promotes thrombosis. It is difficult to rationalize this when there are multiple meta-analyses, systematic reviews, and clinical studies that indicate there is higher risk of flap loss and thrombosis when a single anastomosis is performed as opposed to two [6, 17]. An article by Dornseifer et al. sheds some light on this topic. They evaluated the intrinsic transit time of free flaps in single and two venous anastomosis groups, where intrinsic time is defined as the time it takes dye to travel from the arterial to the venous anastomosis during microangiography to provide information on blood velocity. They found that while performing only a single anastomosis does indeed decrease the intrinsic transit time correlating with a faster flow velocity in the flap; however, this did not result in decreased thrombotic complications. One cannot view flow velocity and intrinsic transit time in isolation or as a linear relationship to flap complications, as blood flow in the "slower" two vein anastomosis group was adequate in this study and shortening the intrinsic time lost its importance beyond a certain point and the "backup drainage" vein may have been more significant. Their conclusion was that the advantage of a second vein anastomosis should be considered as long as this does not excessively prolong the intrinsic transit time [18].

Data Based Recommendations

Review of the published data including the meta-analyses and the physiologic studies suggests that performing two venous anastomoses may reduce the risk of flap failure and thrombotic complications compared to performing only a single venous anastomosis. The benefits and drawbacks of one versus two venous anastomoses are summarized in Table 25.2. While it is often sufficient to perform a single venous anastomosis, based on the included studies one should perform two venous anastomoses when technically feasible (quality of evidence: moderate, strength of recommendation: weak/conditional, grade 2B). This will have to be evaluated on a case by cases basis, as it is not always possible or prudent to perform two venous anastomoses (Table 25.3).

Table 25.2 Comparing one versus two venous anastomoses

	One anastomosis	Two anastomoses
Benefits	Favorable pedicle geometry, shorter operative time, minimize neck/recipient vessel dissection	There is a back-up in the case of venous thrombosis in a single vein
Drawbacks	Rely on a single vein for outflow, no back-up in case of venous thrombosis	Requires additional operative time, requires additional neck/recipient vessel dissection, can distort pedicle geometry

Table 25.3 One versus two venous anastomoses supporting data

Study	n	Results	Type of study	Quality of evidence
Futran et al.	27 single venous anastomosis; 16 double venous anastomoses	No flap loss in either group. Single venous anastomosis provides adequate drainage	Case-control	Moderate
Hanasono et al.	69 single venous anastomosis; 12 double venous anastomoses	Mean blood velocity is greater in flaps with one venous anastomosis compared to two venous anastomoses. Single venous anastomosis results in increased blood velocity and decreased low flow states	Case-control	Moderate
Ross et al.	345 single venous anastomosis; 147 double venous anastomoses	Statistically significant reduced risk of flap failure in two venous anastomoses group. Where possible perform a second anastomosis	Case-control	Moderate
Ichinose et al.	147 single venous anastomosis; 163 double venous anastomoses	Dual venous anastomoses of separate venous systems (superficial and deep) in radial forearm free flap reduce risk of flap failure. Dual venous anastomoses of a single venous system showed no difference from single venous anastomosis	Case-control	Moderate
Riot et al.	4591 single venous anastomosis; 2251 double venous anastomoses	Dual venous anastomoses reduce the risk for flap failure, surgical revision, and venous thrombosis	Systematic review and meta-analysis	High
Khaja et al.	229 single venous anastomosis; 71 double venous anastomoses	No significant difference in flap failure rates. The single vein group had higher rates of re-exploration	Case-control	Moderate
Chaput et al.	1805 single venous anastomosis; 875 double venous anastomoses	Increased failure rate, thrombosis rate, and surgical revision rate in the single venous anastomosis group compared to the dual venous anastomoses group	Meta-analysis	High
Han et al.	112 single venous anastomosis; 89 double venous anastomoses	No difference in the flap success rates between the two groups	Case-control	Moderate
Bai et al.	992 patients total	No statistically significant difference between single and dual venous anastomoses groups	Meta-analysis	High
Ahmadi et al.	3619 patients total	Dual venous anastomoses group had statistically significant lower incidence of venous thrombosis and flap failure compared to the single venous anastomosis group	Meta-analysis	High
Dornseifer et al.	75 single venous anastomosis; 51 double venous anastomoses	Single venous anastomosis group has reduced intrinsic transit time compared to dual venous anastomosis group. However, restriction to one vein does not reduce thrombosis	Case-control	Moderate

While it is often sufficient to perform a single venous anastomosis, based on the included studies one should perform two venous anastomoses when technically feasible (quality of evidence moderate, conditional recommendation).

A Personal View of The Data

We routinely perform single venous anastomosis. However, we do sometimes perform two venous anastomoses when the anatomy is favorable and technically it is easy and expedient, especially if there is any concern about the first venous anastomosis. Ideal situation for two venous anastomoses is when there is another source of venous outflow from the flap that is of sufficient size, and an additional recipient vein is easily identified in the neck, and performing the second venous anastomoses does not kink or twist the pedicle. In this situation, we have found the additional time for an additional venous anastomosis negligible, especially with the use of a venous coupling system.

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Reconstruction for Early Oral Cavity Cancer

26

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Introduction

Surgical extirpation has been established as the mainstay for early oral cavity cancers [1, 2]. For larger defects involving >50% of oral cavity subunits, reconstruction is necessary to restore anatomy and function. In contrast, resection of early tumors usually results in smaller defects which may be amenable to primary closure, healing by secondary intention, and/or the use of prosthetics.

This chapter reviews the evidence for reconstruction versus no reconstruction in patients undergoing surgical excision for early stage oral cavity cancer (T1 or T2 tumors, which by definition are <4 cm). While initial choice is influenced by surgical considerations such as the general condition of the patient, availability of reconstructive services and options, as well as patient preference, pertinent surgical outcomes in relation to choice of closure include functional outcomes such as speech and swallowing, as well as quality-of-life (QoL). For logical analysis of the available literature, this chapter has been grouped into three separate regions based on the relationship of the anatomical subunits of the oral cavity. These are: (1) tongue and floor of mouth, (2) hard palate/inferior maxilla, and (3) gingivo-buccal and retromolar trigone region. Individual flap types, while mentioned, are not compared in this chapter due to the plethora of reconstructive options available.

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Table 26.1 Outcomes of early oral cavity cancer after reconstruction vs. no reconstruction

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with T1/T2 oral cavity tumors undergoing surgical extirpation	Reconstruction with autologous tissue	Primary closure, healing by secondary intention, obturation	Quality of life, speech, swallowing

Search Strategy

Based on the PICO table (Table 26.1), PubMed and CENTRAL databases were used to review the literature. The search incorporated terms that (1) implied method of closure ["management" or "reconstruction" or "closure"], (2) defined the extent of disease ["early oral cavity cancer" or "T1/T2 oral cavity cancer"] and (3) defined the region of the oral cavity ["inferior maxillectomy" or "hard palate" or "glossectomy" or "tongue" or "floor of mouth" or "gingiva" or "buccal mucosa"]. The search was then narrowed down to focus on articles reporting outcome measures of quality of life and speech and swallowing function. As is the inherent weakness of most reconstructive outcomes articles, there is a lack of randomized controlled trials, meta-analyses and large comparative cohort studies. We thus gave preference to reviews and case-control studies, and studies that only had one treatment arm were also included if the method of outcome assessment for the intervention arm was identical to at least one other study analyzing the comparator treatment arm. In addition, the bibliography of included articles was reviewed and referenced articles addressing the topic at hand were reviewed individually for inclusion. The included study articles were published from 1993 to March 2018.

Results

Tongue and Floor of Mouth Defects

The majority of studies for this region focused on resection of tongue tumors resulting in partial or hemiglossectomy defects (Table 26.2). McConnel et al. studied two sets of nine matched patients with partial and hemiglossectomy defects [3]. The first set compared primary closure of the defect with distal flap reconstruction; primary closure gave better swallowing of liquids, less pharyngeal residue, higher conversational intelligibility, but longer oral transit time with food paste. The second set compared primary closure with free flap reconstruction; primary closure proved superior with better swallowing of liquids, less pharyngeal residue, and shorter pharyngeal delay times with food paste. However, most of the defects were partial glossectomies, with only 2 of the 18 matched pairs having defects involving around 50% of the tongue. Thus, the conclusion that can be drawn from this study is that primary closure is superior to reconstruction for partial glossectomy defects.

In a review of 19 partial glossectomies in a Chinese population, Chuanjun et al. compared speech outcomes of 9 patients without reconstruction versus 11 patients

Table 26.2 Tongue and floor of mouth defects

Study	n	Defect	Assessment	Results	Type of study	Quality of evidence
McConnel et al.	18 primary closure; 18 flap (matched)	Mostly partial glossectomy	Speech language pathologist; VFS for swallowing timings	Primary closure better speech intelligibility; and better swallowing	Case-control	Low
Chuanjun et al.	8 non-flap; 11 flap	Partial glossectomy	Taped speech with three blinded listeners	Non-flap reconstruction patients had better articulation, intelligibility	Case-control	Low
Bressmann et al.	8 primary closure; 6 flap	Partial glossectomy	Taped speech with two blinded listeners; tongue motility measurement	Flap patients had better consonant intelligibility	Case-control	Low
Hsiao et al.	6 primary closure; 6 flap	Hemi-glossectomy	Taped speech with two blinded listeners; swallowing timings	Primary closure patients had better speech intelligibility and articulation ratings; flap better ingestion rates	Case-control	Low
Ji et al.	Partial: 15 secondary intention; 7 flap Hemi: 6 secondary; 10 flap	Partial glossectomy; hemi-glossectomy	Korean Speech Mechanism Screening Test; Functional Outcome Swallowing Scale	Secondary intention better for partial glossectomy; flap reconstruction better for hemiglossectomy defects	Case-control	Low
Kazi et al.	27 non-flap; 7 flap	Partial glossectomy	UW-QOL v4	Reconstruction patients with poorer QOL score	Case-control	Low
Canis et al.	20 primary closure; 20 flap	Hemi-glossectomy	EORTC QLQ-C30; QLQ-H&N35	Reconstruction patients with higher QOL score	Case-control	Low
Mochizuki	119 secondary intention (PGA); 132 skin graft	Floor of mouth; buccal	Operation time; time to oral intake; length of stay; mouth opening; speech	PGA faster op, time to oral intake, and discharge; skin graft better speech for tongue/FOM $\geq$12 cm^2	Case-control	Low

with flap reconstruction and found articulation intelligibility to be significantly higher for the non-reconstructed group for anterior portion glossal sounds (77% vs. 94.6%, $p < 0.05$), middle portion glossal sounds (76.3% vs. 92.1%, $p < 0.05$) and posterior portion glossal sounds (84.7% vs. 95.3%, $p < 0.01$) [4].

Bressmann et al. compared 14 patients after partial glossectomy, of whom 8 had primary closure of the defect and 6 underwent reconstruction with platysma flaps [5]. Those with reconstruction performed had a higher mean consonant intelligibility, though the difference was not statistically significant; tongue motility was considered the same for both groups.

Hsiao et al. performed a case comparison study of 12 hemiglossectomy patients, with 6 cases of primary closure and 6 receiving free radial forearm flap reconstruction [6]. Patients with reconstruction had significantly better ingestion rates, measured as the time taken to swallow 175 ml of water. Those without reconstruction had higher speech intelligibility and articulation ratings, although this was not statistically significant. They concluded flap reconstruction, while providing bulk which is beneficial to swallowing, could also restrict movement of the remnant tongue.

Healing by secondary intention was used as an alternative to primary closure in some studies. Ji et al. studied 38 patients were divided into 2 groups: 22 partial glossectomies (15 healing by secondary intention, 7 free flap reconstruction) and 16 hemiglossectomies (6 secondary intention, 10 free flap reconstruction) [7]. Tongue mobility was assessed using the Korean Speech Mechanism Screening Test, and swallowing using the Functional Outcome Swallowing Scale (FOSS). In the partial glossectomy group, those who healed by secondary intention had better tongue mobility, articulation, and speech intelligibility. In the hemiglossectomy group, free flap reconstruction gave better tongue mobility, articulation, verbal diadochokineses and speech intelligibility. Swallowing function was the same within each group. The contrasting results suggest there needs to be a clear distinction between partial and hemiglossectomy defects when considering the optimum treatment.

A few studies reported specifically on the subjective assessment of QoL using questionnaires. Kazi et al. assessed 34 partial glossectomy patients using the well-validated University of Washington Head and Neck QoL (UW-QOL) questionnaire [8]. Reconstruction was associated with a significantly poorer score, together with other treatment variables such as neck dissection, complications and radiotherapy. However, it is unclear if flap patients were more likely to require neck dissection and adjuvant radiotherapy; the impact of flap surgery in isolation remains unknown.

In contrast, Canis et al. compared reconstruction and non-reconstruction in lateral tongue cancer patients that were demographically similar to correct for confounders [9]. 40 patients were involved (20 primary closure, 20 free forearm flap), and 2 different validated QoL questionnaires (EORTC QLQ-C30 and QLQ-H&N35) were used. He found that patients who underwent reconstruction had significantly fewer problems with the swallowing, speech and social eating subdomains of the questionnaires.

As for defects involving the floor of mouth (FOM), isolated floor defects that do not violate the continuity of the oral cavity can be left to heal be secondary intention or skin grafted. Mochizuki et al. compared 119 patients with healing by secondary

intention and polyglycolic acid (PGA) sheets versus 132 with skin grafting for oral cavity wounds [10]. The PGA group had shorter operation time and was able to start oral intake earlier. However, for tongue and floor of mouth defects ≥12 cm^2, skin grafts gave better speech intelligibility. FOM defects that communicate with the neck structures should be reconstructed using flaps to seal off the oral cavity and to avoid tethering the tongue. Locoregional flaps can be used for smaller defects, while free flaps are commonly used to simultaneously resurface the floor of mouth and its adjacent structures such as the tongue and gingival mucosa. To summarize, the evidence for reconstruction versus no reconstruction of smaller tongue defects remains weak and contradictory. The included articles invariably omit important details and definitions including objective measurement of defect size and location.

For partial glossectomy defects (1–49% of the oral tongue), non-flap techniques for closure were at least equivalent or superior to the use of flaps. Reconstruction should be discretionary depending on location of the defect and risk of tongue tethering (quality of evidence low; weak recommendation).

For hemiglossectomy defects involving 50% of the oral tongue, flap reconstruction is recommended over non-flap closure as it provides much needed bulk, improving speech, swallowing and quality of life outcomes (quality of evidence low, weak recommendation).

Hard Palate/Inferior Maxilla Defects

Due to the bony nature of the hard palate requiring structural support, the majority of studies compared flap reconstruction and obturator use (Table 26.3). Direct comparison was often difficult due to the different defect classifications used.

Moreno et al. analyzed 113 maxillectomy patients with 73 obturators and 40 flap reconstructions [11]. Speech pathologist assessment was performed looking for intelligibility and dietary restrictions. The demographics showed a trend towards obturators being preferred for small defects, while flaps were more frequent for larger defects. When corrected for defect size, flap reconstruction had better outcomes for Type III horizontal defects based on the Okay classification.

Eckardt et al. measured the degree of nasalance in 28 patients (10 obturator, 18 flap reconstruction) [12]. The trend was for obturators to be used for smaller defects (Brown Class 1 or Class 2a). Flap reconstruction was performed preferentially for larger defects (Brown Class 2a or 3a). In terms of the degree of nasalance, there was no statistically significant difference between the two groups, although defect size was not corrected for in this analysis.

Rieger et al. assessed the speech nasalance, intelligibility, velopharyngeal orifice opening, and aesthetics of 39 maxillectomy patients (23 obturator, 16 flap reconstruction) [13]. He found no difference between the two groups.

Sreeraj et al. compared mastication function in 20 patients (10 obturator, 10 flap reconstruction + dental prosthesis) with Aramany Class II defects (unilateral defect

Table 26.3 Hard palate/inferior maxilla defects

Study	n	Defect	Assessment	Results	Type of study	Quality of evidence
Moreno	73 obturator; 40 flap	Brown: II, III, IV; Okay: Ia/b, II, III	Speech intelligibility, dietary restrictions	Flap reconstruction better for Okay Type III defects	Case-control	Low
Eckardt	10 obturator; 18 flap	Brown I–IV	Nasalance measurement	No difference	Case-control	Low
Rieger	23 obturator: 16 flap	Okay Ib–III	Speech; velopharyngeal opening; aesthetics	No difference	Case-control	Low
Sreeraj	10 obturator; 10 flap	Aramany Class II	Mastication function; VFS for swallowing timings	Flap patients had better mastication function; no difference in swallowing	Case-control	Low
Genden	4 obturator; 4 flap (matched)	Hemipalato-maxillectomy	Speech, mastication, SWAL-QOL, speech questionnaire	Flap better speech, mastication and QOL	Case-control	Low
Rogers	10 obturator; 18 flap	Brown I–IV	UW-QOL v1, EORTC QLQ-C30; QLQ-H&N35; HAD; BSS; Oral symptom checklist; OFS	Obturator: problems with appearance, anxiety, pain; flap: increased weight gain	Case-control	Low
Breeze	21 obturator; 18 flap	Tumour stage	UW-QOL v4	No difference	Case-control	Low
Wang	18 implant-supported obturator; 20 flap with implants	Brown Ib–III	EORTC QLQ-H&N35, OFS, MHI	No difference	Case-control	Low

lateral to canine) [14]. The group with flap reconstruction and dental prosthesis performed better. When swallowing function was assessed by measuring videofluoroscopic oral transit time; there was no difference between the groups.

Genden et al. published a report of four pairs of matched patients who underwent hemipalatomaxillectomy [15]. Each pair included a patient who underwent flap reconstruction and another who had an obturator placed. Assessment included voice analysis, nasorhinometry, mastication testing, and questionnaires for QOL and donor site morbidity. They reported flap reconstruction giving higher scores in mastication, speech assessment and QOL, without significant donor site morbidity.

When looking specifically at subjective assessment of QoL, Rogers et al. performed a detailed survey of 28 post-maxillectomy patients (10 obturator, 18 free flap reconstruction) [16]. They employed multiple questionnaires including: the UW-QOL, EORTC QLQ C30, EORTC Head and Neck 35; Hospital Anxiety Depression (HAD), Body Satisfaction Scale (BSS); Oral symptom check list; Denture Satisfaction; and the Obturator Functioning Scale (OFS). They concluded that patients with obturators had increased adverse issues with their appearance, anxiety, and pain and soreness in the mouth. Patients who had free flap reconstruction had more weight gain, implying better nutritional status. While there was no subset analysis done based on defect size, and the trend was for flaps being used for larger defects, flap reconstruction still had overall better results. Breeze et al. also used an updated version of the UW-QOL on 39 patients (18 flap reconstruction, 21 obturators) [17]. There was no significant difference between the two groups, even after stratification by defect size.

In a cross-sectional survey of 38 patients (18 implant-supported obturator, 20 flap reconstruction with implants) using the OFS, EORTC HNN and the Mental Health Inventory (MHI) questionnaires, Wang et al. reported no difference in oral function between patients with implant supported obturators and implant supported fixed prostheses in free vascularized flaps after a maxillectomy [18]. The studies reviewed showed that flap reconstruction obtained equivalent or superior results compared to an obturator, with no studies demonstrating a poorer outcome. While this may appear to be evidence of the superiority of flap reconstruction, it also highlights that in select cases obturators can afford similar results without the additional complexity of flap surgery. However, obturator use does imply the need for long-term maintenance, while flap reconstruction affords a more permanent solution.

In patients with smaller maxillectomy defects (Brown Class 1, 2a; Okay 1a/b, selected 2) flap reconstruction is not shown to have superior outcomes compared to obturator use.

