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REVIEW ARTICLE

Role of surgery in the management of head and neck cancer: a contemporary view of the data in the era of organ preservation

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Abstract

Objective: Review of the literature on the role of surgery in the management of head and neck cancer in the era of organ preservation.

Method: Literature search based on the essential practice guidelines set out by the US National Comprehensive Cancer Network.

Results: Despite the increasing popularity of non-surgical treatment options, the surgeon remains a key figure in the multidisciplinary head and neck cancer team, along with the radiation oncologist, the medical oncologist and the speech and swallowing therapist. Even when organ preservation is successful, early and late toxicity may cause serious complications, including laryngeal dysfunction with a 'frozen larynx'. When organ preservation fails, salvage surgery is often associated with increased complications and reduced survival.

Conclusion: There is a definite need to apply more rigorous standards to the use of organ preservation strategies, and to re-evaluate the role of surgery in head and neck cancer treatment.

Key words: Head And Neck Neoplasms; General Surgery; Organ Preservation; Survival

Introduction

Based on 2005 cancer statistics, head and neck cancer is the fifth most common cancer worldwide, with an estimated global incidence of 644 000 cases per year.[1] In Europe, the annual incidence of new head and neck cancer cases is 76 000.[2] More than 90 per cent of head and neck cancers are squamous cell carcinomas (SCCs), mainly originating in the larynx, pharynx and oral cavity.

Over the past decade, the incidence of cancer at the base of the tongue and the tonsils has increased especially in younger patients.[3] Besides alcohol and tobacco, various DNA types of human papilloma virus have changed the risk profile, and have recently emerged as an important aetiological factor for oral carcinogenesis.[4] In the USA, the data registries of the Surveillance, Epidemiology, and End Results Program and the National Cancer Data Base have been useful for evaluating these changes.

At the time of diagnosis, more than 50 per cent of all head and neck SCC cases present with advanced stage III or IV disease, and 15 per cent are already inoperable.[5] Until recently, various studies had reported five-year survival rates of less than 30 per cent for patients with stage IVA/B tumours, and of 40 per cent for patients with locally advanced stages.[6–8]

In the past, surgery represented the accepted standard of care for the curative management of advanced head and neck SCC, followed by adjuvant radiotherapy in cases with advanced tumour (T) stages or positive lymph nodes. Laser surgery has helped to facilitate organ and function preservation, even though overall survival rates have hardly improved significantly.

However, the past three decades have witnessed a change in the treatment of head and neck SCC, with increased use of non-operative treatment modalities and a corresponding decrease in the use of primary surgery.[9] Many authors attribute this trend to the publication of a randomised, controlled, clinical trial by the US Veterans Affairs Laryngeal Cancer Study Group.[10] This landmark study launched the sequential combination of induction chemotherapy followed by either irradiation or surgery, and demonstrated that organ preservation can be obtained in patients with advanced laryngeal cancer by the use of chemoradiotherapy (CRT), without reducing survival; these

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patients would otherwise have undergone total laryngectomy. This study has had a major impact on clinical practice, and the use of CRT has increased for all head and neck SCC patients.[9,11] Nowadays, CRT is widely accepted as a primary treatment option for advanced head and neck SCC, in an attempt to achieve organ preservation.

However, a review of laryngeal cancer data from the US National Cancer Data Base, published in 2006 by Hoffman and co-workers, indicated that this uncritical approach requires serious scrutiny and re-analysis.[12] These data revealed a decrease in laryngeal cancer patient survival in the years immediately preceding the study, coinciding with an observed trend towards increased use of non-operative treatment modalities, which was not due to an increased incidence in advanced-stage disease. Thus, the legitimate role of surgery in the management of head and neck SCC needs to be re-evaluated.

