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