Flap reconstruction should be performed in patients with larger maxillectomy defect can be covered with an obturator while large defects (Brown Class 3b, 4b, any c) (quality of evidence low; strong recommendation).

Gingivo-Buccal and Retromolar Trigone Defects

Articles focused on specifically on gingivo-buccal and retromolar reconstruction were scarce, and definitions of specific defect sizes were lacking (Table 26.4). Due to the proximity of the mandible, many of the articles that were excluded involved segmental resection and bony reconstruction of the alveolus, which is beyond the scope of this chapter. Articles included in the review involved purely soft tissue and mucosal defects, with marginal bony resections at most.

While lacking in patient numbers, a review paper on gingivobuccal mucosal cancers mandated that for smaller defects, skin grafts and skin replacements are preferable to healing by secondary intention, reducing postoperative discomfort, time till wound healing, and the incidence and severity of scar contracture [19].

In his study regarding the use of PGA sheets versus skin grafts for oral cavity wounds, Mochizuki et al. found that while the PGA group had shorter operation time and was able to start oral intake earlier, for buccal defects ≥6 cm^2 skin grafts gave better mouth opening [10].

Girod et al. surveyed 34 patients with oral cavity defects using the EORTC QLQ-C30 and the H&N35 questionnaires [20]. Twelve were skin grafted, and 22 had acellular dermal matrices (ADM) applied. He found that the ADM group had comparable outcomes with lower cost, a natural looking mucosal surface, and lack of donor site morbidity.

Larger gingivobuccal defects are typically reconstructed with flaps to avoid postoperative trismus. In a study of 37 patients with post-extirpation buccal defects, Chien et al. compared reconstruction with skin grafts, pedicled buccal fat pad flaps (PBFPF) and radial forearm free flaps (RFF) [21]. While the RFF was used reconstruct larger defects, the reduction in mouth opening was significantly less (4.8–9.8%) in this group compared to the PBFPF (5–45.5%; $p < 0.001$) and skin graft groups (9.6–44%; $p < 0.003$).

Table 26.4 Gingivo-buccal and floor of mouth defects

Study	n	Assessment	Results	Type of study	Quality of evidence
Mochizuki	119 secondary intention (PGA); 132 skin graft	Operation time; time to oral intake; length of stay; mouth opening	PGA faster operative time, time to oral intake, and discharge; Skin graft better mouth opening for buccal defects ≥6 cm^2	Case-control	Moderate
Girod	22 ADM; 12 skin graft	Cost; aesthetics	ADM lower cost, better aesthetics	Case-control	Low
Chien	10 skin graft; 11 RFF; 16 PBFPF	Mouth opening	Negative effect on the mouth opening was significantly less ($p < 0.05$) in Group RFFF when compared with the Group STSG or Group PBFPF	Case-control	Low

For small and shallow defects of the buccal mucosa, skin grafting or the use of skin substitutes may be performed where flap reconstruction is not available or the patient is unsuited to prolonged procedures (quality of evidence low, conditional recommendation).

For large and deep defects and those exposing bare bone and communicating with the neck, flap reconstruction is recommended to avoid microstomia and catastrophic salivary leakage into the neck (quality of evidence moderate, strong recommendation).

A Personal View of the Data

A recurring theme in reconstructive surgery articles is the general poor level of evidence. This is especially pronounced in head and neck reconstruction, where the myriad of variables, chief amongst them being the configuration of the defect, makes any form of blinded, sizeable, randomized controlled trial impossible. The studies reviewed and included in this chapter are all retrospective case-control studies of small group sizes, where many variables are not described or controlled for. Subjective QoL assessment can be standardized with established questionnaires, but objective assessment of speech and swallowing are difficult to compare across studies. The prevailing evidence does not conclusively support any one treatment method over another.

For the individual clinician, the option to select remains that which they are comfortable with, is readily available, and applicable to the patient and case at hand. This is more likely to yield better results than attempting an unfamiliar procedure. Our algorithm for reconstruction of the different parts of the oral cavity is as follows:

1. For defects of the tongue involving more than 40% of tongue bulk, flap reconstruction is done to maintain swallowing function, and prevent tethering of the remnant tongue. In these instances, we prioritize the ability to achieve oral alimentation.
2. Where there is any floor of mouth defect, the deciding factor for flap reconstruction is whether there is communication of the oral cavity with the neck. Small defects without communication can be left to heal primarily or resurfaced with skin grafts or substitutes.
3. For gingivo-buccal defects, flap reconstruction is preferred to prevent microstomia. This can be achieved with locoregional or free flaps depending on defect size and depth. Flaps for these defects is especially pertinent when bare cortical or cancellous bone is exposed.
4. For hard palate and inferior maxilla defects, our preference is flap reconstruction for any defect size. This is the most convenient, long-term option for the patient and avoids the need for long term maintenance of obturators. Where flap recon-

struction cannot be performed due to technical or patient factors, obturators can be used but require adequate anchoring points.

When reconstruction is chosen, graft or flap choice should be based on defect size, depth, and the need for obliteration of dead space. While it is often impossible to anatomically return like-for like tissue, the chosen modality should adequately resurface the defect, aiming to restore as close to pre-morbid function and appearance as possible.

On a final note, a 2014 retrospective analysis of 20,602 patients with early oral cancer where margins were reported (94.8%) from the US National Cancer Database resulted in positive margins in 7.5% of cases, with incidence of positive margins by institution varying from 0% to 43.8% [22]. Perhaps the biggest contribution that improved availability and techniques in reconstructive surgery has had to the treatment of early oral cavity cancers, is the enablement of confident tumor extirpation without worry of extent of the resultant defect, as almost any surgical wound can be competently reconstructed.

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Part IX

Multidisciplinary

27 Prophylactic Versus Reactive Gastrostomy Tube Placement for Advanced Head and Neck Cancer Patients

Rawan Arif and Mazin Merdad

Introduction

Head and neck cancer (HNC) patients—particularly those in advanced stage diseases or those undergoing chemotherapy and/or radiotherapy, often complain of symptoms such as xerostomia, dysphagia, and dysgeusia. The discomfort from these symptoms makes oral feeding problematic and therefore, increasing the risk of malnutrition [1, 2]. The quality of life of life (QOL) and survival have been shown to be adversely related to malnutrition [3, 4].

To relieve such patients from the discomfort associated with swallowing and offset the risk of malnutrition during treatment, feeding methods such as total parental nutrition (TPN), and enteral feeding via nasogastric tubes (NGT) or gastrostomy tubes (GT) have been widely adopted. There is general consensus in the literature with regard to the benefits of these feeding methods as they usually result in better treatment tolerances and outcomes [5]. There is a pressing need to set indicators that define the optimal medical necessity for the placement of these tubes. Some of the predictive indicators include the tumor stage, and the existing plans for bilateral neck irradiation [6].

In spite of efforts to determine the indicators for the necessity of GT placement, the timing for its placement is another challenging clinical decision. Whereas some clinicians prefer the early prophylactic placement of the GT to decrease treatment interruptions [7], others prefer the reactive placement (i.e. when the need arises).

This chapter aims to shed light on the available evidence regarding the prophylactic and reactive use of GT among advanced HNC patients.

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Table 27.1 Prophylactic versus reactive gastrostomy tube placement for advanced head and neck cancer PICO table

Population	Intervention	Comparison	Outcomes
Adult patients with advanced head and neck cancer	Prophylactic gastrostomy	Reactive gastrostomy	• Frequency/severity of post-treatment dysphagia and swallowing-related outcomes
			• Tube dependence
			• Weight loss
			• Survival
			• Unplanned admission and/or prolonged hospital stay
			• Quality of life

Literature Search Strategy

Based on the PICO format (Table 27.1), PubMed and Google Scholar databases were screened for eligibility using the article title. With the search limited to articles written in English and published within the last decade, relevant possible combinations of the terms head and neck cancer, and gastrostomy were retrieved. Whenever necessary, full articles were obtained, and the references noted.

The search was expanded to include all types gastrostomy, regardless of the method of application. Only articles having two arms comparing prophylactic to reactive gastrostomy; were included. Review articles and consensus statements were not included.

Results

There are few studies in the literature examining the difference in outcomes between prophylactic and reactive placement of GT. The results from across the studies are highly variable and heterogeneous making cross comparison of the data challenging. Some of the reasons for the high variability include:

- Lack of consensus regarding the definitions of prophylactic and reactive placement of GT: whereas in some studies the definition was based on the timing of GT placement, other studies drew the definition from the commencement of feeding after the GT placement [8].
- Differences in population/patient characteristics: data sets were diverse due to different cancer locations, staging, management plans (e.g. chemotherapy, chemo-radiotherapy, surgery, or a combination of treatments), as well as different treatment modalities (e.g. different radiotherapy technique being used within the same cohort) [9, 10].

- Inconsistencies in outcome assessment: there was a general lack of uniformity in measuring outcomes. For instance, some studies used subjective methods such as questionnaires for swallowing evaluation, others used the prolonged duration of use or dependency on GT as an indirect indicator of swallowing complications, while others conducted objective assessment procedure such as esophageal endoscopy [11–13].
- Selection bias: The selection of patients who received prophylactic GTs (pGTs) and patients who received reactive GTs (rGTs) in the same health facility might have introduced some selection bias, as those requiring therapeutic intervention due to difficulties in oral intake or major weight loss are generally more ill [14].

Outcome 1: Frequency/Severity of Post-treatment Dysphagia and Swallowing-Related Outcomes

No clear conclusion can be made as to whether prophylactic GT or reactive GT were associated with the frequency and/or severity of dysphagia and other swallowing related complications. The majority of the studies either favored reactive GT placement or showed no difference between the outcomes of the two GT placement timings [2, 13–16].

A retrospective study using University of Washington's Quality of Life scale revealed that, after 3 months of treatment, 46% of patients with pGT had dysphagia compared to 27% of patients with rGT, with $P = 0.01$ [2]. When follow-up was extended to a treatment period of 6 months, only 5% of rGT patients had dysphagia compared to 34% of their pGT counterparts, with $P < 0.001$ [2].

A recent RCT showed similar trend after 1 year of treatment, when it was impossible for 9% of the pGT group to swallow anything, whereas only 2% of rGT patients could not swallow anything, however, this was statistically insignificant [15].

Another RCT utilized the Quality of Life Questionnaire-Head and Neck 35-questions to evaluate the outcomes of swallowing in the two arms (pGT vs rGT) with no statistical significant difference. Similarly, a retrospective study showed that prolonged cases of dysphagia (running for a period greater than 90 days) were similar in both the pGT and rGT groups (prevalence was 36% and 32% respectively) [14, 16]. Esophageal strictures incidence was found to be low in both groups (1% in both pGT and rGT patients) [14]. Howbeit, a follow up retrospective study revealed several cases of stricture development after the completion of treatment, with $P < 0.001$. The reported incidences were 30% and 6% for pGT and rGT respectively [2].

In summary, only a few studies compared the frequency and severity of post-treatment dysphagia and swallowing-related outcomes between pGT and rGT. Some of the studies didn't clearly report the in-between group differences. All the

studies had a high risk of bias and/or had significant baseline characteristic differences between the pGT and rGT group of patients. Most studies either favored the use of rGT or showed no difference between the outcomes of the two GT placement timings [13] (see Tables 27.2, 27.3, and 27.4 for more details).

Outcome 2: Tube Dependence

Tube dependence is defined as the frequency of GT use over a period of time. Tube dependence can be used as a surrogate for the swallowing status. There were noteworthy statistical differences between the use of pGT and rGT over time. Most studies favored the use of rGT, while a few showed no significant differences between the two groups [2, 15–17].

A retrospective study among 120 advanced HNC patients who received chemoradiotherapy, revealed that the proportion of GT-dependent patients at 6 months post treatment was significantly lower in the rGT group compared to the pGT group (41% and 8%, respectively). Similarly, at 1 year follow-ups for the same cohort, this trend persisted, where 21% of patients in the pGT group were GT-dependent compared to no patients in the rGT group ($P < 001$) [2]. Apart from the dependency, other studies found that patients who started the enteral feeding prophylactically used GTs for a longer period of time compared to patients who started enteral feeding reactively [16, 17]. It is important to note that the differences in the period of usage may actually be accentuated by a lead-time bias. Both categories might have used the GTs for the same period of time but since the pGT patients had them placed earlier, it may appear that the pGT patients have used the GTs for longer periods of time [17] (see Tables 27.2, 27.3, and 27.4 for more details).

Outcome 3: Weight Loss

There was lack of consensus with regards to the impact of pGT and rGT on patient's weight. Most studies either showed no significant change in a patient's weight or indicated results that favored the use of pGT. In a recent RCT, pGT patients who started feeding immediately after the placements of the GTs showed a minor reduction in their weight compared to rGT patients who commenced supplementary tube feeding only when it was indicated. The minor difference in percentage of change in weight loss between the figures was insignificant ($-10.8 \pm 5.6\%$ compared to $-10.9 \pm 6.6\%$ respectively, $P = 0.930$) even after controlling for confounders on multivariable analysis [8].

Another RCT found no significant difference in the Body Mass Index (BMI) of pGT patients and patients who received nutritional support via clinical praxis 2 and

4 months into the treatment. Even when a long term follow-up study was carried on the same cohort 8 years after treatment, there was no significant difference in their BMIs [15, 16]. These results were supported by other retrospective studies [14, 17]. In favor of pGT was a retrospective study of 120 HNC patients undergoing chemoradiotherapy. pGT patients, in this study, reported less net weight change than rGT patients (−8% for pGT and −14% for rGT, with $P < 0.001$) [2] (see Tables 27.2, 27.3, and 27.4 for more details). This is supported by an RCT showing less weight loss in the pGT group at 6 months follow-up, however, these differences weren't statistically significant at 1 and 2 years follow-up [15].

The potential reasons for inconsistencies may include the use of different methodologies to assess weight loss, as well as the recording of data at different points in time.

Outcome 4: Survival

Across different studies, the overall and disease-free survival outcomes were similar between the two groups at different time interval [10, 13, 18, 19]. A historical cohort of 86 patients with HNC who received chemoradiotherapy or adjuvant chemoradiotherapy followed by surgery initially showed a significant difference in the disease free survival (DFS) comparing the pGT to rGT group at 1 year, however after controlling for confounding variables such as tumor stage this difference was no longer significant ($P = 0.95$) [17]. This was supported by another retrospective study showing no differences in the DFS at 3 years after adjustment of common confounders between the two groups ($P = 0.20$) [10]. Similarly, no significant difference in the overall all survival was noted at 2, 3, 5, and 10 years between pGT (77%, 66%, 64%, and 48%, respectively) and rGT (77%, 69%, 64%, and 48%, respectively) [2, 16] (see Tables 27.2, 27.3, and 27.4 for more details).

Outcome 5: Unplanned Admission and/or Prolonged Hospital Stay

The majority of studies found that pGT feeding compared to rGT feeding, doesn't seem to decrease hospitalization episodes or decrease the length of hospital stay. However, a few studies found less gastrostomy related admissions, favoring the pGT approach [2, 8, 14]. An RCT demonstrated approximately equal percentages of unplanned admissions between the two groups, where 47% of rGT group were affected by prologed stay or readmissions compared to 57% of pGT group ($P = 0.27$) [8]. Another retrospective study demonstrated no statistical difference in the percentage of unplanned admission between the two groups ($P = 0.71$) [2]. On the other hand a retrospective study among a large numbers that were selected from two large health cancer center, who adopted different GT placement

approaches; with one center routinely has had placed them prophylactically, and the other center who placed them only reactively; found that the rGT center had two times as many overall unplanned admissions compared to the pGT group (P = 0.001) [14]. Timing consideration in GT placement had no impact on the duration of hospital stay [8, 15].

Outcome 6: Quality of Life (QL)

The majority of studies showed that timing consideration of GT placement made no difference on the quality of patients' life [8, 15, 16]. A recent RCT showed that after 6 months of follow up post-treatment, the pGT group had significant better QL using the Quality of Life Questionnaire-Head and Neck 35-questions (EORTC QLQ-HN35). These differences didn't persist at 1, 2 years of follow up. Similarly, in a second publication and after following the same cohort for 8 years, there was no statistical significant different in most quality outcome domains [15, 16].

Advanced HNC patients, if physically fit and the health care facility is equipped, should place the GTs reactively to decrease the duration of tube dependence (quality of evidence moderate; weak recommendation).

Table 27.2 Studies with no difference between the prophylactic versus the reactive placement of gastrostomy tubes for advanced head and neck cancer

	GT type	N	Study type	Outcome	OR/RR	95% CI	P-value	Quality
Brown et al. [8]	PEG	131	RCT	– Weight change	0.48	2.43–1.46	0.624	Low
				– SGA nutritional status decline	0.78	0.33, 1.83	0.569	
				– Radiotherapy tolerance difference	–	–	0.723	
				– Chemotherapy tolerance difference	–	–	0.418	
				– Unplanned hospital admissions	–	–	0.270	
				– 1-Year survival difference	–	–	0.135	

Table 27.2 (continued)

	GT type	N	Study type	Outcome	OR/RR	95% CI	P-value	Quality
Axelsson et al. [16]	PEG	145	RCT	– (EORTC QLQ-C-30):				Low
				2 Years global quality of life	–	–	0.27	
				8 Years global quality of life	–	–	0.083	
				– (EORTC QLQ-HN35) at 8 years:				
				Swallowing	–	–	0.97	
				Dry mouth	–	–	0.59	
				Opening of the mouth	–	–	0.72	
				– 8 Years BMI mean difference	–	–	0.84	
				– Dependency	–	–	1.0	
				– 2–5–10 Years survival	–	–	NR	
Kramer et al. [17]	PEG	74	Historical cohort	– 1-Year percentage weight change	–	–	0.16	Very low
				– Disease-free survival after adjustments	–	–	0.95	
Olson et al. [14]	Not specified	445	Retrospective	– Weight loss at 1 year	1.44	0.80, −2.61	0.23	Low
				– Dependence at 1 year	1.17	0.60, −2.26	0.65	
				– 5-Year overall survival	–	–	0.73	
				– Treatment disruption	–	–	0.25	
				– Esophageal stricture	–	–	0.63	
				– Dysphagia (≥90 days)	–	–	0.35	
				– GT dependence at 1 year	–	–	0.74	

(continued)

Table 27.2 (continued)

	GT type	N	Study type	Outcome	OR/RR	95% CI	P-value	Quality
Williams et al. [10]	PEG OR RIG	83	Retrospective	– Weight loss	–	–	0.23	Very low
				– 3-Years disease free survival	–	–	0.20	
				– 3 Years overall survival	–	–	0.13	
Chen et al. [2]	PFG	120	Retrospective	– Unplanned admission	–	–	0.71	Very low
				– Incidence of acute toxicities	–	–	0.59	
				– 3-Years survival difference	–	–	0.54	
Silander et al. [15]	PEG	134	RCT	– Hospital stays	–	–	NR	Low
				– 1–2-Year EORTC QLQ-HN35 difference	–	–	NR	
				– 1 Year EORTC QLQ-C-30 difference	–	–	NR	
				– 2 Years weight loss difference	–	–	0.38	
				– 1-Year dysphagia scale difference	–	–	0.047	

N sample size, *PEG* percutaneous endoscopic gastrostomy, *PFG* percutaneous fluoroscopic gastrostomy, *ACRT* adjuvant chemo-radio therapy, *RCT* randomized controlled trial, *QL* quality of life, *ttt* treatment, *SGA* subjective global assessment, *pPEG and rPEG* prophylactic and reactive PEG, *NR* not reported, *SRT* combined systemic and radiation therapy, *RIG* radiologically inserted gastrostomy

Table 27.3 Studies favoring prophylactic application of gastrostomy tube for advanced head and neck cancer

	Type	N	Study type	Outcome	OR/RR	95% CI	P-value	Quality
Olson et al. [14]	Not specified	445	Retrospective	– Less admission	–	–	0.001	Low
Silander et al. [15]	PEG	134	RCT	– Less weight loss percentage at 6 months after treatment	–	–	0.03	Low
Chen et al. [2]	PFG	120	Retrospective	– Less weight loss	–	–	0.01	Very low

Table 27.4 Studies favoring reactive application of gastrostomy tube for advanced head and neck cancer

	Type	N	Study type	Outcome	OR/ RR	95% CI	P-value	Quality
Kramer et al. [17]	PEG	74	Cohort	– Shorter PEG duration	–	–	<0.02	Very low
Olson et al. [14]	Not specified	445	Retrospective	– Less tube complications	–	–	<0.001	Low
				– Less dependence at 90 days post radiation therapy	–	–	<0.001	
Silander et al. [15]	PEG	134	RCT	– Less average duration of GT placement after treatment	–	–	<0.0001	Low
Chen et al. [2]	PFG	120	Retrospective	– Less frequency of dysphagia at 3 and 6 months	–	–	<0.01	Very low
					–	–	<0.001	
				– Less dependency at 3, 6, 12 mx	–	–	<0.001	
				– Less incidence of esophageal stricture	–	–	<0.001	

A Personal View of the Data

The use of GT has become more frequent among advanced head and neck cancer patients particularly those undergoing radiotherapy. By closely reviewing the literature, highly variable and heterogeneous data were evident, as previously discussed, making the available results less generalizable and hard to compare. Additionally, there is insufficient evidence to establish a result of effectiveness or to determine the ideal method of enteral feeding. The decision of gastrostomy placement timing is challenging, and should be individualized to each patient baised on the desired outcomes.

pGT does not offer clear advantages regarding nutritional outcomes, dependency, frequency/severity of dysphagia, or survival. Hence, a rGT approach might be a preferable over pGT approach when the healthcare facility is equipped for prompt GT placement when needed. Finally, conducting well designed randomized controlled trials, prospective studies, and properly controlled observational study while controlling for different confounders is recommended.