The current paper presents a contemporary review of the literature based on the essential practice guidelines set out by the US National Comprehensive Cancer Network, which suggest an evidenced-based treatment algorithm for the management of early- and advanced-stage head and neck SCC.[13]

Practice guidelines of the National Comprehensive Cancer Network

According to the National Comprehensive Cancer Network guidelines, early-stage head and neck SCC (i.e. stages I and II) is best treated by one modality alone: either surgery or radiotherapy.[13,14] Surgery has the advantages of: (1) providing the treatment team with a precise tumour histology; (2) achieving effective local tumour control, even if there is possible compromise in function and aesthetics; and (3) avoiding irradiation in cases with recurrence.[9,11] Primary radiotherapy might be equally effective, especially in early-stage laryngeal tumours. However, the surgeon must seriously consider the risk of long-lasting side effects such as xerostomia, dysgeusia, tissue fibrosis and osteoradionecrosis.

For more advanced head and neck SCC (i.e. stages III and IV) with regional spread or aggressive growth, a combination of surgery and CRT is recommended. Such multimodality treatment is nowadays considered the accepted standard of care for advanced-stage head and neck SCC.[13] The impact of surgery on organ function is related to the tumour size and the primary tumour site; some cases require reconstruction after extensive resection. The surgeon's decision of whether to pursue primary surgery (with or without reconstruction) followed by CRT, versus induction CRT with the option of salvage surgery for treatment failures, remains controversial, and depends on many factors such as resectability, local expertise, goals of organ preservation and patient preference.[9] Various studies have reported poor outcomes for salvage surgery undertaken following the failure of primary concomitant CRT, with complications including wound breakdown or necrosis, mucocutaneous fistula, and dysphagia.[14]

However, a review of the literature suggests that, even in the current era of organ preservation, surgery plays an essential part in multimodality treatment. It enables (1) significantly better local tumour control, (2) rehabilitation of function after surgical reconstruction, and (3) reduced CRT toxicity even in cases of tumour debulking.[9] In contrast, although concomitant CRT might have the advantage of better long-term control, this comes at the cost of early and late toxicity.

Oral cavity and oropharynx

Early stage (I and II)

In most centres, primary surgery remains the accepted standard of care for most patients with cancer of the oral cavity or oropharynx.

In 2007, a large, retrospective study of the outcome of surgery in oral cavity cancer patients was published in Finland by Mäkitie *et al.*[15] Between 1995 and 1999, these authors analysed data on 235 patients, including results from a five-year follow-up period. In their literature review, these authors concluded that, especially in early-stage disease, surgery remained the standard treatment, providing the treatment team with precise histological information including depth of tumour infiltration.[16,17]

Similar surgical results have been described by Walvekar *et al.* for oropharyngeal cancer treated with primary surgery, namely, a general local control rate of 88 per cent and a five-year overall survival rate of 83 per cent.[18] The number of failures depended on local and regional metastasis at the time of diagnosis.

According to the National Comprehensive Cancer Network guidelines, early-stage oropharyngeal cancer can be treated with equal efficacy by single treatment alone – either primary surgery or radiotherapy – with adjuvant radiation therapy reserved for advanced pathological features such as loco-regional failure, nodal involvement, second primary tumours or perineural invasion.

O'Hara and McKenzie assessed surgical versus non-surgical procedures in the treatment of early-stage oropharyngeal cancer.[19] Bearing in mind the shift towards primary chemoradiation, these authors aimed to determine whether surgery was still indicated for early-stage oropharyngeal disease. In their study, the surgery group had a five-year overall survival rate of 60 per cent and a disease-specific survival rate of 69 per cent, whereas the primary radiotherapy group had a five-year overall survival rate of 50 per cent and a disease-specific survival rate of 60 per cent. Even though there was no statistically significant difference in disease-specific survival between the surgery and radiotherapy groups, the authors regarded primary surgery as a more favourable option in early-stage,

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node stage (N) 0 cases which could be treated by a single modality therapy.

