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HEAD AND NECK

Long-term outcome analysis after surgical salvage for recurrent tonsil carcinoma following radical radiotherapy

Gideon Y. Bachar · Christopher Goh · David P. Goldstein · Brian O'Sullivan · Jonathan C. Irish

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Abstract The objective of this study is to report the long-term outcomes of salvage surgery following local and/or regional failure of tonsillar carcinoma treated with standard fractionation radiotherapy. All cases of carcinoma of the tonsil treated by radical radiotherapy at the Princess Margaret Hospital between January 1970 and December 1990 were reviewed retrospectively. Patients who underwent salvage surgery for local and/or regional recurrent squamous cell carcinoma of the tonsil following radiation therapy were included for analysis. 239 out of 640 patients with tonsillar carcinoma recurred post radiotherapy. 175 patients were deemed candidates for surgical salvage. At the time of the last follow-up, only 13 patients were alive and 162 patients had died. The majority of patients ($n = 96$, 59%) died with disease. The median time to death was approximately 1.3 years following salvage surgery. The 5-year overall survival rate was 23%. The 5-year cause-specific survival was 40%. The probability of death due to disease was higher than the probability of death due to other causes. Both N-classification and T-classification were found to be significant predictors of time to death. In conclusion, in spite of the fact that the patients in this study had been treated prior to the widespread introduction of altered fractionation and concurrent chemoradiation for advanced tonsil carcinoma, it demonstrates the poor prognosis of recurrent disease. Despite the poor prognosis, 20% of patients will be alive at 5 years and therefore salvage surgery should be considered when possible.

Keywords Tonsillar carcinoma · Salvage · Surgery · Radical radiotherapy · Outcome

G. Y. Bachar (✉) · C. Goh · D. P. Goldstein · J. C. Irish
Department of Otolaryngology—Head and Neck Surgery, Princess Margaret Hospital, University of Toronto, 610 University Av 3-954, Toronto, ON M5G2M9, Canada
e-mail: gidybahar@gmail.com

G. Y. Bachar · C. Goh · D. P. Goldstein · J. C. Irish
Department of Surgical Oncology, Princess Margaret Hospital, University of Toronto, 610 University Av 3-954, Toronto, ON M5G2M9, Canada

B. O'Sullivan
Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

Introduction

Tonsillar squamous cell carcinoma (SCC) is the most common oropharyngeal cancer and the second most common malignancy of the upper aerodigestive tract. Patients often present with advanced-stage disease [1]. Early stage tonsil SCC is usually treated with surgery or radiation, both of which show similar locoregional control and survival rates [2]. Treatment approaches for advanced-stage disease include protocols of radiation (altered or standard fractionation) with or without concurrent chemotherapy or molecular targeted agents, neoadjuvant chemotherapy with radiation, or surgery and postoperative radiation. Each treatment modality has its proponents and critics and support for any one of the treatments can be found in the published literature [3–8] with the caveat that case selection of the different options makes comparisons problematic.

Prior to 1990, management of tonsil carcinoma involved standard fractionation radiotherapy. Currently, the management philosophy at the Princess Margaret Hospital is to offer standard fractionation radiotherapy for early stage disease and intensive schedules of radiation (often altered fractionation) with or without concurrent chemotherapy or molecular targeted therapy (i.e., cetuximab) for advanced-stage

disease. Surgery is reserved for salvage of persistent or recurrent-regional disease. This treatment rational is based on the desire to maximize anatomic and functional preservation. Invariably a number of patients will fail treatment and develop local and/or regional recurrence. Salvage surgery is typically the treatment modality of choice for recurrent disease in patients managed primarily with radiation [9]. There is very limited data on long-term outcomes of salvage surgery for tonsillar carcinoma.

The objective of this study is to report the long-term outcomes of salvage surgery following local and/or regional failure of tonsillar carcinoma treated with standard fractionation radiotherapy. While strategies in the management of tonsil carcinoma have changed over the past 10 years with an intensification of treatment, we feel it is important to gain an understanding of outcomes with salvage surgery following standard radiation in order to have a baseline to compare outcomes with the newer techniques.

Materials and methods

All cases of carcinoma of the tonsil treated by radical radiotherapy at the Princess Margaret Hospital between January 1970 and December 1990 were reviewed retrospectively. Patients who underwent salvage surgery for local and/or regional recurrent squamous cell carcinoma of the tonsil following radiation therapy were included for analysis. Patients with recurrent disease treated with palliative intent were excluded. Also excluded were patients who had recurrent disease prior to radiation therapy, previous cancers or synchronous second primary tumors other than cutaneous basal cell carcinomas, and those who had prior head and neck irradiation. Approval was obtained from the institution's Research Ethics Board.