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Is Antibiotic Therapy Warranted in Clean-Contaminated Head and Neck Surgery Beyond 24 h?

28

Jessica Yesensky, Palmila Liu, and Louis Portugal

Introduction

Perioperative antibiotics have been implemented to prevent post-surgical infections. This practice has become standard of care in otolaryngology, clean-contaminated cases. These cases are defined as those that violate the mucosal surface of the aerodigestive system. The incidence of wound infection after clean-contaminated head and neck oncologic surgery without antibiotic prophylaxis varies from 24% to 87% [1]. With the introduction of antibiotic prophylaxis, this number has decreased to 10–25% [2–4]. The development of wound infection is often devastating and can lead to wound breakdown, the development of fistulae, sepsis, and death. It results in longer hospital stays, additional interventions, delay in adjuvant therapies, and ultimately, a higher burden for both the patient and healthcare system [1, 5].

Conversely, the overuse of antibiotics poses a risk to the patient. Inappropriate antibiotic use increases the likelihood of drug-related adverse effects, allergic reactions, diarrheal illnesses caused by *C. difficile*, mucosal infections caused by *Candida*, and the development of drug-resistant organisms [1]. Therefore it is important to understand the appropriate application of perioperative antibiotics; however the optimal agent and duration of prophylaxis remain controversial. This chapter aims to clarify current evidence regarding antibiotic therapy in clean-contaminated head and neck surgical cases.

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Literature Search Strategy

Based on the PICO table (Table 28.1), Pubmed searches incorporating the terms "antibiotic" and "prophylaxis" and "clean contaminated" and "head and neck surgery" were used to review the literature. The resulting, applicable articles were then reviewed. In our final selection of literature (Table 28.2) we gave preference to randomized controlled trials, meta-analyses, and systematic reviews. In the absence of these studies, prospective and retrospective cohort studies were evaluated. We reviewed studies that only targeted clean-contaminated cases and included those in which free-flap reconstruction was used. The studies included in this review were published between 1983 and 2017.

Table 28.1 Perioperative antibiotics in clean-contaminated head and neck surgery

Population	Intervention	Comparison	Outcomes
Adults (>18 years) with a diagnosis of head and neck cancer, undergoing clean-contaminated surgery	Perioperative antibiotic prophylaxis against surgical site infection for 24 h	Prophylactic regimens extending beyond 24 h and varying in antibiotic agent(s) used	Rate of post-operative surgical site infection

Table 28.2 Comparative studies evaluating post operative antibiotic prophylaxis in clean-contaminated head and neck procedures

Source	Study design	Antibiotic comparison groups	Surgical site infection outcomes	*P* value	Quality of evidence
Piccart et al. [6]	RCT	Clindamycin 4 d (n = 37) vs. Clindamycin + netilmicin 4 d (n = 43)	16% vs. 9%	0.58	High
Johnson et al. [7]	RCT	Cefoperazone 1 d (n = 53) vs. 5 d (n = 56)	18.9% vs. 25%	>0.05	High
Johnson et al. [8]	RCT	Clindamycin 1 d (n = 52) vs. Clindamycin + gentamicin 1 d (n = 81)	3.4% vs. 3.4%	NS	High
Gerard et al. [9]	RCT	Perioperative ticarcillin/clavulanic acid (n = 58) vs. Clindamycin + amikacin (n = 55)	10% vs. 36%	<0.05	Moderate
Weber et al. [10]	RCT	48 h Ampicillin/sulbactam (n = 105) vs. Clindamycin (n = 107)	13.3% vs. 27.1%	0.02	High
Mustafa et al. [11]	RCT	Cefotaxime 1 d (n = 30) vs. 7 d (n = 30)	13% vs. 10%	>0.05	High
Rodrigo et al. [12]	RCT	Perioperative a moxicillin/clavulanate (n=57) vs Clindamycin + gentamic in (n=52) vs cefazolin (n=50)	22.8% vs 21.2% vs 26%	0.8	High
Carroll et al. [13]	RCT	Clindamycin 1 d (n = 35) vs. 3 d (n = 39)	11% vs. 10%	0.99	Moderate

Table 28.2 (continued)

Source	Study design	Antibiotic comparison groups	Surgical site infection outcomes	*P* value	Quality of evidence
Skitarelic et al. [14]	RCT	Perioperative cefazolin (n = 92) vs. Amoxicillin/clavulanate (n = 97)	24% vs. 21%	>0.05	High
Liu et al. [15]	RCT	Clindamycin 1 d (n = 26) vs. 3 d (n = 27)	30.7% vs. 18.5%	0.473	Moderate
Sepehr et al. [16]	RR	Cefazolin + metronidazole ≤5 d (n = 202) vs. >5 d (n = 205)	7% vs. 13%	0.06	Moderate
Mitchell et al. [17]	RR	Multiple abx regimens ≤1 d (n = 96) vs. >1 d (n = 331)	57% vs. 42%	0.16	Moderate
Langerman et al. [18]	RR	≤4 d Ampicillin/sulbactam or cefazolin + metronidazole (n = 863) vs. Clindamycin (n = 287)	5.1% vs. 17.4%; OR 3.87; 95% CI 2.31–6.49	<0.0001	Moderate
Langerman et al. [19]	RR	Ampicillin/sulbactam DOS vs. DOS + 1 d	OR 0.28; 95% CI 0.13–0.61	0.01	Moderate
Pool et al. [20]	RR	Cefazolin + metronidazole (n = 225) vs. "Alternative" therapy (n = 41; clindamycin, clindamycin + metronidazole, or clindamycin + gentamicin), duration NA	8% vs. 27%; OR 3.78, 95% CI 1.37–10.47	0.01	Moderate
Cohen et al. [21]	RR	Multiple abx regimens 2 d	Clindamycin OR 6.44; 95% CI 1.64–25.37	<0.008	Moderate
Bartella et al. [22]	RCT	Ampicillin/sulbactam only during surgery (n = 25) vs. 5 d (n = 25)	36% vs. 4%	0.011	High

RCT randomized controlled trial, *RR* retrospective review, *NA* not available, *NS* not significant, *d* day

Prophylactic Antibiotic Therapy

The Centers for Disease Control and Prevention guidelines recommend perioperative antibiotics, with no additional doses of prophylactic antibiotics after the surgical incision is closed in all clean-contaminated cases [23]. These recommendations are not specific to head and neck surgery. Therefore, the American Society of Health-Systems Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) released a joint statement recommending 24 h of cefazolin or cefuroxime plus metronidazole, ampicillin/sulbactam, or clindamycin in patients with a penicillin allergy in clean-contaminated head and neck

procedures [24]. To date, there have been multiple studies evaluating the most appropriate type and duration of antibiotics specifically in clean-contaminated head and neck procedures without a clear consensus.

A number of studies have not shown a reduction in surgical site infections with prolonged post-operative prophylactic antibiotics. Johnson et al. pioneered the development of prophylactic antibiotic regimens in clean-contaminated head and neck procedures [7]. The authors performed a randomized trial of 1 or 5 days of cefoperazone for patients who received a free-flap and found no difference in rates of SSI (18.9% vs. 25%, $P > 0.05$), and concluded prophylactic antibiotics over 24 h are unnecessary. Another randomized trial performed by Mustafa and Tahsin compared 1 or 7 days of cefotaxime and found no difference in SSI (13% vs. 10%, $P > 0.05$) [11].

The most recent meta-analysis looking at type and duration of antibiotic prophylaxis in patients undergoing clean-contaminated head and neck resection did not find evidence to support antibiotic therapy >24 h after surgery [25]. This review analyzed four RCTs which included 340 patients and demonstrated the pooled relative risk of wound infection was 0.98 (95% CI, 0.58–1.61; $P = 0.718$) in patients receiving 1 day vs. 5 days of prophylaxis. While the studies differed with regards to the antibiotic studied, each patient group was compared with the same class of antibiotic within the individual trial. Antibiotics included cefazolin, clindamycin, clindamycin plus gentamicin, cefoperazone, and cefotaxime. The studies evaluated did include patients that underwent local, regional or free flap reconstruction.

Another meta-analysis reviewed 722 patients across seven RCTs evaluating rate of post-operative SSI with a l day antibiotic course compared with prolonged regimens (5-, 4-, or 3-day therapy) for a clean-contaminated head and neck procedures [26]. Overall, there was no significant difference in the rate of infection between the two antibiotic groups. Subgroup analysis again demonstrated no difference in SSI between 1 day and 3 or 4 days of antibiotics (OR, 1.291, 95% CI, 0.606–2.749; $P = 0.508$). Similarly, 1 day and 5 days of antibiotics demonstrated no difference in SSI (OR, 0.909, 95% CI, 0.498–1.656, $P = 0.754$). Further subgroup analysis regarding patients undergoing flap reconstruction showed no significant difference between 1-day versus 5-day therapy. There was insufficient data to analyze high-risk subgroups, including patients with prior radiation therapy, malnutrition, diabetes, or other immunocompromised state.

There have been studies that support the use of extended prophylactic antibiotics. Langerman et al. conducted a retrospective multi-institutional analysis utilizing the University HealthSystem Consortium data, yielding data on 8836 patients who underwent clean-contaminated head and neck surgery [19]. They evaluated the rate of surgical site infection (SSI) in those who received antibiotic prophylaxis on the day of surgery (DOS) alone versus on the day of surgery and 1 day after (DOS + 1). In patients that received ampicillin/sulbactam, there was over a two-thirds reduction in SSI in those receiving antibiotics DOS + 1 vs. DOS (OR, 0.28; 95% CI, 0.13–0.61; $P = 0.001$). However this effect was not seen with clindamycin. The odds of SSI were not significantly different between those treated only on the day of surgery and those treated beyond the day of surgery when only clindamycin is considered

(OR, 1.82; 95% CI 0.93–3.56, $P = 0.078$). This study concluded there may be some advantage to longer courses of ampicillin/sulbactam, while there was no benefit to a longer course of clindamycin. The majority of data from RCTs, however, have demonstrated no benefit from prolonged (>24 h) antibiotic prophylaxis in clean-contaminated head and neck procedures [25, 26].

Interestingly, several studies suggest clindamycin monotherapy is associated with an increased risk of SSI. This is likely related to the lack of Gram-negative coverage with clindamycin alone or an increased prevalence of clindamycin-resistant pathogens. In a randomized, double blind trial of 212 patients, Weber et al. compared SSI rates between patients receiving 48 h of ampicillin/sulbactam and those receiving clindamycin for clean-contaminated head and neck procedures [10]. There were significantly more wound infections in patients receiving clindamycin as compared to ampicillin/sulbactam (27.1% vs. 13.3; $P = 0.02$). It is important to note that 29 of the 36 wound infections in the clindamycin group were found to be from Gram-negative organisms.

Gerard et al. completed a RCT comparing SSI in patient receiving perioperative ticarcillin/clavulanic acid or clindamycin plus amikacin and found significantly higher rates in group receiving clindamycin plus amikacin (36% vs. 10%; $P < 0.05$) [9]. Saunders et al. retrospectively reviewed 72 patients that underwent head and neck procedure with free flap reconstruction and received 7 days course prophylactic antibiotics [27]. Authors noted clindamycin was associated with a significantly increased rate of wound infections (OR 14.38, $P = 0.02$).

In another review, Langerman et al. utilized the University Health Consortium database to explore the relationship between antibiotic choice and SSI in 1865 patients undergoing total laryngectomy [18]. Similar to the findings of previous studies, there was an association between use of clindamycin and SSI, wound dehiscence, and antibiotic-induced complications. It was concluded that clindamycin use alone may not offer effective prophylaxis for clean-contaminated head and neck surgery cases, particularly given the lack of Gram-negative coverage.

Of note, Carroll et al. and Liu et al. both compared 1 day of clindamycin to 3 days of clindamycin and found no difference in rates of wound infection; however both studies had a small number of patients in each treatment arm [13, 15].

Studies have not been able to show benefit from the addition of Gram-negative coverage with aminoglycosides in preventing SSI. Piccart et al. randomized patients undergoing clean-contaminated head and neck procedures to receive 4 days of clindamycin or 4 days of clindamycin plus netilmicin and found no difference in SSI (16% vs. 9%; $P = 0.58$) [6]. Similarly another RCT evaluated 1 day clindamycin compared to 1 day clindamycin plus gentamicin and rate of SSI was 3.4% for both groups [8]. Addition of added Gram-negative coverage with aminoglycoside has yet to show improvement in surgical site infection rates.

As free flap reconstruction has become more commonly employed in head and neck reconstruction, there has been a recent focus on antibiotic prophylaxis in these cases. There is still limited data regarding optimal antibiotic prophylaxis in patients receiving free flap reconstruction in the head and neck. Patients receiving free flaps tend to have risk factors for developing post-operative infections,

including long procedure duration, prior radiation and chemotherapy, and often poor nutritional status. Surgical site infections in patients with free flap reconstruction can potentially have devastating complications including flap loss. Therefore appropriate antibiotic regimen in this subset of patients is paramount. In one prospective review, Bartella et al. compared head and neck free flap patients that received antibiotic prophylaxis only during surgery with those that were given antibiotic prophylaxis until the fifth post-operative day. Patients were given ampicillin and sulbactam, or, in the case of known allergic reaction, clindamycin. They found patients receiving antibiotics until the fifth post-operative day to have statistically fewer surgical site infections (4% vs. 36%, $P = 0.011$), but did not include data on the number of patients receiving ampicillin and sulbactam or clindamycin in each group [22].

Khariwala et al. reviewed short-term (≤2 days) of prophylactic antibiotics compared to long-term (>2 days) in 147 patients who underwent head and neck surgery with free flap reconstruction [28]. Surgical site infection was not significantly different in the two groups (23.4% vs. 21.2%; $P = 0.78$). There was however a difference noted when comparing short-term and long-term SSI in those receiving clindamycin with longer course yielding higher infection rates. It is interesting to note that those receiving long-term antibiotics had a significantly higher rate of pneumonia (24.7% vs. 10.9%; $P = 0.03$). Authors additionally identified risk factors for SSI, including higher BMI, history of chemotherapy, and history of radiation.

In another review, Mitchell et al. retrospectively reviewed patients that underwent free flap reconstruction and evaluated the risk of SSI [17]. Antibiotics for less than 24 h as compared to prolonged course of prophylactic antibiotics was not associated with increased risk of post-operative infections (OR, 0.63; 95% CI, 0.34–1.19; $P = 0.18$). Upon further analysis authors specifically found the use of clindamycin (OR, 2.54; 95% CI, 1.25–5.14; $P = 0.01$) was associated with an increased risk of post-operative infection.

It is also important to consider that head and neck cancer surgical candidates are perceived as high-risk for SSI due to the invasive nature of the procedure and pre-existing morbidity. Previous studies have shown tobacco use, American Society of Anesthesiologists (ASA) classification, history of radiation therapy, length of surgery, and blood loss during surgery as risk factors for the development of SSIs [20]. Therefore, in order to minimize SSI, it is necessary to reliably identify high-risk patients. A retrospective review analyzed rates of SSI in 418 patients that underwent clean-contaminated head and neck surgery. Authors of the study demonstrated increased risk of SSI in patients with advanced stage disease requiring major resection and presence of tracheostomy [29].

Other studies have failed to demonstrate significant increase in SSI when evaluating various patient characteristics. In a retrospective review of 266 patients undergoing clean-contaminated head and neck procedures, authors found patient age, sex, tobacco use, BMI, and prior radiation did not correlate with increased rate of SSI [20]. Additionally, Johnson and Yu found the pre-operative existence of tracheotomy or prior radiation therapy had no demonstrable effect on the incidence of wound infection post-operatively [8].

There are studies that have looked to establish better antibiotic regimens for patients deemed high risk. Sepehr et al. retrospectively reviewed clean-contaminated head and neck procedures to compare short versus long antibiotic prophylaxis in the setting of malnutrition, diabetes, and tracheotomy [16]. Diabetics did not demonstrated higher risk of SSI as compared to non-diabetic patients (12% vs. 23%; $P = 0.13$), while those considered malnourished had significantly higher rates SSI than well-nourished patients (3% vs. 18%; $P = 0.0001$). However, among the malnourished patients, there was no difference in rates of SSI between those placed on ≤4 days compared to >4 days of prophylactic antibiotics. This study suggested that despite high-risk patient characteristics, prolonged prophylactic antibiotics did not improve rates of wound infection. In other words, there should be a focus on targeting modifiable, pre-operative risk factors, such as malnutrition, uncontrolled diabetes mellitus, tobacco use, which has been shown to decrease SSI in other surgical settings [2].

While a number of the discussed studies have not shown antibiotics beyond 24 h to be associated with a lower rate of SSI, it is important to note that the antibiotic regimens and durations examined in these studies are heterogeneous, as are the patient populations. Limitations to the existing literature warrant additional randomized studies in order to determine ideal duration recommendations in different patient subsets, such as those undergoing free flap reconstruction or those with a history of radiation. However, based on available evidence, broad-spectrum antibiotics that cover Gram-positive, Gram-negative, and anaerobic organisms are recommended for 24 h post-operatively. For patients with penicillin allergies, clinicians should explore whether it is a true allergy and consider use of second or third generation cephalosporins, given the low rate of cross-reactivity. [30, 31] Currently the data does not support prolonged antibiotic therapy beyond 24 h in patients undergoing free flap reconstruction. Additionally, there is no data to support prolonged prophylactic antibiotics beyond 24 h in patients that are considered high risk for development of post-operative infections.

Short duration of antibiotics (<24 h) are as effective as long durations (>24 h) and avoid unnecessary antibiotic exposure in patients undergoing clean-contaminated head and neck procedures, including those with free-flap reconstruction (quality of evidence moderate, weak recommendation).

Post-operative antibiosis with clindamycin should be avoided (quality of evidence moderate, weak recommendation).