As Gourin and Johnson have pointed out, the main drawback of primary surgery is post-operative morbidity with regard to speech and swallowing; however, such surgery has the advantage of avoiding radiation and CRT, and of permitting reduced radiation doses in the post-operative setting.[9]

Table I summarises published findings on surgical and non-surgical outcomes for early-stage oropharyngeal disease.[20,22,24–28] Primary external radiation or brachytherapy has not been recommended as the treatment of choice for early oral cavity carcinoma, as it usually causes long-term morbidity and carries the risk of major side effects such as lifelong xerostomia, temporary or permanent dysgeusia, advanced dental caries, soft tissue fibrosis, and osteoradionecrosis.[25] Moreover, in most cases radiotherapy can be offered only once at radical therapeutic doses of 66–72 Gy, and significant functional morbidity may also occur because of acute and late toxicity associated with radiotherapy or CRT.[18]

Advanced stage (III and IV)

In patients with more advanced tumour stages (i.e. T_3 or T_4 plus N_0, or any T stage plus N_+), the five-year overall survival rate varies between 30 and 60 per cent. In patients with distant metastasis, the five-year survival rate drops to 5 to 10 per cent.[26] In general, surgery should be considered to be the accepted standard of care for advanced oral cancer, with concurrent CRT.[27] The risk of occult cervical metastasis increases at advanced tumour stages. Therefore, the patient requires not only local tumour resection but also elective neck dissection for occult cervical lymph node metastasis. In a multimodality treatment setting, surgery is highly effective in achieving loco-regional control compared with CRT alone, which might be able to control distant metastasis but has worse outcomes as regards local control, and which does not necessarily reduce the incidence of severe dysphagia in patients with oropharyngeal cancer.[28,29] Bernier *et al.* have suggested that the use of combined CRT after surgery offers improved progression-free survival and reduced loco-regional relapses, compared with adjuvant radiation alone.[30] It is important to consider that the risk of early and/or late toxicity is greater for patients receiving radiation doses of 70 Gy or more as their primary CRT regimen, compared with an adjuvant CRT regimen with a radiation dose of 60 Gy.

Hypopharynx

Early stage (I and II)

Hypopharyngeal cancer is associated with the poorest survival of all head and neck cancers, as tumours in this region generally remain silent until the disease has reached an advanced stage. At the time of diagnosis, neck metastasis is seen in more than 65 per cent of patients, and more than 75 per cent present at a locally advanced stage. Occult nodal disease is generally present in 30–40 per cent.[8,26,31] Patients with early-stage disease (i.e. T_1–T_2 and N_0–N_1) have a five-year overall survival rate of 70–90 per cent.[26,32]

In 2010, members of the International Head and Neck Scientific Group published a study on recent trends in the management of hypopharyngeal cancer.[33] Although emphasis has shifted to non-surgical treatments over the past few years, surgical procedures still play a key role in hypopharyngeal cancer therapy, not only as an option for initial treatment but also for salvage, tumour surveillance, and management of complications and functional impairment. As indicated by our literature review (see Table II) and recommended by the National Comprehensive Cancer Network guidelines, early stage I or II hypopharyngeal disease can be treated either with surgery or with radiation therapy.[13,34–43] Regarding perilymphatic invasion and angioinvasion, surgery has the advantages of providing exact histological information and assisting the decision on whether adjuvant treatment is necessary or not.[9] Local control rates for early-stage disease range from 77 to 89 per cent, with five-year disease-specific survival rates of up to 69 per cent.[34,44–46] Gourin and Terris have advocated

TABLE I
OVERVIEW OF RECENT STUDIES ON THE SURGICAL (1–4) AND NON-SURGICAL (5–6) OUTCOME OF EARLY-STAGED OROPHARYNGEAL CANCER.

Study site and year	Tumor site and stage	Treatment	*n*	OS (%)	DSS (%)	LC (%)	LRC (%)
1. Zürich 2009 (1990–2006)[21]	All sites, Stage I and II	Surgery, all transoral	53	ND	81	ND	ND
2. France 2004 (1995–2000)[22]	All except base of tongue Stage I and II	Surgery, mainly transoral	53	73	100	ND	89
3. Pittsburg 2000 (1981–1995)[23]	Tonsil, Stage I and II	Surgery, mainly transoral	30	ND	90	ND	ND
4. Pittsburg 2008 (1984–2004)[22]	All sites, Stage I and II	Surgery	49	ND	83	ND	ND
5. France 1989 (1970–1982)[24]	Tonsil, T1-2 no tumor stages given	RT alone	193	58	–	88 T1	–
					–	79 T2	–
6. Florida 2006 (1964–2004)[20]	Tonsil, all stages	RT alone	503	53	–	88 T1	66 Stg I
					–	84 T2	75 Stg II

OS (%): 5-years overall survival rate, DSS (%): disease-specific survival rate, LC: local control rate, LCR: locoregional control rate, ND: no data, RT: radiotherapy, Stg: stage

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TABLE II
TREATMENT OUTCOMES FOR HYPOPHARYNGEAL CANCER: RECENT STUDIES

Treatment	Study	Pts (*n*)	OS (%)		DSS (%)	
			3-y	5-y	3-y	5-y
TLP	Krause *et al.*[34]	132	30	ND	41	ND
	Bova *et al.*[35]	180	33	ND	52	ND
	Ogura *et al.*[36]	57	ND	36	ND	ND
Partial surgery	Chevalier *et al.*[37]	48*	47	ND	ND	ND
	Mekeieff *et al.*[38]	87*	60	ND	ND	ND
Laser surgery	Steiner *et al.*[32]	129	71 stage I & II	ND	95 stage I & II	ND
			47 stage III & IV	ND	69 stage III & IV	ND
	Martin *et al.*[39]	172	68 stage I & II	ND	96 stage I & II	ND
			64 stage III	ND	85 stage III	ND
Radiotherapy	Godballe *et al.*[40]	101	16	ND	28	ND
	Rabbani *et al.*[41]	123	35	ND	61	ND
CRT	Lefebvre *et al.*[42]	100	ND	57	25	43

*Tumour stage I and II. Pts = patients; OS = overall survival; DSS = disease-free survival; y = year; TLP = total laryngopharyngectomy; ND = no data; CRT = chemoradiotherapy

surgery as a primary treatment option in early-stage hypopharyngeal cancer as second primary tumours are seen in 10 per cent of cases, often necessitating non-operative treatment which cannot be used if applied initially as primary therapy.[46]

Advanced stage (III and IV)

Patients with advanced hypopharyngeal cancer have the poorest survival of all head and neck SCC patients, and advanced hypopharyngeal disease is associated with a high incidence of medical comorbidity and poor nutrition.[26,33] In the literature, the reported five-year overall survival rate for T_2 to T_4 disease plus any N stage varies between 15 and 30 per cent.[26,40] The poor survival of hypopharyngeal cancer patients is attributed to their late presentation with usually advanced disease, but is also due to the disease's higher affinity for regional lymph node metastasis.

In the 1970s and 1980s, the accepted standard of care for advanced hypopharyngeal carcinoma was radical resection and reconstruction followed by post-operative radiotherapy.[47,48] Overall survival rates reported from different centres worldwide ranged from 20 to 48 per cent.[44] In recent years, organ preservation programmes (including sequential or concomitant chemoradiation) have had a major impact on the treatment of hypopharyngeal carcinoma.[13] Various studies have shown that, with chemoradiation, laryngeal preservation is feasible.[49] In patients who responded to chemotherapy and who were given post-operative radiotherapy, 60 per cent had their larynx preserved.[50] However, as stated by Wei, a laryngeal preservation protocol is only applicable when the patient responds to chemotherapy and completes the entire treatment regimen.[43] In hypopharyngeal cancer patients for whom organ preservation fails, salvage surgery is associated not only with an increased complication rate and low success rate, but also with an extremely low chance of larynx preservation.