A Personal View of the Data

Existing guidelines are a product of collaboration between multidisciplinary groups and recommend 24 h of post-operative antibiotic prophylaxis in clean-contaminated head and neck surgery. The guidelines also comment on antibiotic regimen and

recommend cefazolin or cefuroxime plus metronidazole, ampicillin/sulbactam, or clindamycin in patients with a penicillin allergy [24]. These antibiotics target the most common pathogens encountered in the aerodigestive system and broadly cover Gram-positive, Gram-negative, and anaerobic organisms. Although it is recommended to use clindamycin monotherapy for patients with penicillin allergy, there is robust data to suggest higher rates of surgical site infections when used for short or long durations. There is no data to support the addition of Gram-negative coverage (e.g. aminoglycoside) and subsequent reduction in wound infections. Additionally there are no studies evaluating antibiotic regimens other than clindamycin in penicillin allergic patients undergoing head and neck surgery. Recently there has been a paradigm shift in treating penicillin-allergic patients with cephalosporins. In fact, evidence indicates that the incidence of cross-reactivity with cephalosporins in penicillin-allergic patients varies with the chemical side chain similarity of the cephalosporin to penicillin or amoxicillin. First generation cephalosporins have the potential, albeit low, for cross-reactivity, however most second and third generation cephalosporins are highly unlikely to be associated with cross-reactivity based on differences in their chemical structure [30]. In fact, the American Academy of Pediatrics practice guidelines for the management of acute bacterial sinusitis and otitis media endorsed the use of second and third generation cephalosporin antibiotics for patients with reported allergies to penicillin, provided that the penicillin reaction is not severe. It is important to note that many patients with a history of penicillin allergy have not had a true IgE-mediated reaction to penicillin rather just an intolerance. Therefore, it may be prudent to further evaluate true penicillin allergies in order to minimize use of clindamycin.

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What Is the Best Imaging Modality to Predict Extracapsular Nodal Extension?

29

Majid Khan, Benyamin Deldar, and Nafi Aygun

Introduction

Presence of extracapsular spread (ECS) in metastatic lymph nodes is indicative of advanced disease in head and neck squamous cell carcinoma (HNSCC). ECS is associated with increased number of nodal metastases, increased prevalence of regional recurrence and distant metastases with each of these individually contributing to increased mortality [1]. Presence of ECS having significant implication of poor prognosis can be ascertained by meta-analysis by Dunne et al. showing a 5-year-survival rate between 17% and 55.8% for neck metastases with ECS and 44.6–76% for patients with neck metastases without ECS and further more presence of ECS in multiple lymph nodes is presumed even to be a worse prognostic sign [2]. ECS and positive resection margins are major high-risk factors that warrant the use of adjuvant chemotherapy in addition to RT among advanced HNSCC patients [3].

The pathological diagnosis of ECS is not straightforward. A high degree of inter-reader and intra-reader variability among pathologists has been documented by multiple studies [4]. The current diagnosis of ECS is based on criteria formulated by the College of American Pathologists, wherein the presence or absence of any full thickness extension through the nodal capsule with or without the presence of a surrounding desmoplastic stromal reaction is consistent with ECS [5].

The degree at which ECS becomes prognostically significant is a matter of debate. Greenberg et al. found no prognostic difference between ECS greater than 2 mm and ECS less than 2 mm and no linear correlation between lymph node size and prevalence of ECS. Wreesman et al. performed an empirical quantitative analysis finding the exact cut off for the prognostic significance of ECS to be 1.7 mm [5].

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A 5-tier ECS grading scheme showed that increasing degrees of ECS correlated with poorer outcomes although the value of ECS in independently predicting outcomes was limited when the T-stage and other variables were factored in [6, 7]. Certain tumoral characteristics such as size, depth of invasion and HPV positivity also pertain to changes in prognosis and management. Importance of ECS has been shown in various subsites of the head and neck cancers, including the oral cavity and oropharynx and larynx [3, 8, 9] however, the literature has not adequately addressed the possibility that prognostic value of ECS may be modulated based on the site of the primary SCC. One group of investigators have examined ECS in HPV-positive oropharyngeal cancer [7], however, the importance of ECS in HPV-positive oropharyngeal cancer remains unclear. The importance of ECS in HNSCC becomes even more relevant especially with the advent and increased usage of minimally invasive surgical techniques such as trans-oral robotic surgery (TORS) and laser microsurgery (TLM). With increasing number of OPC patients undergoing primary surgical therapy, prognostic markers, such as ECS, can help to identify those patients who may or may not benefit from adjuvant chemoradiation therapy (CRT).

Notwithstanding the difficulties with pathological diagnosis of ECS, imaging diagnosis of ECS has significant implications on management of HNSCC. Several studies have looked at features that predict ECS on CT and MR imaging including infiltration of fat around the node, nodal capsule contour irregularity, irregular contrast enhancement with presence of nodal necrosis and focal hyperdensity within the node on non-contrast enhanced scans [10]. While far from being perfect the imaging (preoperative) diagnosis of ECS plays a vital role in characterizing the disease extent and thus, directing candidacy for non-operative therapies.

Literature Search Strategy

Based on the PICO table (Table 29.1), Pubmed and Cochrane central register of controlled trials searches incorporating the terms “Extracapsular” and “head and neck squamous cell carcinoma” and/or “CT”, “MRI” “PET/CT” or “Ultrasound” were used to review literature. The search was broadened to include epidemiological and histopathological data of ECS. Due to the sparsity of the literature, no study was excluded due to outdating, however most of the studies dated under 20 years (1999–2018). The range of the searches completed dated back to September 1983. Preference was given to meta-analyses but consensus statements and review articles were also included for completeness.

Table 29.1 Utility of imaging methods for sensitively and specifically diagnosing ECS

Population	Intervention	Comparison	Outcomes
Adults with HNSCC before neck dissection	CT, MRI, PET/CT or ultrasound ECs and imaging	Neck dissection followed by histopathology	Sensitivity and specificity

Results

CT

High resolution CT with Iodinated contrast has been utilized and studied extensively for the evaluation of HNSCC. The diagnostic criteria for describing lymph node metastatic spread in HNSCC was first described by Mancuso et al. in 1983 [11]. Currently, the criteria for diagnosis of ECS with CT includes; presence of an irregular, spiculated, blurred lymph node border; loss of fat plane around the node; irregular capsular enhancement; CNN; and/or tumoral infiltration into soft tissue and vascular structures (Figs. 29.1, 29.2 and 29.3).

Few studies have looked at whether the presence of the described characteristics are sensitive for identifying ECS when comparing to histopathological analysis. Of the prospective studies in the literature Steinkamp et al. compared CT scans to histological data from neck dissections for 165 patients with HNSCC. This study looked at radiologist impression of ECS characterized by infiltration into cervical muscle and the jugular vein. They reported a sensitivity of 81%, specificity of 73% and overall accuracy of 76% [12].

Similarly, King et al. employed similar criteria of tumoral infiltration into surrounding fat, muscle and vasculature but also characterized ECS by indistinct nodal margins and irregular capsular enhancement. This study examined 17 patients with HNSCC prospectively. Contrast enhanced CT scans at 4 mm thickness were obtained and blindly reported by two radiologists. The study reported a sensitivity of 65% and specificity of 93% [13].

In 1992 Yousem et al. reported an accuracy of 91–96%, sensitivity of 94–100% and specificity of 94% for detection of CNN and ECS in a retrospective cohort of 24

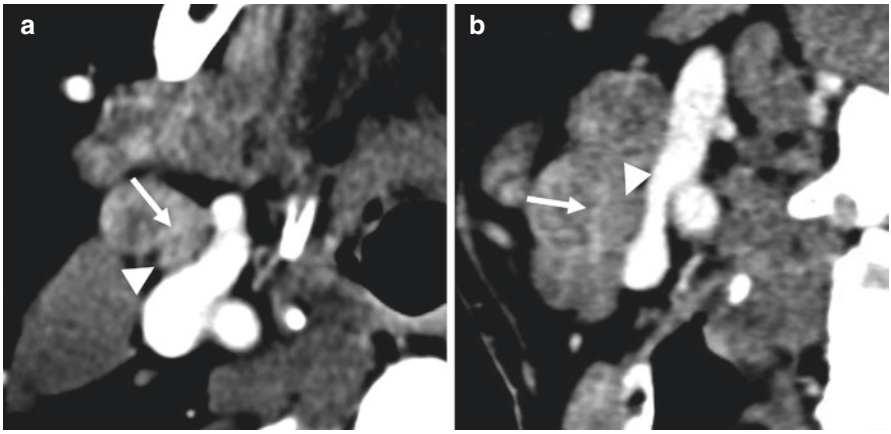

Fig. 29.1 Oropharyngeal SCC with right level 2 adenopathy. Axial (**a**) and oblique coronal (**b**) CT show smooth and well delineated nodal margins surrounded by "clean" fat (arrows). Arrowheads on image (**b**) point to vessels about the node. Pathology revealed no ECS

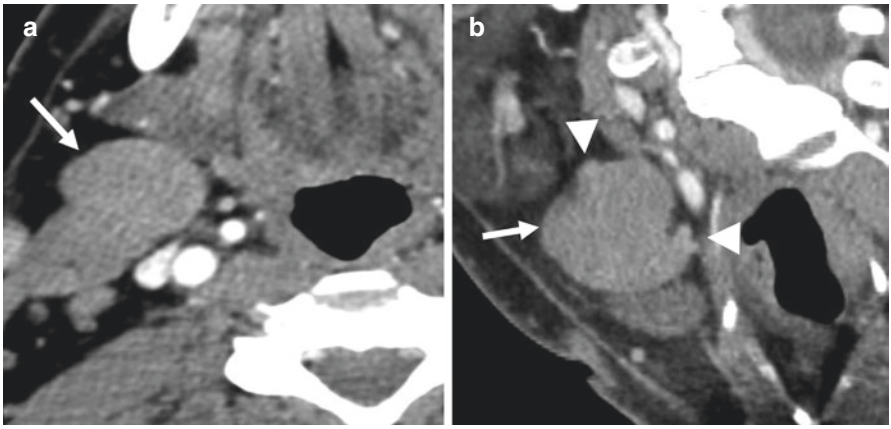

Fig. 29.2 Oropharyngeal SCC with right level 2 adenopathy. Axial (**a**) and oblique coronal (**b**) CT show slight irregularity of the nodal capsule (arrows) with a nodular soft tissue medial to the capsule (arrowhead) compatible with ECS. Pathology showed ECS measuring 12 mm

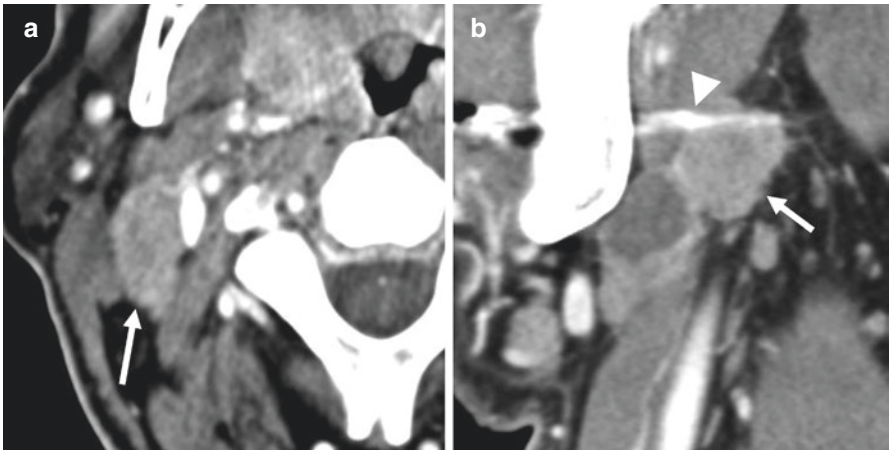

Fig. 29.3 Oropharyngeal SCC with right level 2 adenopathy. Axial (**a**) and oblique coronal (**b**) CT show irregular nodal capsule contour with nodularity (arrows). Arrowhead on image (**b**) points to artifact from dental amalgam. Pathology revealed ECS

patients using 5 mm contrast enhanced CT, however, this study was more than 20 years old and pathological confirmation was only obtained in 14 patients with 10 patients refusing surgery [14]. Comparably, Souter et al. discovered 113 ECS from 149 HNSCC CT's used for the detection of ECS of metastatic head and neck squamous cell carcinoma, by experienced head and neck neuroradiologists. Presence of ECS by the aforementioned criteria including thickening of the capsular wall. The images were examined by two radiologists, reporting a sensitivity of 80% and 66% and a specificity of 90% and 91% respectively [15].

Kann et al. [16] retrospectively assessed ECS as an independent prognosticator in 111 patients with stage III and stage IV oropharyngeal carcinoma. Their study found a significantly worse overall survival, worse progression free survival, and worse distant control in the group with radiographic evidence of ECS. They did note that due to the small number of cases that included surgery, they could not reliably address the accuracy with which radiographic ECS predicted pathologic ECS.

As CT further ingrains itself as a useful diagnostic tool in identifying ECS, newer studies have begun to identify which diagnostic features bears most weight in distinguishing ECS. Randall et al. in a prospective comparison study of 40 patients looked at the power of central nodal necrosis (CNN), indistinct nodal margins and irregular capsular enhancement for defining ECS in HNSCC. Randall et al. found that central node necrosis independently could be used to identify ECS with a sensitivity of 91% and specificity of 50% when compared to final histopathologic results from surgical excision [17]. Zoumalan et al. similarly retrospectively analyzed a sample of 17 patients with 26 histologically identified necrosis centrally within lymph node. The aim of this study was to assess whether central node necrosis was an identifiable risk factor for ECS. They documented sensitivity of 95% and specificity of 85% in using central node necrosis to indicate ECS when compared with the gold standard of histopathological analysis [18].

Although central necrosis may be a useful and pertinent diagnostic criterion in assessing ECS it must be noted that the prevalence of central node necrosis increases with the lymph node size. Don et al. for example, noted that central necrosis is more prevalent in lymph nodes of greater than 20 mm [19]. With this in mind, 25% of ECS still occurs in nodes under 10 mm [20]. Therefore, the sensitivities described above must be taken with caution as this likely represents ECS of larger lymph nodes. Prabhu et al. conducted a large-scale retrospective study of 432 patients with HNSCC. Of these patients, 46 were identified at neck dissection to have ECS with CT criteria for ECS yielding a low sensitivity and specificity of 43.7% and 97.7% respectively [21]. Interestingly, both of these studies only took indistinct nodal margins and peri-nodal soft tissue infiltration as diagnostic criteria for ECS (Fig. 29.4 and Table 29.2).

MRI

Standard MRI protocols including T1 and T2 imaging with and without the use of gadolinium contrast agent and fat suppression have been utilized effectively for many head and neck pathologies. The benefit of MRI is due to its high contrast resolution in soft tissue structures. Many studies have gone to examine the utility of MRI for identifying ECS in HNSCC and have found that the diagnostic characteristics to be similar to those of CT. The use of fat suppression can be utilized to identify tumoral infiltration as peri-nodal soft tissue infiltration and enhancement becomes readily apparent on fat-suppressed scan. Unenhanced T1 inhomogeneities may be indicative of irregular nodal margins and the use of gadolinium contrast can identify enhancing lymph node borders and central node necrosis [14]. Lymphatic channel obstruction may also be caused by tumor metastasis which can lead to an

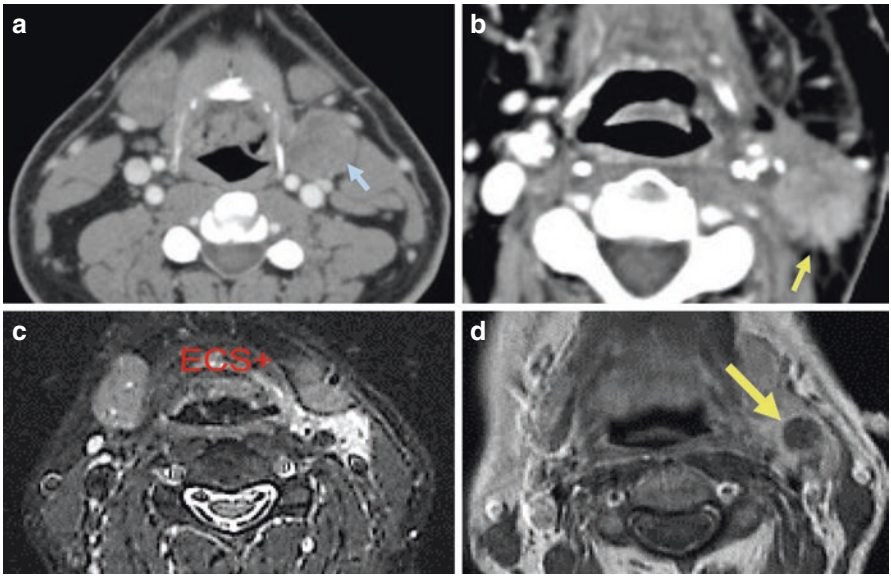

Fig. 29.4 (**a**) Axial CT with contrast shows left Level II enlarged lymph node (arrow) with smooth wall contours with no surrounding infiltration. ECS negative. (**b**) Axial CT with contrast shows left Level II enlarged lymph node with irregular capsule with prominent spiculation (arrow) and surrounding infiltration. ECS pose. (**c**) MR axial STIR image shows irregular hyperintense level II lymph node with surrounding interstitial infiltration. ECS positive. (**d**) MR axial T1w image after contrast shows prominent central nodal necrosis (arrow) and wall contour irregularity and surrounding infiltration. ECS positive

imbalance between lymph production and absorption and this may lead to disruption of the lymph node capsule allowing leakage around the capsule, a finding positive for ECS from interstitial edema. This can be seen on fat suppressed T2- weighted imaging with high signal at the edges and surrounding the lymph nodes. In one study this was found to have a specificity as high as 93% and a diagnostic accuracy rate of 88% [10]. However, lymphatic obstruction may also occur as a result of interference from inflammation and other factors, so that histological changes similar to what is seen with tumors can be elicited.

In a prospective analysis of 110 patients with MRI, Steinkamp et al. assessed the presence of tumoral extension in to surrounding adjacent tissue and reported sensitivity of 74.4% and specificity of 72.2% when compared to gold standard histopathological classification [12].

Similarly, both King et al. and Yousem et al. compared MRI utility to CT for detecting ECS. Neither study found a benefit of MRI over CT imaging. King et al. reported no significant difference in sensitivity or specificity reporting these values at 78% and 86% respectively when using indistinct nodal margins, irregular capsular enhancement, tumoral soft tissue infiltration as diagnostic criteria. Yousem et al. reported sensitivity and specificity of 91 and 94% respectively. Yousem et al. assessed ECS with the criteria of T1/T2 inhomogeneous signal intensity and

Table 29.2 Studies reporting on CT in predicting extracapsular nodal extension

Author	Year	Imaging modality	N	Diagnostic criteria	Sensitivity	Specificity	Quality of evidence
Steinkamp et al.	1999	CT	165	Tumoral soft tissue infiltration	81%	73%	Moderate
King et al.	2004	CT	17	Indistinct nodal margins, irregular capsular enhancement, tumoral soft tissue infiltration	65%	93%	Low
Yousem et al.	1992	CT	24	Indistinct nodal margins, irregular capsular enhancement, tumoral soft tissue infiltration, central node necrosis	91% and 96%	94% and 100%	Low
Souter et al.	2009	CT	149	Indistinct nodal margins, irregular capsular enhancement, tumoral soft tissue infiltration, wall thickening	66% and 80%	91% and 90%	Moderate
Randall et al.	2012	CT	40	Central node necrosis	91%	50%	Low
Zoumalan et al.	2010	CT	17	Central node necrosis	95%	85%	Low
Prabhu et al.	2014	CT	432	Indistinct nodal margins, tumoral soft tissue infiltration	43.7%	97.7%	Moderate
Maxwell et al.	2015	CT	55	Indistinct nodal margins, tumoral soft tissue infiltration	55% and 47%	70% and 85%	Low

hypointense non-enhancing central area post contrast for 24 patients with cervical metastases. They reported a reduced sensitivity of 78% and specificity of 90% when compared to CT evaluation. Although MRI is superior for soft tissue differentiation, no notable study has found superiority in its sensitivity for ECS when compared to CT evaluation for ECS.

Lodder et al. [22] retrospectively studied the ability of MRI to detect ECS in 39 patients with HNSCC that had been evaluated pre-operatively and subsequently had neck dissection. Using nodal measurements in conjunction with radiological and surgical designated neck nodal levels, a retrospective topographical correlation was performed. Sixty lymph nodes were selected for radiographic study by two radiologists with 20 felt to represent ECS by overall MR characteristics. The overall radiologist impression yielded a sensitivity of 60% and specificity of 93%. Using more specific criterion for infiltration of surrounding soft tissue around the capsule of the lymph node was seen to have a sensitivity of 50% and a specificity of 100%.

One major factor that may influence the results of MRI diagnosis of ECS is the difference in radiologists' understanding and subjective judgement of the diagnostic criteria. A new diagnostic criterion—TIC (Time intensity curve) has been suggested to reduce the influence of more subjective factors in the diagnosis of ECS. Focal cancer metastasis, damaged lymphoid tissue and necrosis leads to a unique tissue distribution of blood flow dynamics, and pixelated TIC analysis can be conducted after obtaining dynamic contrast enhanced (DCE) MRI Images. Sumi et al. [23] obtained time-signal intensity curve (TIC) profiles of 54 histologically proven metastatic nodes (26 ECS-positive and 28 ECS-negative) from 43 patients with head and neck squamous cell carcinoma (SCC) and retrospectively analysed these patients to determine the effective TIC criteria for ECS-positive nodes. The TICs were semi-automatically classified into four distinctive patterns (flat, slow uptake, rapid uptake with low washout ratio, and rapid uptake with high washout ratio) on a pixel-by-pixel basis. The combined MRI criteria of nodal size (>25 mm) and TIC profile (>44% nodal areas with slow-uptake TIC patterns) yielded the best results for differentiation between ECS-positive and ECS-negative nodes, with sensitivity of 96%, specificity of 100%, accuracy of 98%, positive predictive value of 100% and negative predictive value of 97%.

Ultrasound

Ultrasound may also have utility in diagnosing ECS. Currently it is used extensively to diagnose lymph node metastases due to its dynamic profile. Under ultrasound, nodes with ECS should show jagged, irregular edges, internal echo and calcified or necrotic areas. Only one study by Steinkamp et al. has gone on to extensively study this in a prospective comparison study of 110 patients. They found a high sensitivity of 78.6% and specificity of 81.8% when compared to histological classification [12]. Ishii et al. looked at whether there was any difference between CT and Ultrasound in their ability to diagnose ECS. They found no significant difference in sensitivity or specificity [24]. A particular drawback of ultrasound of the neck is the reliance on

operator experience and high interobserver variability. With the developments of high-resolution ultrasound and its ability to dynamically image and perform guided fine needle aspirations, further research should be implored as to whether this imaging modality can provide increased diagnostic value.

PET/CT

18-F-fluorodeoxyglucose (FDG) PET/CT is another useful tool in identifying ECS. FDG PET/CT has some benefits over conventional CT in that functional information of the node may also be acquired. In addition, FDG PET/CT is superior to conventional anatomic imaging due to its superiority in detecting, staging and monitoring HNSCC. High lymph node SUV max levels have independently been shown to predict worse prognosis in HNSCC [20]. Recently, SUV max levels have been further studied to see if a cut off value can reliably diagnose ECS. Chun et al. in a study comprising of 78 patients undergoing FDG PET/CT prior to neck dissection, found SUV max levels of 3.83 and greater to be heavily predictive of ECS with a sensitivity of 85.7% and specificity of 85.6%. The presence of ECS and median SUV_{max} (using 3.85 as a cut-off) were found to have a significant adverse effect on 5-year disease-specific survival by univariate analysis. The multivariate analysis showed a significant association of 5-year disease-specific survival with ECS (hazard ratio (HR) = 32.3 in cervical metastasis with ECS and HR = 19.6 in cervical metastasis without ECS [25]. Joo et al. has considerably researched whether SUV max values effectively predict ECS. In one retrospective analysis of 57 patients with hypopharyngeal SCC ECS was shown to have a median SUV max value of 2.65 at a sensitivity of 85% and specificity of 93% [26]. For 80 patients with oropharyngeal SCC's, Joo et al. reported ECS to be prevalent at SUV max value of greater than 2.25 at a sensitivity of 85% and specificity of 88% [27]. SUV max along with the anatomical information acquired from contrast enhanced CT scans has shown substantial promise however it should be kept in mind that SUV max values are subject to fluctuations with changes in blood glucose uptake time, respiratory motion and tumor size (Table 29.3).

CT is an effective modality to predict extracapsular nodal extension when characteristics of extracapsular fat infiltration, nodal wall thickening, and central nodal necrosis are present (quality of evidence low, conditional recommendation).

The combination of analysis of T1 weighted image together with fat saturated T2 weighted and fat saturated post contrast T1 weighted images are useful for detection of nodal ECS using MRI. The utility of MRI using slice thickness of 3–5 mm in the detection of ECS in small nodal disease burden is lower (quality of evidence low, conditional recommendation).

Table 29.3 MRI, PET/CT and US in predicting ECS

Author	Year	Imaging modality	N	Diagnostic criteria	Sensitivity	Specificity	Quality of evidence
Steinkamp et al.	2002	MRI	110	Indistinct nodal margins, tumoral soft tissue infiltration	74.4%	72.2%	Low
King et al.	2004	MRI	17	Indistinct nodal margins, irregular capsular enhancement, tumoral soft tissue infiltration	78%	86%	Low
Yousem et al.	1992	MRI	24	Indistinct nodal margins, tumoral soft tissue infiltration, central node necrosis	81% and 61%	96% and 89%	Low
Lodder et al.	2013	MRI	39	Tumoral soft tissue infiltration	50%	100%	Low
Steinkamp et al.	2003	US	110	Irregular capsular edge, internal echo, calcified or necrotic regions	78.6%	81.8%	Low
Kimura et al.	2008	MRI	109	High signal in interstitial tissues, nodal Size	77%	93%	Moderate
Chun et al.	2016	PET/CT	89	SUV max > 2.8	85.7%	85.6%	Low
Joo et al.	2013	PET/CT	57	SUV max > 2.65	85%	93%	Low
Sumi et al.	2011	MRI	43	MR DCE and TIC	96%	100%	Low

A Personal View of the Data

Extension of tumor cells beyond the nodal capsule defines ECS. Gross ECS is an easy diagnosis regardless of the imaging modality. Notwithstanding the ambiguity in its clinical significance minimal ECS is a difficult imaging diagnosis. All the morphological features analysed on MRI and CT are subjectively assessed which is the main reason for high inter-reader variability. Variable accuracy reported for CT and MRI is attributable to differences in image quality, observer experience and size of the metastatic node. Patient factors such BMI may play a role as ECS in a node completely surrounded by fat is easier to see than ECS in a node abutted by muscles or vessels. Further confounding this issue is the variability in pathologic diagnosis which can account for the reported decrease in accuracy of imaging between older and contemporary studies as with heightened awareness pathologists tend to diagnose more minimal ECS cases. High resolution images allow better identification and characterization of small structures. Given that the spatial resolution of CT is superior to that of MRI, this can account for why MRI does not confer an advantage over CT in ECS diagnosis despite its superior soft tissue contrast resolution. Looking back at the improvements in spatial resolution of MRI and CT in the last decades it is expected that the difference between imaging resolution and microscopic resolution will continue to narrow in both imaging modalities thus improving the accuracy of ECS diagnosis. Texture analysis is an emerging field in radiology that assists in analysing imaging data in a quantitative fashion. Many applications of texture analysis show great promise and ECS may be particularly suitable for this tool. Time-signal intensity-curves generated by dynamic MRI evaluate the vascularity and blood flow of nodal masses. Preliminary studies show promise although the pathophysiologic basis of the observed changes and their relation to ECS is poorly understood. Likewise, SUV in PET demonstrates some utility but lacks a pathologic correlate which is what the current definition of ECS is based on. Because there is no pathologic correlate for these functional parameters they are difficult to externally validate and are unlikely to become more than diagnostic adjuncts in the near future. Nodal necrosis as seen on CT and MRI shows utility in predicting ECS. In my opinion, this is more of an associated finding in conjunction with ECS, but does not constitute a pathologic definition of ECS.

In clinical practice, there is no substantial difference between the accuracies of MRI and CT in ECS thus, selection of imaging modality for assessment of HNSCC is based on the site and stage of the primary tumor and factors related to cost and availability. Both radiologists and clinicians should understand that the accuracy of imaging diagnosis of ECS is less than perfect and both false positive and false negative results occur. Radiologists should be more critical of subtle and ambiguous findings on radiologic imaging to increase the diagnostic accuracy of their interpretations. Because a positive ‘call’ for ECS on radiologic imaging is usually used to justify a non-operative treatment in certain head and neck cancer sites such as the oropharynx, we strive for a higher positive predictive value in our interpretations which inevitably decreases our negative predictive value.

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Is There a Role for Triple Endoscopy in the Staging of Head and Neck Cancer?

30

Thomas S. Y. Ho and Raymond K. Y. Tsang

Introduction

The occurrence of multiple tumors in the upper aerodigestive tract was first described by Billroth and Von Winiwarter [1] in 1883. This was further elaborated by Slaughter et al. [2] with the concept of 'field cancerization', who hypothesized that the exposure of the upper aerodigestive tract mucosa to the two main exogenous carcinogens, tobacco and alcohol, can result in multifocal tumors in the head and neck region, esophagus and lung. The rate of second primary tumors following head and neck squamous cell carcinomas (HNSCCs), including synchronous and metachronous primaries is variable in the literature, and can be as high as 23% [3–6]. It had been reported that survival following a second primary tumor can significantly be reduced by up to 50% when compared to that of first primaries [3]. In addition, discovery of a second primary cancer may also help in avoiding unnecessary and often mutilating radical treatment of the primary tumor. Triple endoscopy (laryngoscopy, esophagoscopy and bronchoscopy) has therefore been utilized for the aim of diagnosing synchronous and/or metachronous tumors [7–9]. However, routine use of triple endoscopy is still debatable, as it could increase treatment cost, extend the waiting time before initiation of treatment and may also carry certain risks [10–13]. This chapter reviews the role for triple endoscopy in the staging of HNSCCs.

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Literature Search Strategy

We employed the "Population, Intervention, Comparison and Outcome" (PICO) model to analyze if triple endoscopy offers benefits. Based on the PICO table (Table 30.1), Pubmed and MEDLINE searches incorporating the terms ['triple endoscopy' or 'panendoscopy'] and 'head and neck cancer' were used to review the literature. The bibliography of applicable articles was also reviewed. The search focused on evaluating the rate of synchronous and/or metachronous second primary tumors, paying particular attention to those in esophagus and lung and clinical factors that would affect the likelihood of developing second primary tumors. Articles stating the efficacies of triple endoscopy, impact of discovering second primary tumors on treatment strategy and possible benefit in terms of survival would also be included. Articles were included if they were published from March 1999–February 2018 (20-year period) and only English articles were included.

Rate of Second Primary Tumors in Patients with HNSCCs

Triple endoscopy had been a traditional option for detecting synchronous and/or metachronous tumors along the upper aerodigestive tract in patients with HNSCCs [7–9]. Laryngoscopy allows biopsies of the primary lesion to confirm histology and for proper assessment of the extent of disease and for its resectability. Whereas esophagoscopy and bronchoscopy have the role of screening for second primary tumors in their respective regions, they carry certain drawbacks such as increase in cost, delaying initiation of treatment and complications such as perforation of esophagus, although rare [10–13].

To justify routine triple endoscopy in all patients with HNSCCs, it is imperative to study the yield of triple endoscopy. Literature review of the last 20 years revealed that the rate of second primary tumors is highly variable and can range from 2.4% to 25% (Table 30.2). Historically, a meta-analysis of 24 studies consisting of 40,287 patients [39] reported the overall rate of second primaries was 14% and in which 4% were synchronous lesions. Among these synchronous lesions, 35% were in head and neck region and could be detected on physical examination, 25% in the lung and would have been detected by CT scan or chest X-ray but not by routine bronchoscopy; 31% would be in distant regions other than head and neck region, lung and esophagus and 9% would arise in esophagus. Based on the above statistics, it can be delineated that in every 1000 patients presenting with a new head and neck

Table 30.1 Is there a role for triple endoscopy in the staging of head and neck cancer?

Population	Intervention	Comparison	Outcomes
Patients with primary head and neck cancers	Triple endoscopy (laryngoscopy, esophagoscopy, bronchoscopy)	No triple endoscopy	Rate of second primaries in esophagus/lung Survival affected by use of triple endoscopy in patients with HNSCC

Table 30.2 Rate of second primary tumors, synchronous esophageal cancers and synchronous lung cancers

	Year	n	Rate of second primary tumors (%)	Rate of synchronous esophageal cancers (%)	Rate of synchronous lung cancers (%)	Type of study
Cianfriglia et al. [14]	1999	200	14	0	N/A	RR
Tincani et al. [15]	2000	60	N/A	8.3	N/A	PCS
Davidson et al. [16]	2000	154	2.6	0	1.3	PCS
Stoeckli et al. [17]	2001	365	16.2	1.1	1.4	RR
Muto et al. [18]	2002	389	N/A	13.8	N/A	RR
Scherübl et al. [19]	2002	75	N/A	5.3	N/A	PCS
Guardiola et al. [20]	2004	487	3	2	1	RR
Hujala et al. [21]	2005	203	3.9	0	1.5	RR
Hashimoto et al. [22]	2005	326	N/A	7.3	N/A	PCS
Moschler et al. [23]	2006	87	N/A	11.5	N/A	PCS
Tsao and Damrose [24]	2007	375	N/A	0	N/A	RR
Chuang et al. [25]	2008	99,257	10.9	N/A	N/A	IMS; RR
Chow et al. [26]	2009	118	N/A	10	N/A	RR
Lee et al. [27]	2010	69	N/A	30.4	N/A	PCS
Rodriguez-Bruno et al. [28]	2010	64	6.3	0	N/A	RR
Rennemo et al. [29]	2011	2016	2.4	N/A	N/A	RR
Ikawa et al. [30]	2012	171	N/A	4.1	N/A	RR
Priante et al. [31]	2013	135	25.2	4.4	1.5	PMPA
Chung et al. [6]	2013	129	N/A	23.3	N/A	PCCS
Su et al. [32]	2013	1592	N/A	4.5	N/A	RR
Hung et al. [33]	2013	2965	N/A	2.19	N/A	CSCS
Shahangian and Damrose [34]	2015	168	N/A	N/A	0	RR
Krishnatreya et al. [35]	2015	4184	1.43	0.8	0.04	RR
Koo et al. [36]	2015	112	9.7	N/A	N/A	RR
Huang et al. [37]	2016	248	N/A	15	N/A	PCS
McGarey et al. [38]	2016	601	N/A	0	N/A	RR

RR retrospective review, *PCS* prospective cohort study, *IMS* international multicenter study, *PMPA* prospective matched pair analysis, *PCCS* prospective case control study, *CSCS* cross sectional comparison study

primary cancers, simultaneous primary tumors would be detected in 40 patients. Among them, 14 will occur in the head and neck region and would be detected by physical and/or fibre-optic examination, 10 will occur in the lung and be detectable by radiological means and only 3 will occur in the oesophagus and be potentially detectable by esophagoscopy. Therefore, for every 1000 esophagoscopies done, there would be a gain of 3 esophageal malignancies, i.e. 333 esophagoscopies for screening out one esophageal malignancy. Stoeckli et al. [17] reported an incidence of a second primary tumor at 16.2% in 358 patients presenting with previously

untreated squamous cell carcinoma of the oral cavity, pharynx, or larynx, yet in only 3.1% of all patients, a synchronous tumor was clinically silent and only revealed by means of triple endoscopy. Hujala et al. [21] found 8 patients (3.9%) with synchronous second primaries in a review of 203 consecutive patients. In a prospective study by Rennemo et al. [29], 2016 HNSCCs patients' data were recorded and an incidence of 2.4% was recorded, but within that only 1.4% was detected in areas covered by triple endoscopy. Priante et al. [31] had yielded a highest rate of second primary tumors at 25%. However, this rate was a cumulative of patients with synchronous and metachronous tumors and in combination with those detected during physical examination. The actual yield of second primary tumors in the study by triple endoscopy was 8.5%. Krishnatreya et al. [35] reviewed 4184 patients and had a yield of 1.4% of patients with second primary tumors detected with triple endoscopy.

Rate of Second Primary Tumors in Esophagus

The rate of synchronous esophageal tumors in patients with HNSCCs ranged from 0% to 30.4% according to the literature in last 20 years (Table 30.2). The role of esophagoscopy had recently been challenged amongst literature. Cianfriglia et al. [14], Hujala et al. [21] and Davidson et al. [16] all reported no synchronous esophageal cancer was discovered during triple endoscopy. Comprehensive review by McGarey et al. [38] showed that there was a trend of decreasing prevalence of synchronous esophageal cancers in patients undergoing triple endoscopy for staging for head and neck cancers in the United States and Canada. Whereas most studies in the 1980s showed a rate of synchronous esophageal cancers ranged from 0–8%, there was no North American study reporting a single synchronous esophageal cancer on staging esophagoscopy since 2000 in McGarey et al.'s review [38]. In contrast, most of the studies conducted in Hong Kong and Taiwan still found substantial incidence of synchronous esophageal cancers. In a retrospective review by Chow et al. [26] of 118 patients undergoing esophagoscopy as part of workup for HNSCCs patients, clinically important lesions were found in 10% of patients (9 carcinomas and 33 dysplastic lesions). Lee et al. [27] utilized narrow-band imaging with magnifying endoscopy for screening of esophageal cancer in 69 patients of HNSCCs and found 21 patients (30.4%) of synchronous esophageal cancers, in which 9 (42.9%) were asymptomatic, and 10 (47.6%) had early-stage neoplasia. Further studies in Taiwan by Huang et al. [37] and Chung et al. [6] noted that there were still substantial rates of synchronous esophageal cancer at 14.8% and 23.3% respectively. The relatively higher rates of synchronous esophageal cancer noted in Asia and especially Taiwan can be explained by the higher incidence of squamous cell carcinoma of esophagus in Asia [40] and also with the high rate of betel nuts chewing in Taiwan, which can be a common carcinogen for both HNSCCs and esophageal cancer [33, 37].

Rate of Second Primary Tumors in Lung

The rate of synchronous lung cancers with HNSCCs was summarized in Table 30.2, and it ranged from 0% to 1.5%. Comparing to esophagoscopy, the use of bronchoscopy as a routine screening modality for patients with HNSCC had been less utilized amongst authors. This can be explained by the non-invasive and readily available alternative options of screening including chest X-ray, CT chest scan as well as PET-CT imaging. The use of bronchoscopy had appeared to be inferior to CT chest scan for early screening of lung cancers [41, 42]. Davidson et al. [16] detected all 4 malignant lung lesions radiologically out of 154 patients with HNSCCs, giving an actual 0% yield of bronchoscopy. Guardiola et al. [20] had found a rate of 1% synchronous lung cancer and Shabangian et al. [34] identified no synchronous lung cancers in a series of 168 patients undergoing bronchoscopy. Chow et al. [26] had now reserved bronchoscopy only for symptomatic patients or if abnormality is present on chest X-ray or CT chest scan. Recent guideline by the French ENT society concluded that bronchoscopy is not indicated in early staging of HNSCCs particularly in the presence of a normal CT chest scan [43].