When considering the issue of organ preservation, one should especially bear in mind the findings of the only randomised, prospective, phase III trial to investigate the role of CRT in hypopharyngeal cancer, which was conducted by the Head and Neck Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer.[42] In this study, patients with T_2–T_4 disease who required total laryngectomy were randomised to receive either induction chemotherapy followed by definitive radiotherapy, or surgery followed by post-operative radiotherapy. The study found no significant difference between the CRT arm and the surgery–radiotherapy arm in regard to local or regional recurrence or five-year disease-free survival. The larynx preservation rate at five years was low, with only 17 per cent of patients treated with CRT alive and laryngectomy-free.

A critical issue is the fact that the terms 'organ preservation' and 'larynx preservation' are not always defined clearly. Organ preservation should not be confused with function preservation. In hypopharyngeal cancer, function includes both voice and swallowing. According to Takes *et al.*, function may even be better preserved after removal of the larynx, as this facilitates aspiration-free deglutition and the use of a prosthetic voice, rather than leaving intact a functionless, 'frozen' larynx.[33] Samant *et al.* reported that up to 30 per cent of their patients with pyriform sinus carcinoma were unable to swallow after the completion of aggressive CRT.[51]

Another important concern regarding concomitant CRT is toxicity.[52] Adelstein *et al.* reported a 74 per cent incidence of moderate to severe acute toxicity in patients receiving combined modality treatment, with a higher incidence of acute grade 3 and 4 toxicity, significant mucositis, and myelosuppression.[50,52] In contrast, Pearson *et al.* have demonstrated that surgical reconstruction, even after extensive resection involving total laryngopharyngectomy, enables the

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restoration of solid or soft diet in over 90 per cent of patients.[53]

Larynx

Early stage (I and II)

Laryngeal cancer at the glottis has a different metastatic behaviour from cancer affecting the supraglottis, oral cavity and pharynx. Glottic cancer is well differentiated, grows slowly and metastasises late. This is due to the limited lymphatic drainage of the true vocal folds. Whereas supraglottic cancer has a metastasis prevalence of up to 50 per cent in neck levels II to IV, glottic cancer has a metastasis rate of only 10 per cent.[26]

Early stage (i.e. I or II) laryngeal cancer responds well to either surgery or radiation alone, with similar functional and oncological outcomes.[13] Surgical techniques for supraglottic and glottic cancer comprise partial laryngectomy or minimally invasive laser surgery. Published results indicate that surgery can obtain local tumour control in 82–100 per cent of patients, with larynx preservation in 87–100 per cent of those. Following primary radiation therapy, local tumour control rates of 61–93 per cent and larynx preservation rates of 73–98 per cent have been reported.[54] Tumour control and overall survival tend to be significantly better after surgery than after radiotherapy; however, voice rehabilitation is reported to be better after radiation (Table III).[55–63]

Advanced stage (III and IV)

Over the past few decades, the treatment regimens for pharyngeal and laryngeal cancer have shifted from traditional, radical surgery to less destructive, larynx-preserving surgery.[13] The latter approach was notably launched by a landmark study from the US Veterans Affairs Laryngeal Cancer Study Group.[10] This randomised, controlled, clinical trial demonstrated that, in patients with advanced laryngeal cancer (who would otherwise have undergone total laryngectomy and post-operative radiotherapy), organ preservation with CRT could be performed without reducing survival. The authors emphasised that the rate of larynx preservation was much higher in the chemoradiation arm (64 per cent) than in the surgery arm. The local recurrence rate was worse in patients receiving CRT compared with those receiving surgery plus radiotherapy, but the distant recurrence rate was much better.