> Bronchoscopy is not recommended as a staging tool for patients with HNSCCs, in particular in the presence of a normal CT chest scan (quality of evidence moderate, conditional recommendation).

Factors Affecting the Rate of Second Primary Cancers

HNSCC Subsites (Hypopharynx)

The hypopharynx and esophagus are continuous structures anatomically and they are exposed to similar exogenous or endogenous substances and carcinogens including alcohol and cigarette. Strong associations between hypopharyngeal cancer and esophageal cancer had been proven in many population-based association studies [25, 33, 37] in Asia as well as in the western population [17, 20]. Stoeckil et al. [17] had reported that patients with hypopharyngeal cancers had synchronous second tumors only in the esophagus. In a review of 487 patients with HNSCCs, Guardiola et al. [20] observed that 9.2% of patients with hypopharyngeal cancer are associated with esophageal cancer, the highest rate amongst other subsites of the head and neck region. In a population based study of 2965 subjects with first time diagnosis of oral/oropharyngeal/hypopharyngeal cancer in Taiwan [33], the study group was matched with a comparison group randomly retrieved from the Longitudinal Health Insurance Database in Taiwan, which had an enrollment rate of 97% of Taiwanese population. The study group was matched with the comparison group in terms of gender and age group. Odds ratio of esophageal cancer for

Table 30.3 Factors affecting the occurrence of second primary tumors

	Factor	OR or RR	95% CI	p value	Type of study
Chung et al. [6] (for occurrence of esophageal cancers)	Stage of HNSCCs (III and IV vs. I and II)	OR = 2.98	1.11–7.99	0.030	Prospective case control study
	Alcohol drinking	OR = 5.90	1.23–26.44	0.020	
Hung et al. [33] (for occurrence of esophageal cancers)	Oral, oropharyngeal and hypopharyngeal cancers vs. comparison subjects	OR = 55.33	29.86–102.52	<0.001	Cross sectional comparison study
	Subgroups vs. comparison subjects:				
	• Oral cavity cancers	OR = 18.41	8.50–39.85	<0.001	
	• Oropharyngeal cancers	OR = 40.49	15.11–108.64		
	• Hypopharyngeal cancers	OR = 240.96	125.49–462.69		
Koo et al. [36]	Smoking	RR = 1.140	1.026–1.272	0.031	Retrospective review
	Alcohol drinking[a]	RR = 1.138	0.994–1.303	0.043	
Huang et al. [37] (for occurrence of esophageal cancers)	Alcohol drinking[b]	OR = 6.95	1.52–31.82	<0.05	Prospective cohort
	Nodal staging: N3	OR = 2.41	1.01–5.73	<0.05	

[a]Defined as having an average weekly alcohol intake of greater than 20 standard units
[b]Defined as those consuming any alcoholic beverage during a week

subjects with oral/oropharyngeal/hypopharyngeal cancer was 55.33 (95% CI: 29.86–102.52; $p < 0.001$) compared to comparison subjects (Table 30.3). Furthermore, compared to comparison subjects, odds ratios for esophageal cancer were respectively 18.41 (95% CI: 8.50–39.85; $p < 0.001$), 40.49 (95% CI: 15.11–108.64; $p < 0.001$), and 240.96 (95% CI: 125.49–462.69; $p < 0.001$) for study subjects with a malignancy of the oral cavity, oropharynx, and hypopharynx, hence with the highest odds ratio for hypopharyngeal cancer patients. In another prospective evaluation of 248 patients with newly diagnosed hypopharyngeal cancers and without previous head and neck cancer in Taiwan, Huang et al. [37] had found a prevalence of 14.8% of patients with esophageal cancers and with dysplasia occurring in 9.4% of patients. In the latest guideline by the French ENT society, they had concluded that esophagoscopy is indicated in initial staging for patients with hypopharyngeal cancers [43].

HNSCC Subsites (Oral Cavity)

In contrast to patients with primary cancer in hypopharynx, a lower incidence of second primary tumors was reported in patients with primary oral cavity tumors. Two studies [20, 36] had reported no synchronous second primaries associated with

patients with oral cavity cancers. In Chow et al.'s study [26], synchronous esophageal lesion was only present in 2% of patients with isolated oral cavity cancer. With univariate analysis and multivariate analysis comparing significant factors on univariate analysis, oral cavity tumors showed less propensity in developing synchronous esophageal lesions when comparing with tumor arising from other sites ($p = 0.002$ in univariate analysis; $p = 0.009$ in multivariate analysis, controlling for age, gender and alcohol drinking behavior).

Alcohol and Smoking

Smoking and alcohol are well known risk factors for second primary tumor development with the field cancerization theory [2]. Studies had shown that there are lower rates of second primary tumors in patients who do not smoke or consume alcohol [28, 36]. In a study of patients with tongue cancer (Table 30.3) [36], tobacco and alcohol usage were found to increase the relative risk of second primary development (RR: 1.140 and 1.138 respectively; $p = 0.031$ and 0.043 respectively), while non-smoking, non-drinking status led to a decreased risk of second primary development (RR: 0.861; $p = 0.017$). Alcohol consumption was also reported to be a significant predictor of synchronous esophageal lesion in patients with HNSCCs ($p = 0.047$) [26]. In a study of patients with newly diagnosed head and neck cancer [6], alcohol drinking was associated with an increased risk of esophageal neoplasia (OR 5.90, $p = 0.020$). A Taiwanese study consisting of patients with newly diagnosed hypopharyngeal cancers found that alcohol drinking was an independent risk factor for the presence of cancerous or dysplastic esophageal lesions (OR: 6.95; $p < 0.05$) (Table 30.3). In the latest guideline by the French ENT society, it had been concluded that chronic alcohol intoxication is a risk factor independent of smoking and increases the risk of development of a second primary esophageal tumor and esophagoscopy is indicated in this group of patients [43].

> Esophagoscopy is recommended as a staging tool for patients with HNSCCs, in particular patients with hypopharyngeal cancer and alcoholics (quality of evidence moderate, strong recommendation).

Staging

Advanced staging had been reported to be associated with a higher rate of second primary tumors. Chung et al. [6] reported advanced stage (stage III and IV) of index HNSCCs to be risk factor for synchronous esophageal cancer (OR 2.98; 95% CI: 1.11–7.99; $p = 0.03$) (Table 30.3). Huang et al. [37] also reported N3 nodal classification to be a risk factor for presence of esophageal lesions in 248 patients with newly diagnosed hypopharyngeal cancers (OR 2.41; 95% CI: 1.01–5.73; $p < 0.05$) (Table 30.3).

HPV Status of Index Tumor

Incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinomas (OPSCCs) had increased significantly in recent years [44–49] and is a major etiological factor of OPSCCs among non-smokers [50–52]. There is also a major paradigm shift with OPSCCs, from a primarily tobacco-associated malignancy and with strong association with the field cancerization theory, to a malignancy that is caused by the oncogenic human papillomavirus. A population based cohort study of 64,673 patients from 1979 to 2008 had shown that OPSCCs carried the highest risk of second primaries in the 1970s and 1980s; however, the risk had gradually declined and currently OPSCCs carried the lowest risk of second primaries [53]. Multivariate analysis of 150 patients with OPSCCs showed that HPV negativity was a significant unfavorable risk factor for the occurrence of metachronous second primary malignancy (OR 0.288, 95% CI: 0.102–0.810; $p = 0.014$) [54]. The incidence rate of second primaries had also been shown to be significantly lower in p16-positive patients (0.7 per 100 patient-years vs. 8.5 in p16-negative, $p < 0.0001$) [55] and there was a decrease in diagnostic yield in p16 positive patients for workup with triple endoscopy and whole body PET-CT (2.8% vs. 10.2% in HPV-negative patients, $p = 0.02$) [55]. A recent study [56] had a paired analysis of tumor tissue from the same patient with HNSCC and synchronous esophageal cancer and showed that none were concomitantly positive for HPV. These all showed that future screening practices for HNSCCs patients might be benefited by tailoring with HPV status of patients' HNSCCs.

How Triple Endoscopy Affects Survival of Patients with HNSCCs

Currently, up to our knowledge, few studies had outlined the impact of triple endoscopy on survival outcomes of patients with HNSCCs with second primaries. Priante et al. [31] had found an incidence of 25.2% of second primary tumors and there was no significant difference in cancer-specific survival between the triple endoscopy group and control group. No significant differences were found in the overall survival of the subgroups according to the location of the primary tumor. However, it was widely reported that survival outcomes with second primary tumors of HNSCCs were substantially poorer than survival expected with first primary diagnosis [3, 5, 57, 58]. Early detection at presentation might have allowed appropriate curative-intent treatment for both the primary HNSCCs and the second primary tumor and changed the original treatment strategy of the primary tumor.

Alternative Choices of Investigation

Advancement of imaging techniques had challenged the role of triple endoscopy in initial staging of tumor as well as in identifying second primaries. CT chest scan had been suggested to be the first line examination for second primaries in lung and bronchoscopy is not indicated in the initial staging of HNSCCs in the presence of

normal CT chest scan [43]. PET-CT had been reported to be beneficial for the detection of locoregional disease, second primary tumors, and distant metastases [59, 60] and had considerable impact on treatment decisions [61–63]. Schwartz et al. [64] staged 33 HNSCCs patients with PET-CT and found three synchronous cancers (in esophagus, lung and colon respectively), giving an incidence of second primary cancers of 9.1%. Strobel et al. [65] reviewed 589 consecutive patients diagnosed with HNSCC and found 69 suspected second primaries in 62 patients of which 56 were finally confirmed in 44 patients. Of the 56 second cancers, 15 were found in head and neck region (17%), 26 were found in the lung (46%), and 5 in the esophagus (9%). In Haerle et al.'s study [66], PET-CT was able to reveal a second primary tumor in 6.1% of patients, comparing to 4.5% identified by triple endoscopy. All true positive tumors identified by triple endoscopy were detected by PET-CT, i.e. a 100% sensitivity comparing with 74% sensitivity by triple endoscopy. PET-CT was also able to detect five additional second primary tumors comparing with triple endoscopy alone, in which four of the five lesions were in peripheral bronchial system and could not be reached by bronchoscopy. Nonetheless, PET-CT was not without drawbacks, false positive rate was detected at 31% in one study [66] and there was cost incurred.

Emerging Technologies

Improvements in endoscopic visualization technologies have steadily improved the quality of the images provided by each newer generation of endoscopes. The current generation of flexible videoendoscopes are smaller yet provide better lighting and sharper images compared to the rigid endoscopes used 30 years ago. The new endoscopes are able to reach sites in the oesophagus and bronchi that are previously difficult for rigid endoscopes to access. The new generation of videoendoscopes also have optical and digital zooming that allowed a more detail examination of the mucosa to detect early dysplastic changes [67]. Moreover, there are now new technologies in image processing that allowed better detection of mucosal dysplasia and early cancers of the hypopharynx and oesophagus. Narrow band imaging (NBI) is one of the technologies that have shown to improve the detection of oesophageal dysplasia, compare to traditional white light endoscopy [68]. A recent randomized control trial has shown that NBI endoscopy is better in detecting a second esophageal cancer or second head and neck cancer in patients suffering from primary esophageal cancer [69]. Unfortunately, there is still no study showing the increased in detection rate when employing these new endoscopic technologies in detecting second primary in HNSCC patients.

Our Personal View

The role of triple endoscopy in the initial staging of patients with HNSCCs had all along been controversial within the literature. In one hand, it may help in the discovery of a second primary tumor in early stage and may impact the treatment

plan. In another hand, proceeding with routine use of triple endoscopy as a staging tool for patients with HNSCCs may pose additional treatment cost, delay treatment and may not be efficacious.

Esophageal cancer is still relatively common in our locality [70]. We recommend to routinely perform esophagoscopy in all patients with newly diagnosed hypopharyngeal cancer and alcoholics in view of the evidence above. We do not recommend bronchoscopy as a universal screening tool for patients with HNSCCs as the yield of bronchoscopy remained low in literature. With the availability of transnasal flexible endoscopes, the complication rate of triple endoscopy is extremely low, and we observe no complications of perforation of esophagus/bronchus amongst triple endoscopies done at our unit.

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31 Is There a Role for Induction Chemotherapy in the Treatment of Advanced Head and Neck Cancer?

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Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is a diverse group of malignancies encompassing tumors diagnosed in the oral cavity, pharynx (further subdivided into oropharynx, hypopharynx, and nasopharynx), and larynx. Each subsite has unique challenges and recommendations for treatment. Many patients present with advanced loco-regional disease and treatment focuses on protocols that provide functional organ preservation without compromising survival. These protocols focus on the addition of chemotherapy to either surgical or radiation-based regimens in three delivery formats: induction, concurrent with radiation, or adjuvant. The hypothesis behind the use of induction chemotherapy is to provide systemic control of disease to prevent distant metastasis (DM) [1].

The meta-analysis of chemotherapy in Head and Neck Cancer (MACH-NC) examined 87 trials with 16,485 patients and found an absolute survival benefit of 4.5% at 5 years with the addition of chemotherapy [2]. Induction chemotherapy did not have an effect on locoregional control but it did show a potential negative effect on development of DM. However, this meta-analysis found timing of chemotherapy in favor of concurrent chemotherapy with radiation (CRT) over induction chemotherapy (IC). Therefore, the standard treatment for most locally advanced HNSCC is CRT, and induction chemotherapy is used in subsite-specific situations (e.g., hypopharynx, larynx nasopharynx) based on National Comprehensive Care Network

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(NCCN) guidelines [3]. Treatment with IC in the hypopharynx is category 2a and IC can be considered in the setting of larynx preservation.

However, the trials included in this meta-analysis used older chemotherapy regimens that included PF [cisplatin-5-fluorouracil (5-FU)] [2] and combined all head and neck subsites when the benefit of IC may have been seen in only the nasopharynx subsite. The PF regimen has now been supplanted by the addition of taxanes (TPF) [4–6]. In addition, radiation regimens have evolved with the introduction of intensity-modulated radiation therapy (IMRT) and surgical techniques are more advanced that provide more complete resection using minimally invasive techniques. Herein, we describe a contemporary investigation of the role of induction chemotherapy in HNSCC.

Search Strategy

We employed the PICO strategy to identify relevant articles addressing the outcomes in patients treated with induction chemotherapy with advanced stage HNSCC (Table 31.1). The focus of our search was studies published after 2007, as this date corresponds to the publication of the TAX 323 and TAX 324 trials confirming the superiority of TPF over PF. PubMed search terms using the terms "induction chemotherapy", "neoadjuvant chemotherapy", "head and neck cancer", and the individual subsites, "nasopharynx", "sinonasal", "oral cavity", "oropharynx", "larynx", "hypopharynx", "pharynx" were incorporated into our review of the English language literature. We included meta-analyses and phase III randomized trials in our search. Given the lack of significant randomized data comparing neoadjuvant treatment and surgery to surgery alone, phase II trials using surgery as primary treatment were also included in the search.

Results

The use of chemotherapy as an induction regimen was popularized when used in the organ preserving trials for the larynx (VA Laryngeal Cancer Study Group) [7] and the hypopharynx (EORTC 24891) [8]. These trials found that overall survival was not compromised when using IC + RT compared to surgery + RT. However, local control rates were low (36% of patients required laryngectomy in VA Study and 65% of patients required laryngectomy in the EORTC trial). Therefore, RTOG 91-11 found the administration of CRT was superior to IC followed by RT with

Table 31.1 PICO template for induction chemotherapy evaluation

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with locoregionally advanced HNSCC	Induction chemotherapy	Concurrent chemotherapy and radiation or definitive surgery	Overall survival, progression free survival, overall response rate, complications from therapy

regards to 2-year laryngeal preservation rate (88% vs. 75%, respectively) [9]. The results of this trial led to CRT being the standard first-line treatment for organ preservation in HNSCC.

These trials used PF as the induction regimen; therefore, investigators sought out different drug combinations to improve outcomes. Subsequently, phase III trials in Europe (TAX 323/EORTC 24971) and the US (TAX 324) found that TPF induction regimen was superior to PF [4, 10]. Patients were found to have improved overall survival (OS), progression-free survival (PFS) and lower loco-regional failures (LRC) with improvements in tolerance and compliance to the TPF regimen. In addition, larynx preservation rates with TPF were better than PF (70% vs. 57%, respectively) [5]. Moreover, a meta-analysis that pooled data from five phase III trials confirmed that TPF IC had increased benefits for patients compared to PF [6]. These results reignited the debate on the use of IC in head and neck cancers and whether the use of IC with definitive therapy (C/RT or surgery) is superior to standard of care C/RT or surgery with or without adjuvant C/RT. This section will highlight the results of these contemporary studies using IC and is divided into two parts: IC followed by C/RT and IC followed by surgery.

Induction Chemotherapy Followed by Radiation Therapy

After review of the English language literature, we found seven studies comparing IC + CRT to CRT alone in HNSCC. Six studies included oral cavity, oropharynx, hypopharynx and larynx. One study evaluated only the nasopharynx. The results are summarized in Table 31.2.

Table 31.2 Summary of data from randomized control trials comparing IC + CRT to CRT

Study	Patients	Subsites	IC	CRT	OS	PFS	LRC	Quality
Haddad et al. [11]	145	OC, OP, Lx, HP	TPF	Docetaxel-RT or carboplatin-RT in treatment arm; cisplatin-RT in control arm	NS	NS	NS	Moderate
Cohen et al. [12]	273	OC, OP, Lx, HP	TPF	TFHX for both arms	NS	NS	NS	Moderate
Hitt et al. [13]	439	OC, OP, Lx, HP	TPF or PF	Cisplatin-RT for both arms	NS	NS	NS	Strong
Sun et al. [14]	480	NP	TPF	Cisplatin-RT for both arms	HR: 0.59	HR: 0.68	NS	Strong
Ghi et al. [15]	414	OC, OP, Lx, HP	TPF	Cisplatin-5-FU-RT or Cetuximab-RT for both arms	HR: 0.74	HR: 0.72	HR: 0.74	Moderate

Abbreviations: *OC* oral cavity, *OP* oropharynx, *Lx* larynx, *HP* hypopharynx, *NP* nasopharynx, *TPF* docetaxel, cisplatin, 5-FU, *PF* cisplatin-5-FU, *RT* radiation therapy, *NS* non-significant, *HR* hazard ratio. Reported values are statistically significant

The PARADIGM study was an open-label randomized phase III multi-institutional trial in the US and Europe [11]. It included 145 patients (70 in IC + CRT group and 75 in CRT) with Stage III/IVA carcinomas of the oral cavity, oropharynx, hypopharynx, and larynx with primary endpoint being overall survival with secondary endpoints being PFS and toxicity. This study was halted due to poor accrual. There was no significant survival benefit noted for IC + CRT in this study. The PARADIGM study was flawed due to differences in chemotherapy regimens given with RT. Non-responders in the IC group would receive docetaxel with RT and responders would receive carboplatin. The CRT arm of this study received high-dose cisplatin with RT. Therefore, it is difficult to draw any significant conclusions from this trial.

During the same time period of PARADIGM, a similar trial led by the Spanish Head and Neck Cancer Cooperative Group (TTCC) also found similar results [13]. The TTCC study was a randomized study of 439 patients with three treatment arms: CRT (n = 128), TPF + CRT (n = 155), and PF + CRT (n = 156). Overall, no significant survival benefit was noted for IC + CRT over CRT alone. However, significant benefits in PFS and time to treatment failure (TTF) were noted for the TPF + CRT vs. CRT alone (HR 0.72; 95% CI, 0.53–0.98) suggesting a role for TPF + CRT in select patients. A concerning feature of this trial was the significant toxicity associated with IC with 11 treatment-related deaths in the IC + CRT arm compared to only two treatment-related deaths in the CRT arm.