In 2003, another landmark study, involving 547 patients, was published by Forastiere *et al.* of the Radiation Therapy Oncology Group.[64] This three-armed treatment study evaluated the effect of (1) concurrent CRT, versus (2) induction chemotherapy followed by radiotherapy, versus (3) radiotherapy alone, as regards organ preservation in advanced laryngeal cancer. Two years after treatment, larynx preservation was best in the concurrent CRT group (88 per cent), compared with 75 per cent in the induction chemotherapy plus radiation group and 70 per cent in the radiotherapy group. Similar results were obtained for local control rates. Based on the results of trial 91-11 of the Radiation Therapy Oncology Group, induction CRT regimes were replaced by concurrent CRT regimes, and became a widely accepted primary treatment regime for advanced head and neck SCC.[65]

However, according to the 2006 American Society of Clinical Oncology clinical practice guidelines, this larynx-preservation approach is only appropriate for advanced T_3 and T_4 cancers without tumour invasion into the cartilage or adjacent soft tissue structures.[66] Special expertise and multidisciplinary team input (including head and neck surgeons) are necessary to estimate the likely advantages and disadvantages of larynx-preservation options.[11,13,43,66]

Furthermore, non-surgical treatment regimes increase the rate of early and late toxicity. Totti *et al.* demonstrated that, in patients receiving CRT for head and neck cancer, mucositis was an inevitable and severe form of acute toxicity, with consecutive weight loss causing substantial morbidity and necessitating hospitalisation for feeding tube placement and intensive supportive care.[67] The mere presence of a preserved larynx after non-surgical treatment does not always ensure laryngeal function. Machtay and co-workers rightly emphasised that exposure to chemotherapeutic agents and radiation produces many co-factors for severe late toxicity, depending on patient age, tumour stage and tumour site.[68] Their study analysed a subset of three previously reported Radiation Therapy Oncology Group trials of concurrent CRT for locally advanced head and neck SCC, with special emphasis on severe late toxicity effects. Typical radiation-related toxic effects were xerostomia, osteoradionecrosis and continued speech disturbance, with post-treatment oedema and fibrosis resulting in dysphagia and hoarseness. The most common chemotherapy-related toxic effects were ototoxicity,

TABLE III
TREATMENT OUTCOMES FOR EARLY-STAGE GLOTTIC CANCER: RECENT STUDIES

Study	Pts (*n*)	T stage	LRC (%)	LP (%)	Ca death (%)
Eckel *et al.*[55,56]	161	T_1	87	94	ND
	93	T_2	82	93	ND
Ambrosch *et al.*[57]	248	pT_{1a}	92	99	ND
	35	pT_{1b}	80	94	ND
	128	pT_2	84	96	ND
Motta *et al.*[58]	432	T_1	85	97	ND
	236	T_2	66	83	ND
Sjögren *et al.*[59]	189	T_{1a}	89	96	ND
Peretti *et al.*[60]	404	pT_1	95	98	ND
	109	T_2	86	95	ND
Mendenhall *et al.*[61]	291	T_1	93	95	2
	146	T_2	80	82	4
Johansen *et al.*[62]	482	T_1	85	89	ND
	228	T_2	61	74	ND
Smeet *et al.*[63]	356	T_1	83	ND	5
	142	T_2	72	ND	15

Pts = patients; T = tumour; LRC = loco-regional control; LP = larynx preservation; Ca death = cancer-related death; ND = no data; p = pathologically determined

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nephrotoxicity, neurotoxicity and lung fibrosis, necessitating prolonged hospitalisation.[67,68]

Conclusion

There is a definite need to apply more rigorous standards to the use of organ preservation strategies for head and neck SCC treatment, and to re-evaluate the role of surgery. Despite the increasing popularity of non-surgical treatment regimes, primary surgery plays an important role in head and neck SCC therapy. The surgeon remains a key figure in the multidisciplinary team, along with the radiation oncologist, the medical oncologist and the speech and swallowing therapist. Even when non-operative treatment is successful, the risk of early and late toxicity (including laryngeal dysfunction and 'frozen larynx') must be taken into serious consideration. When non-operative organ preservation approaches fail, salvage surgery is often associated with increased complications and reduced survival.

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