Knowing that select patients may benefit from IC, specifically the TPF drug combination, investigators led by the University of Chicago initiated a trial in patients at high-risk for distant metastasis [12]. The Docetaxel Based Chemotherapy Plus or Minus IC to Decrease Events in Head and Neck Cancer (Decide) included patients with N2 or N3 disease who were deemed a high-risk for DM [16] with the hypothesis that IC would reduce DM, therefore, improving survival. In this study, 273 patients were randomized to either IC + CRT (n = 138) or CRT (n = 135). This study was unable to meet its intended accrual target (400 patients). Induction regimen was TPF and CRT was docetaxel, 5-FU, hydroxyurea with twice daily RT. Significant toxicities were associated with IC + CRT group compared to the CRT alone group, with five treatment-related deaths in the IC + CRT arm compared to no treatment-related deaths in the CRT alone arm. Again, no survival benefit was found between the two groups. However, significant reductions in DM were noted in the IC + CRT arm and there was a trend toward improved survival in patients with N2c and N3 disease who were in the IC + CRT arm.

Although the data from DeCIDE demonstrated no significant survival benefit from the addition of IC, there are many important conclusions to draw from this study. First, the study had a significant number of patients with oropharynx primary (60% of all patients), of which many of these patients have human papilloma virus (HPV) associated disease that carries an excellent prognosis, thus, any intended survival benefit for the test arm may not have been realized. Second, this study a trend toward improved survival in higher nodal stage indicating a role for IC in these patients.

Subsequent to this study, a meta-analysis that pooled the data from these three studies and included preliminary data from a phase II–III trial [15] and a single

institution study that did not use standard treatment regimens [17]. The results of this analysis found that IC + CRT did not provide a significant survival benefit compared to CRT alone and patients experienced significant toxicity from IC. However, there was significant reduction in DM in patients receiving IC (HR 0.58, 95% CI 0.39–0.85). As a result, IC was not a recommended course of treatment for HNSCC based on this meta-analysis.

These trials did not include the nasopharynx subsite in their inclusion criteria. Patients with nasopharynx carcinoma (NPC) have a 15% risk of development of DM over 5 years [18]. One must consider the role of IC in this subsite at high-risk to understand if reduction in DM truly portends improvement in survival. Yun, et al., led a phase III trial in China comparing IC (TPF) + CRT (n = 241) to CRT (n = 239) in a well-constructed study in NPC patients [14]. CRT regimens were the same with high-dose cisplatin and RT. Patients in the IC group were found to have significant benefits in 3-y PFS (HR 0.68, 95% CI 0.48–0.97), OS (HR 0.59, 95% CI 0.36–0.95), and reduced DM (HR 0.59, 95% CI 0.37–0.96). As expected, the IC group had more adverse events related to receiving IC with only 17 patients withdrawing from the study. Only one death was attributed to IC, but this patient was reported to have poor adherence to supportive care. Therefore, IC + CRT is an acceptable treatment in NPC with improvements in survival without significant toxicity.

An additional study from China furthered the benefit of IC in their analysis of quality of life after treatment for NPC and whether RT treatment fields can be altered based on IC response [19]. This investigation randomized RT treatment volume after IC to cover either the remnant tumor volume post IC vs. RT covering the pre-IC tumor volume. The results of this study found no survival difference between the two groups but did find that patients had significant improvements in dry mouth, pain, and cognitive function in the reduced tumor volume group. Therefore, the cytoreduction by IC may result in definitive treatments that result in improvements in long-term side effects without compromising survival in NPC.

The potential for dose reduction in definitive treatment without affecting survival is an important point of consideration in HPV-associated disease given the excellent survival in this subset of patients [20]. A phase II trial of 80 patients with HPV-associated oropharynx carcinoma led by the Eastern Cooperative Oncology Group (ECOG-1308) [21] using the induction regimen paclitaxel, cisplatin and cetuximab found 70% of patients had a complete response after IC and went on to 23% reduction in RT dose (54 Gy vs. 69.3 Gy). OS at 2-y for the 54 Gy group was 94% and PFS at 2-y was 80%. Most importantly, patients who received 54 Gy reported less difficulty swallowing solids compared to the patients who received 69.3 Gy (40% vs. 89%, respectively, $p = 0.01$) and also reported less nutritional impairment (10% vs 44%, $p = 0.03$).

Induction Chemotherapy Followed by Surgery

Surgery is primary treatment modality for oral cavity carcinomas (OSCC) due to the significant survival benefit compared to nonsurgical therapy [22]. Nonsurgical therapy is limited to patients with unresectable disease or patients who are poor surgical

Table 31.3 Randomized trials comparing IC + surgery to surgery

Study	Patients	Subsite	IC	OS	PFS	LRC	Quality
Bossi et al. [24]	198	OC	PF	NS	NS	NS	Strong
Zhong et al. [26]	256	OC	TPF	NS	NS	NS	Strong

Abbreviations: *OC* oral cavity, *TPF* docetaxel, cisplatin, 5-FU, *PF* cisplatin-5-FU, *RT* radiation therapy, *NS* non-significant

candidates. The role of IC in OSCC has been attributed to reduction in large volume reductions, including mandibulectomy, and studies have been designed to evaluate this issue [23].

A phase III trial of 198 patients with OSCC randomized to receiving PF then surgery vs upfront surgery found no difference in OS or PFS between the two groups [24]. Interestingly, long-term follow-up data found no difference in DM development between the two groups. However, IC did reduce the number of mandibulectomy (31% vs. 52%) and less patients required adjuvant RT (33% vs. 46%) [25]. The reduction in adjuvant RT resulted in decreases in late fibrosis and dysphagia.

A contemporary phase III trial of 256 total patients with OSCC from China using TPF as the IC regimen also did not find any survival benefit for IC + surgery vs. surgery alone [26]. This study did not report on whether IC reduced extent of surgery or the prescription of adjuvant therapy. These results are summarized in Table 31.3.

The current evidence using contemporary IC regimen of TPF has not shown a significant survival benefit over CRT or surgery in treatment of HNSCC. The benefit of IC is seen only in the nasopharynx subsite and in the setting of larynx preservation where treatment would require total laryngectomy. Based on the available data, CRT should be the primary treatment for stage III/IVA HNSCC (quality of evidence strong, conditional recommendation).

Personal View of Data

Randomized controlled trials have failed to show a benefit for IC over CRT; therefore, CRT is the guideline-recommended treatment for unresectable HNSCC. These studies also showed the addition of IC increased toxicity in these patients. However, subset analysis of these studies has found IC reduces DM in patients with high risk for development (advanced nodal disease). Moreover, IC may have survival benefit in NPC. Therefore, it is reasonable to consider IC in these scenarios. In addition, two assessments of IC in surgical trials have found response to IC resulted in less morbid resections and made unresectable OSCC amenable to surgery.

The major concern of these studies is the heterogeneity of the chemotherapy regimens and the definitive treatments, so it is difficult to conclude that IC is not

definitively worse than not having IC. Also, these trials are never adequately powered to provide the dramatic improvement in survival necessary to change the treatment paradigm.

In conclusion, the addition of IC does not provide any significant benefit in terms of OS, PFS and LRC. However, its role in the future treatment of HNSCC may be related to altered treatment plans that result in improved functional outcomes in patients without having an effect on disease control and survival.

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Is Routine Carotid Imaging Warranted Following Radiation Treatment of Head and Neck Cancer

32

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Introduction

The incidence of radiation-induced carotid artery disease and subsequent cerebrovascular accident after radiation therapy to the head and neck has been well documented [1–3]. In addition to neck radiation, other independent risk factors such as diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking, and increasing age have been linked to the development of carotid atherosclerosis [4, 5]. Given the increasingly longer life expectancy in patients with head and neck malignancies and the association between radiation therapy and risk for subsequent neurovascular complications, there has been a movement towards carotid-sparing radiation with Intensity-Modulated Radiation Therapy (IMRT) and measures to identify and prevent its occurrence [6–9]. As several mechanisms are presumed to lead to the development of carotid damage [10] and subsequent CVA after radiation therapy [1, 3, 11, 12], routine carotid imaging has been studied as a means of detecting carotid stenosis in order to prevent fatal and non-fatal CVAs. Currently there are no consensus guidelines for routine carotid artery screening in this patient population. This chapter reviews the utility of routine carotid imaging following radiation therapy for adults with head and neck cancer.

Search Strategy

Based on the PICO table (Table 32.1), a Pubmed search incorporating the terms Radiation Therapy and Head & Neck and Cancer and Carotid and Imaging were used to review the literature. The search was narrowed to focus on routine use of

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Table 32.1 Routine carotid imaging after radiation therapy for patients with head and neck cancer

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with head and neck cancer treated with radiation therapy	Imaging of carotid arteries	Observation/no imaging of carotid arteries/no contralateral radiation	Detection of carotid stenosis, survival, incidence of cerebral vascular accident, cost, and quality of life

carotid imaging from 1995 to 2018. The citations of applicable articles were also reviewed and the most appropriate articles were added to our review. Articles specifically about the treatment of carotid stenosis with surgical or pharmacologic measures were excluded. Since there are no randomized controlled trials, our review consists of mainly prospective and retrospective cross-sectional and cohort studies. We chose to focus on carotid ultrasound, as it has been the most widely studied in the literature. A few other modalities have been cited in the literature including magnetic resonance imaging/magnetic resonance angiography, auscultation, conventional angiography, and dental panorex imaging. In an effort to be concise, we have limited our discussion to the aforementioned carotid ultrasound modalities: brightness-mode (B-mode) ultrasound, color Doppler ultrasound, duplex ultrasound (CDUS), and contrast-enhanced ultrasound (CEUS).

Results

CDUS is the most commonly utilized ultrasound modality and is comprised of brightness-mode B-mode ultrasound and Doppler ultrasound. B-mode offers high spatial resolution images, which are capable of assessing carotid intima-media thickness (CIMT) and plaque deposition. Color Doppler ultrasound assesses flow velocity, with the peak systolic velocity as the most frequently recorded measurement to gauge the degree of stenosis. Another ultrasound modality is contrast enhanced ultrasound (CEUS), which utilizes a continuous flow or burst of contrast during imaging and may help aid the examination of plaque composition and possible instability [13]. A summary of these modalities may be found in Table 32.2.

Baseline CIMT measurements have found to be independent predictors of cardiovascular events in asymptomatic patients without risk factors [14, 15]. However, the 2013 American College of Cardiology Foundation/American Heart Association guideline for the assessment of cardiovascular disease risk does not recommend routine use of CIMT for primary prevention given the concerns over measurement standardization [16]. These concerns were echoed in the most recent USPSTF recommendation against routine carotid ultrasound in the general adult asymptomatic population as the variability in measurements could lead to overtreatment and harm [17]. Also in 2011, several professional organizations including the American Stroke Association, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Society for Vascular

Table 32.2 Carotid ultrasound modalities

	Brightness-mode	Color Doppler	Duplex	Contrast enhanced
Effective?	Yes	Yes	Yes	Yes
Benefits	– High spatial resolution images – Non-invasive	– Assess the degree of hemodynamic changes associated with the degree of stenosis – Non-invasive	– Combines B-Mode and Doppler to characterize plaque and provide physiologic measurements of hemodynamic changes – Most commonly used modality – Non-invasive	– Can detect intraplaque neovascularization
Drawbacks	– User dependent (i.e. changes in the view may increase or decrease assessed degree of stenosis)	– User dependent (i.e. changes in the angle of incidence can change the calculated stenosis)	– User dependent	– User dependent – Slightly invasive – Uses IV contrast

Surgery, and Society for Vascular Medicine recommended an initial CDUS for routine screening in asymptomatic patients with known or suspected carotid stenosis. CDUS was reasonable for patients who had a carotid bruit and to annually assess for progression/regression of carotid stenosis or response to therapeutic interventions. Carotid ultrasound might be considered to detect stenosis in asymptomatic patients but with two or more risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history of a first-degree relative of atherosclerosis prior to age 60, or a family history of ischemic stroke [18]. Although radiation therapy to the head and neck is not currently listed as a risk factor under current ultrasound screening guidelines, there have been several studies showing higher rates of carotid stenosis in areas that have been irradiated. We will now discuss the various carotid ultrasound modalities and the utility in predicting subsequent neurovascular events.

Carotid B-Mode Ultrasound

A prospective cohort study from Loyola University followed 36 patients treated with radiation and compared their CIMT measurements to age-matched controls from epidemiology studies [19]. The authors found a statistically significant increase in CIMT measurements 1 year after completing radiation, which was 21 times faster than age-matched controls. Two of these treated patients developed neurologic events and developed (≥75%) carotid stenosis.

There have been several institution retrospective studies using B-mode ultrasound for screening in radiation cohorts. One from The University of Pennsylvania

compared conventional CVA risk models (Framingham Risk Score and Pooled Cohort Atherosclerotic Cardiovascular Disease Risk Equation) with CIMT measurements from B-mode ultrasound [20]. The researchers demonstrated that CIMT measurements were able to identify 74% of their patients as high risk for CVA, defined as an IMT measurement >75 percentile or the presence of a carotid plaque, and initiate subsequent aspirin or statin. Conventional risk calculators failed to capture half of these patients as high risk and initiate medical therapy. Another study from Italy measured CIMT prior to EBRT, 6 months after EBRT, and 12 months after EBRT [21]. There was a statistically significant CIMT increased at both time points and this correlated with an increase in carotid stenosis at 12 months. However, there were no associated CVAs or TIAs reported. Another study, from the Netherlands, used internal self controls and measured bilateral carotid CIMT measurements in 42 patients treated with radiation to the unilateral head and neck [22]. After a median follow-up of 10 years, an increase in the mean CIMT measurements of 0.3 mm was found in the irradiated carotid artery when compared to the non-irradiated carotid. The researchers concluded that patients with a favorable prognosis and other atherosclerotic risk factors should be screened, but they fail to mention how frequently. A summary of these studies can be found in Table 32.3.

B-Mode Ultrasound can be utilized to detect radiation induced accelerated carotid atherosclerosis, however this modality does not predict the occurrence of subsequent neurovascular events (quality of evidence low, conditional recommendation).

Carotid Doppler Ultrasound

The most recent and profound study examining Doppler ultrasound comes from researchers at the Prince of Wales Hospital [23]. Here, researchers performed a prospective cross-sectional study comparing 71 patients treated with radiation and 51 patients newly diagnosed with nasopharyngeal carcinoma. To address confounders between the groups, risk factors including: hypertension, smoking, and hypercholesterolemia were examined and were not significantly different between the groups. With the use of color Doppler ultrasound, the researchers found a significant degree of stenosis in the post-treatment group (77%) when compared to the newly diagnosed group (22%). All of the patients that developed severe stenosis (>50%) resided in the treated group. The significant degree of stenosis was not just limited to the common carotid or internal carotid, but also the external carotid (45% vs. 2%) and vertebral arteries (7% vs. 0%) (Table 32.3).

Color Doppler Ultrasound can be utilized to detect radiation induced carotid stenosis, but does not accurately predict for subsequent neurovascular events (quality of evidence low, conditional recommendation).

Table 32.3 Summary of evidence for routine carotid ultrasound after head and neck radiation

Brightness-mode	**Muzaffar K, Laryngoscope 2000** – Increase in CIMT 21× faster than controls – Two patients developed stenosis ≥75% and neurologic events	**Jacoby D, Clin Cardiol 2015** – 74% of their patients were deemed high risk for CVA and able to initiate aspirin/statin – ½ of these patients would not be identified based on FRS and ASCVD Risk Models	**Faruolo M, Clinical and Translational Oncology 2013** – Increase in CIMT seen at 6 and 12 months post-EBRT and correlated with carotid stenosis at 12 months	**Dorresteijn LDA Eur J Cancer 2005** – Average 0.3 mm increase in CIMT in irradiated carotid when compared to non-irradiated carotid
Color Doppler	**Lam WW, Cancer 2001** – Significant stenosis noted in 77% post-RT vs. 22% pre-RT – All of the patients with common/internal carotid stenosis >50% were in the post-radiation group – Significant stenosis also noted in external carotid (45% vs. 2%), and vertebral arteries (7% vs. 0%)			
Duplex	**Chang YJ, J Vasc Surg 2009** – Stenosis (>50%) in 13% of RT group vs. 0% in no-RT group – Patients <41 years old, and men had more severe response to RT – Two CVAs in the RT group	**Greco A, Clin Otolaryngol 2012** – Mild/moderate stenosis in 60% (surgery + RT) vs. 16% (surgery alone) – Stenosis (>50%) in 23% of surgery + RT group – Total of 62% worsening stenosis in surgery + RT group	**Steele SR, The American Journal of Surgery 2004** – 10 years, 40% with (>50%) stenosis, 25% with (>70%) stenosis, 15% with complete occlusion, 15% with bilateral (>50%) stenosis – 7.5% CVAs in 10 year time period	**Brown PD, Int J Radiat Oncol Biol Phys 2005** – Significant stenosis: neck dissection + RT (32%) vs. neck dissection alone (4%) – 10–15 years, ipsilateral vs. contralateral stenosis: 4.8/100 vs. 0/100 people-years – 15 years, ipsilateral vs. contralateral stenosis: 21.3/100 vs. 5.3/100 people-years
	Cheng SW, Am J Surg 1999 – Stenosis (≥70%) associated with age >60, history of cerebrovascular signs and symptoms, interval of RT >5 years, and patients with NPC, larynx, and HPC cancers	**Carmody BJ, J Vasc Surg 1999** – 6.5 years, (≥70%) stenosis in 22% (RT group) vs. 4% (control group)		
Contrast-enhanced	**Shah BN Cardiovascular Imaging 2016** – IPN in 78% of head and neck radiation patients – IPN on 81% irradiated side vs. 41% contralateral side			

Abbreviation key: *CIMT* carotid intima-media thickness, *CVA* cerebrovascular accident, *FRS* Framingham Risk Score, *ASCVD* Atherosclerotic cardiovascular disease, *RT* radiotherapy

Carotid Duplex Ultrasound

A prospective cross-sectional study examined 290 consecutive patients with 192 previously treated with radiation and a control group of 98 patients that had not received radiation [24]. There was no reporting of atherosclerotic baseline risk factors between the groups. Plaque scores and degree of stenosis were significantly increased in the RT group, with 13% in the irradiated group having severe stenosis (≥50%) and none in the non-irradiated group ($p < 0.001$). Of interest, the researchers demonstrated that patients <41 years of age had a more severe response to irradiation than older cohorts, and that irradiated women had less stenosis than men. These findings underlie the possibilities of age-related and hormonal influences on accelerated atherosclerosis. After 5 years of follow-up, there were only two CVAs in the irradiated group. The authors attribute this to frequent neurology appointments and early antiplatelet therapy initiation to those with significant carotid stenosis.

A prospective cohort study from Italy compared surgery with adjuvant radiation versus surgery alone [25]. The researchers performed baseline CDUS and again 3 years after surgery. In the adjuvant radiation group, 60% of patient progressed from mild to moderate stenosis, compared to only 16% in the surgery group. 23% of patients in the radiation group progressed to severe stenosis (≥50%) compared with only 6% in the surgical group. Overall, 62% of patients that received adjuvant radiation developed significant worsening stenosis. However, the researchers did not report on the incidence of neurovascular events.

Using a prospectively maintained database, researchers from Fort Lewis in Washington identified a "high risk" cohort of 40 patients treated with head and neck radiation to a minimum of 55 Gy [26]. This cohort of patients underwent screening with CDUS. After 10 years of follow-up, 40% had significant carotid stenosis identified as ≥50%, 25% with stenosis ≥70%, 15% with complete unilateral carotid occlusion, 15% with significant (≥50%) bilateral carotid stenosis, and 7.5% suffered a CVA during this study period.

A historical prospective cohort study from the Mayo Clinic examined 44 patients treated with unilateral head and neck radiation [27]. The authors reported that patients who underwent an ipsilateral neck dissection in addition to radiation had significant stenosis (32% with neck dissection vs. 4% without a neck dissection). They identified that increased age and time since completion of radiation were also associated with significant stenosis (≥50%). Between 10–15 years of follow-up, the rate of significant ipsilateral vs. contralateral stenosis was 4.8/100 people-years vs. 0/100 people-years. After 15 years, the rate of stenosis was 21.3/100 people-years vs. 5.3/100 people-years.

Researchers from the Queen Mary Hospital in Hong Kong performed a cross-sectional study on 240 patients using routine CDUS [28]. They separated patients into two groups based on the assumption that nasopharynx, larynx, and hypopharynx (group 1) received radiation to neck levels II, III, and IV routinely. Group 2 comprised of other primary subsites with less frequent radiation to those same neck levels. On multivariate stepwise logistic regression analysis, carotid stenosis

(≥70%) was significantly associated with age >60 years (OR: 2.9), history of cerebrovascular symptoms (OR: 22.9), interval of radiation >5 years (OR: 8.5), and patients in group 1 (OR: 5.6).

A smaller case-control study from Washington, DC identified 23 patients treated with radiation and compared them with age-matched controls [29]. There were no differences in cardiovascular risk factors between the groups. After an average of 6.5 years, 22% in the radiation group vs. 4% in the control group had significant stenosis (≥70%) noted on CDUS. A summary of these studies can be found in Table 32.3.

Carotid Duplex Ultrasound can detect radiation induced stenosis in patients who have undergone head and neck radiation and identify those with a higher risk profile for neurovascular events (quality of evidence—moderate, conditional recommendation).

Contrast-Enhanced Ultrasound

CEUS has the ability to detect intraplaque neovascularization (IPN), which may predispose to intraplaque hemorrhage and subsequent instability. In an internally controlled cross-sectional study from the United Kingdom, researchers performed B-mode, color Doppler, and CEUS on bilateral carotid arteries of 49 patients treated with unilateral radiation [30]. The cardiologist performing the ultrasound was blinded to the laterality of the radiation. 78% of patients had plaque with significantly more on the irradiated side. Of these patients, 81% had IPN on the irradiated side, vs. 41% on the contralateral side ($p = 0.004$). The highest grade and most extensive IPN were significantly higher in the irradiated carotids (Table 32.3).

Contrast-Enhanced Ultrasound has utility in detecting radiation induced intraplaque neovascularization however there is limited data for this modality to show its efficacy in predicting the likelihood of subsequent neurovascular events (quality of evidence—low, weak recommendation).

A Personal View of the Data

There is strong evidence that irradiation accelerates the development of carotid stenosis. However, there is currently a lack of evidence showing that routine surveillance can decrease the incidence of cerebrovascular events, reduce morbidity, or increase survival. It is unlikely that any randomized controlled trials will be conducted on the utility of routine carotid imaging in the near future, so we must settle for low-moderate quality data for guidance.

While irradiation induces carotid damage and predisposes to a risk of neurovascular events, the magnitude of benefit that would be conferred by screening remains unknown as a result of low quality data. Few studies report the frequency of CVA and those that do often fail to report the laterality of the CVA in connection with the laterality of radiation. Other limitations include a failure to identify patients lost to follow-up, dose to the carotid, volume of carotid irradiated and whether confounding factors such as elective neck dissections were present. Also, the majority of data comes from duplex ultrasound, the most commonly utilized modality, but it has not been compared to the various other ultrasound modalities in a rigorous manner. Moreover, the studies fail to consider the frequency of screening.

The prevalence of severe carotid stenosis increases with comorbid risk factors (diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking), increasing age, total radiation dose, volume irradiated and time since completing treatment. Another little reported risk factor is the role of ipsilateral neck dissection in conjunction with radiation therapy. As cure rates improve, our patients are continuing to live longer and are at risk for such complications.

We consider the best way to minimize the risk of radiation induced or accelerated carotid stenosis is by using carotid-sparing IMRT whenever possible. While we believe that some form of surveillance with CDUS is warranted, there is little data to provide guidance of the optimal timing. We currently recommend CDUS of the irradiated neck 5 years after treatment as a baseline for all patients. Additional imaging studies should be based upon the findings. Earlier CDUS should be considered for patients with additional risk factors.

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Should Perineural Invasion Warrant Adjuvant Therapy in Surgically Treated Head and Neck Cancer

33

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Introduction

In cancers of the head and neck, adjuvant therapy is often recommended in the presence of aggressive tumor features such as positive margins, higher T or N stage, lymphovascular invasion, extranodal extension, and perineural invasion. In this chapter, we explore the relationship of perineural invasion (PNI) to locoregional control (LRC) and further define which scenarios may warrant post-surgical adjuvant therapy. It is important to recognize that "head and neck cancer" can encompass several histologically distinct tumor types including cancer of the squamous epithelium of the skin and mucosal surfaces, exocrine glands, and endocrine tissue. We will be discussing PNI in terms of the first three but will not be discussing it with regard to thyroid cancer.

PNI can be found in varying proportions from 5–83% depending greatly on tumor histology [1–3]. Tumor invasion into local neural structures is thought to be an indication of more aggressive cancer biology and allows for more effortless spread along these nerve highways. Furthermore, PNI is associated with other adverse tumor features such as lymphovascular invasion, extracapsular spread, and differentiation [4]. In head and neck cancer, the presence of PNI portends a worse prognosis with worse LRC and decreased survival [5–9]. These more aggressive tumor characteristics with PNI lead practitioners to prescribe aggressive post-surgical treatments. However, direct and consistent evidence demonstrating a benefit of post-operative radio- or chemotherapy does not exist.

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Table 33.1 Does post-operative therapy affect outcomes of head and neck cancer with perineural invasion

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with cancer of the head and neck exhibiting perineural invasion	Surgery excision with post-operative radiotherapy and/or chemotherapy	Surgical excision with or without neck dissection	Locoregional recurrence, disease free survival, and overall survival

Search Strategy

In order to establish a comprehensive literature base, we searched both PubMed and Google Scholar for works focused on "perineural invasion" and "head and neck cancer". Since the chapter's purpose was to define the effectiveness of post-operative treatments, as seen in the Patients, Intervention, Comparator, and Outcomes (PICO) table we refined the search with terms such as "surgery", "radiotherapy", and/or "chemotherapy" (Table 33.1). The bibliographies of the produced articles were also searched to further identify and confirm original research regarding PNI and post-operative treatment. Occasionally, cancer of the head and neck is defined by the specific subtype instead of the broad "head and neck cancer" term. Thus, terms such as "squamous cell carcinoma", "cutaneous squamous cell carcinoma", and "salivary" were also mixed with the other terms in order to identify the highest yield articles. Lastly, only English language articles published after 2000 up until 2018 were included. Exceptions to this were only in cases of widely cited literature in the bibliographies of other original research.

Results

After an exhaustive search of the literature, most articles found were retrospective reviews of patients with head and neck cancer and very few were prospective, leading to a large selection bias in the literature. Secondly, a significant proportion of the original research did not compare two treatment strategies. If there were two comparison groups, then it was often the case that PNI was not the only major difference between the arms, thus potentially confounding the data (Table 33.2). Furthermore, the definition of PNI was not uniform throughout the research. Some studies grouped all forms of neural invasion into PNI while others differentiated between perineural and intraneural invasion, while others separated large vs small nerve involvement [5, 8, 10]. Rarely were different cancer subtype categories together in any single study. Cutaneous squamous cell carcinoma (cSCC) was reported separate from salivary gland carcinoma as well as mucosal squamous cell carcinoma (mSCC). This division of cancer type is pertinent since their surgical treatment strategies are incongruent and the pathology and prognosis of PNI also variable. Thus, the following sections are grouped by cancer subtype within the head and neck.

Table 33.2 Summary of the current literature on head and neck cancer and PNI treatment

Study	Patients	Groups	Type of study	Major finding	Quality of evidence
Salivary gland carcinoma					
Chen et al. [31]	140	Sx ± PORT	Retrospective	No difference ± PORT	Low
Hsieh et al. [33]	91	Sx and PORT ± Chemo	Propensity match	Better LRC with adjuvant chemotherapy	Low
Chen et al. [32]	140	Sx ± PORT	Retrospective	PORT resulted in reduced skull base recurrence	Low
Cutaneous squamous cell carcinoma					
Panizza et al. [28]	21	Sx ± PORT	Retrospective	No direct comparison made	Very low
Leibovitch et al. [1]	44	Sx ± PORT	Retrospective	No direct comparison made	Very low
Mucosal squamous cell carcinoma					
Chinn et al. [21]	20	Sx ± PORT	Retrospective	Better LRC with PORT	Low
Liao et al. [20]	68	Sx ± PORT	Retrospective	No difference in DFS and OS	Low
Chatzistefanou et al. [5]	39	Sx ± PORT	Retrospective	No difference in DFS and OS	Low
Argiris et al. [19]	67	Sx and PORT ± Chemo	Prospective trial	No difference in DFS and OS	Low

Table key: *Sx* surgery, *PORT* post operative radiation therapy, *Chemo* chemotherapy, *LRC* locoregional control, *DFS* disease free survival, *OS* overall survival

Mucosal Squamous Cell Carcinoma

Perineural invasion in squamous cell carcinoma of the aerodigestive track is found less often than in salivary gland malignancies but more often than cSCC. The proportion of mSCC of the head and neck with PNI is about 13–30% [2, 4, 6, 11]. PNI has been shown to be predictive of worse outcomes [2, 6, 7]. Thus, the mainstay of therapy for mSCC is surgical excision with PORT for aggressive tumor features [12, 13]. The survival benefit of adjuvant radiotherapy and chemotherapy for aggressive tumor features was seen in two 2004 publications from the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [11, 14, 15]. In the RTOG 9501 trial, the addition of chemotherapy to post-operative radiotherapy (PORT) for patient with extracapsular extension, positive margins, or extensive nodal disease had a significant survival benefit [15]. In the EORTC 22931 trial, a different set of aggressive features was assessed, including PNI. The addition of chemotherapy with PORT lead to significantly superior locoregional control and overall survival [11]. Both

studies though did not contain a subgroup analysis to assess specific aggressive features. A further comparison study goes on to discuss that while the addition of chemotherapy to PORT confers greater disease-free and overall survival for patients with aggressive features, "inferences about the entire group need to be considered" and not taken individually [14]. The assumption that the EORTC 22931 trial makes, is that the presence of PNI confers a worse outcome and thus PORT is indicated, without any evidence that it is effective in combating the potential worse outcomes it is associated with.

In contradiction to the notion that PNI presence is a poor prognostic factor, there is some evidence to suggest that PNI is not predictive of outcomes but rather its frequent occurrence with other adverse features is confounding [16, 17]. As an example, patients with N+ disease have a higher proportion of PNI which can often be a confounder [4]. Although, as recognized in Tai et al. patients with an clinical N0 neck had a survival benefit with elective neck dissection if PNI was present, suggesting that the disease can be managed surgically without the need for adjuvant radiation or chemotherapy.

With regard to direct comparative literature, there have been a few studies that have difference in outcomes in patients with PNI. Ferris et al. performed a Phase II trial adding panitumumab to adjuvant radiotherapy and cisplatin to patients with at least one high risk factor and demonstrated that the addition improves progression free and overall survival [18]. In a similar fashion, Argiris et al. performed a phase III trial adding carboplatin to adjuvant radiation therapy in high-risk head and neck mSCC but conversely found no disease-free survival benefit and questionable overall survival benefit [19].

Focusing on the role for adjuvant radiotherapy in patients with PNI, Liao et al. retrospectively reviewed 68 patients with T1-3 and N0 mSCC of the oral cavity [20]. They compared PORT to no adjuvant treatment and found that there was no significant difference in disease free and overall survival between the groups. While not the focus of the article, Chatzistefanou et al. showed patients with PNI did not have a reduction in recurrence if they received PORT [5]. In contrast to these two articles, Chinn et al. demonstrated in a small cohort of 88 people, patients with PNI+/N0 disease had better disease-free interval and LRC with PORT compared to those who did not [21]. Unfortunately, this is the extent of the comparative data to date and large, controlled prospective trials are lacking. A possible reason for the discrepancy between studies include the selection bias, which is inherent in retrospective reviews. Difference in PNI definition may also account for some of the differing outcomes, with some studies such as Chinn et al. potentially utilizing a stricter definition of PNI [21]. To summarize, for patients with mSCC, there is limited evidence directly comparing PORT vs no therapy in patients with PNI. Chinn et al. demonstrated in a small retrospective group that the addition of RT after surgery improved disease-free interval and LRC, however overall survival and disease specific survival was not different [21]. Conversely, Chatzistefanou et al. did not see a benefit to LRC with PORT [5]. A similar outcome was seen in Liao et al. for isolated oral cavity mSCC [20]. The addition of carboplatin did not significant affect LRC or overall survival in Argiris et al.,

however this may be due to low sample size and low power [19]. Overall, the data concerning use of adjuvant therapy regimen and its effect on locoregional control and survival for perineural invasion in mucosal SCC is of low to moderate quality.

Post-operative radiotherapy for perineural invasion in mucosal head and neck squamous cell carcinoma should be utilized (quality of evidence moderate; conditional recommendation).

Cutaneous Squamous Cell Carcinoma

For patients with cSCC of the head and neck, PNI is estimated to occur in 10–20% of patients [1, 22]. Nerve involvement can be classified if it presents incidentally on histopathologic analysis vs clinically. Clinical nerve involvement is described as a motor or sensory weakness related to the primary tumor [23]. The most common large nerves affected in the head and neck are the trigeminal and facial nerves [24]. Similar to other subsites, the presence of PNI indicates a more aggressive tumor biology with cancers for a worse prognosis. Patients with PNI tend to have worse overall and disease-free survival when compared with their PNI-free counterparts [25]. This may be due to PNI often being found in conjunction with other aggressive features such as recurrent tumors, high grade tumors, larger tumors, and midface locations [1, 24]. Clinical nerve involvement also confers a worse prognosis when compared to incidental PNI with regard to LRC and survival [8, 9, 23, 26]. Another feature of PNI which is concerning is the possibility for 'skip lesions', i.e. presence of distant nerve involvement outside of the resected sample but undetected to the practitioner when the cancer has been resected with a negative margin. Concern for this phenomenon is sometimes used as a rationale for some practitioners to justify use of adjuvant therapy. Recent work though is starting to cast doubt on the idea of skip lesions. Panizza et al. found that in 51 patients with prior clinical evidence of perineural involvement in cutaneous squamous cell carcinoma, histopathological analysis showed that the perineural spread was contiguous, and no skip lesions were found [27].

Despite the plethora of research on cSCC, there are no current, large, prospective trials on post-operative treatment for PNI. Original research which directly compares post-operative treatment to no post-operative treatment are smaller retrospective studies. In another study by Panizza et al. patients with clinical nerve involvement were monitored prospectively [28]. However, only 21 patients were studied and the majority received PORT thus no significant comparison group was established. In Leibovitch et al. 44 patients were identified as having PNI, some of whom went on to receive PORT [1]. However, there were not enough patients to provide a comparison between the two groups. Overall patients did well with a local control rate of about 93% at 5 years regardless of PORT.

Unlike salivary gland carcinoma and mSCC treatment, the method of surgical excision for cSCC may also plays a roll in outcomes. Microsurgical excision may be superior to standard surgical excision in preventing local and regional recurrence [29]. Although, this is only if PNI is closely assessed during the microsurgical procedure. However, the data is still not present to say strongly one way or the other whether PORT should be given. Overall, PNI is still a marker of aggressive tumor biology and patients may benefit from more aggressive treatment strategies which include a post-operative therapy regimen.

For cutaneous squamous cell carcinoma of the head and neck, we recommend the use of adjuvant radiotherapy in patients with perineural invasion (quality of evidence-very low; weak recommendation).

Salivary Gland Carcinoma

In patients with salivary gland carcinomas, PNI is more common, especially in those patients with adenoid cystic carcinoma (ACC) where the PNI rate can be from 48–83% [3, 30]. Similar to the existing data for cutaneous squamous cell carcinoma, there is variability in the definition of PNI, which can complicate its prognostic value. However, as with squamous cell carcinoma, PNI is felt to be a predictor of worse prognosis and is still often treated as an aggressive tumor feature, with PORT. While salivary gland malignancies can be extremely variable depending on the tumor location and histologic subtype, the major of research regarding PNI, its prognosis and treatment has been carried out in ACC.

In the literature, there are a few retrospective articles which directly address the benefit of adjuvant therapy after surgical excision and the data is mixed. In Amit et al., a retrospective review from a pooled multicenter cohort of patients was performed of 495 patients with adenoid cystic carcinoma, 239 of which had some form of nerve involvement [30]. This was defined as PNI, perineural inflammation, and intraneural nerve invasion. Multivariate Cox regression modeling was performed, and it was shown that intraneural nerve invasion but not PNI was predictive of worse overall and disease specific survival. PNI alone was not associated with other adverse histopathological characteristics.

In another retrospective study, Chen et al. reviewed 140 patients with ACC and compared outcomes based on whether they received post-operative radiotherapy or not [31]. Perineural invasion and major nerve invasion were predictive of worse local control in patients receiving surgery only. PNI was not predictive of local control in patients who received PORT. While there were no direct comparisons between PNI+ and PNI− groups, the conclusion that was reached was that PORT negated the increased risk of local failure in patients with PNI because it was not predictive of local failure in the group that received PORT. A possible further finding in support of this were that 40% of patients who had surgery only had local failure compared to only 12% of patients with PNI who received surgery and

adjuvant radiation. This comparison however was not evaluated statistically and thus conclusions drawn from it are speculative. A later study by Chen et al. also found that patients with salivary gland malignancies and PNI had a lower rate of skull base recurrence than patients who did not undergo adjuvant radiotherapy (5% vs 15%, p = 0.03) [32]. Lastly, Hsieh et al. performed a propensity score matching study of patients with ACC and PNI and found that the addition of concurrent chemotherapy to PORT regimens improved locoregional control but not overall survival [33]. Thus, for patients with salivary gland malignancies, PNI appears to be predictive of loco-regional recurrence. However, this effect may be diminished if frank nerve involvement is separated from PNI, a detail which many articles fail to distinguish. The addition of adjuvant radiotherapy and possibly chemotherapy to patients with ACC and PNI likely improves LRC.

For patients with salivary gland adenoid cystic carcinoma ACC and PNI, postoperative adjuvant therapy is recommended to reduce locoregional (quality of evidence low; conditional recommendation).

A Personal View of the Data

Despite the overall lack of quality evidence for PORT, it is widely recommended and prescribed for patients with head and neck cancer patients with PNI. This is likely due to the practitioners being hesitant to de-escalate care based on limited information and a desire to give patients the highest chance of cure. The benefit of the studies discussed in this chapter, is that they can be used to create a framework from which to design a clinical trial to further assess the question of adjuvant therapy for PNI. While randomized prospective data is most revered, a clinical trial of this nature would be difficult to achieve given the overall scarcity of head and neck cancer patients with appropriate early stage disease and PNI without confounding adverse histopathological features that would result in the use of adjuvant therapies. A matched prospective case-control design would be the most influential and informative next step which could potentially circumvent the lower incidence rates. Lastly, there needs to be increased standardization regarding the definition of PNI. Further delineating clinical vs histopathological PNI and studying outcomes based on these will provide more clarity on the subject.

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