Six hundred and forty patients with carcinoma of the tonsil were treated with radiotherapy with curative intent between 1970 and 1990. 239 (37.3%) developed local and/or regional failure with no distant metastasis. 175 of the 239 (73%) patients were deemed candidates for surgical salvage. 64 patients (27%) were ineligible due to patient co-morbidity, refusal or unresectable disease. Of the 175 surgical candidates, 67 (38.3%) had disease confined to the primary site, 66 (37.7%) had experienced both local and regional failures, and 42 (24.0%) had regional failure only. Pathologic staging was not performed or reported regularly at our institution during this period of time and therefore was not included in this analysis. It is our current practice to stage all recurrences.

Statistical analysis was performed using SAS software. Demographic and treatment related information was summarized using descriptive statistics. Outcomes of interest were overall recurrence rates, time to recurrence, survival, and cause-specific survival. Event times were recorded from the date of initial diagnosis (biopsy date) of the recurrent tumor to either the outcome of interest or date of last recorded follow-up. Patient outcomes were last updated in March 2008. Cause-specific survival and overall survival estimates were determined using the Kaplan–Meier (product-limit) method [10]. The cumulative incidence function was used to determine the probability of any recurrence (local, regional, locoregional) happening by partitioning the probabilities for each type of recurrence. Similarly, cumulative incidence functions were also used to determine the probability of death following salvage surgery. The analysis was carried out using competing risks.

Results

Of the 175 patients with recurrence who underwent salvage surgery, the median age at the time of diagnosis was 60 years with a range from 36 to 85 years. The male to female ratio was approximately 2:1. At initial presentation, T1 lesions were documented in only ten patients. Stages 2 and 3 accounted for the majority of patients (66 and 65 patients respectively), while 34 patients were T4. Regional involvement at initial presentation was found in 162 cases. Based on N classification 60 were N1, 47 were N2 and 5 were N3.

The follow-up time from the date of recurrence after radiotherapy ranged from 1 month to 21.8 years with a mean time of 1.3 years. The mean radiation dose was 52 Gy. 51% of the patients ($n = 90$) received 50 Gy in 20 fractions delivered over 4 weeks. Techniques designed to treat the primary site and the ipsilateral neck (homolateral technique) with curative radiotherapy had been used in 55 patients. In the other 120 patients, both sides of the neck were treated in addition to the primary disease (bilateral technique).

Of the 175 patients with recurrent disease who underwent surgical salvage, 67 were for local recurrence only, 42 for regional recurrence only and 66 for both local and regional recurrence. Table 1 shows the percentage of patients developing local, regional, locoregional recurrence based on time. The majority of patients (63%) who developed local recurrence had advanced local disease (T3/T4) at the time of initial diagnosis. Of the patients who developed regional recurrences only, 89% (39/44) were node positive at presentation.

Of the 108 patients who developed regional recurrences, the majority failed in the ipsilateral neck. Only six patients failed in both necks and four failed in the neck contralateral to the side of the primary. While none of the patients who received bilateral radiation failed in the contralateral neck, four patients treated with homolateral technique failed in the contralateral neck.

Table 1 The percentage of patients developing local, regional, locoregional (LR) recurrence based on time

	Local recurrence only	Regional recurrence only	LR recurrence
Year 1	51 (76%)	33(81%)	60 (91%)
Year 2	12 (18%)	6 (15%)	5 (8%)
Year 3	2 (3%)	1(2%)	1(1%)
Total	67	42	66

Surgical complications

Of the 175 patients who underwent surgical salvage, 7 (4.3%) died from complications related to surgery; 2 from carotid artery rupture secondary to pharyngocutaneous fistula, 2 from pharyngocutaneous fistula, 1 from severe wound infection and cellulitis, 1 from a tongue base hemorrhage and 1 from a stroke. Six of these seven patients had their salvage surgery done before 1984 prior to the introduction of free tissue transfer at our institution.

Survival following salvage surgery

At the time of the last follow-up, only 13 patients were alive and 162 patients had died. The majority of patients ($n = 96$, 59%) died with disease. Cause of death is presented in Table 2. There were 25 patients who developed a second primary tumor, 17 (68%) of which were in the upper aerodigestive tract. Eighteen of these patients died from their second primary. Sixteen (9%) patients developed distant metastasis after salvage surgery, all of which died. Of these patients, 9 (56%) developed distant metastasis within the first year following salvage surgery. The median time to death was approximately 1.3 years following salvage surgery. The 5-year overall survival rate was 23%. The survival rate decreased very quickly within the first year following salvage surgery and continued to decline over the 5-year time period (Fig. 1). The vast majority of deaths occurred within the first 3 years. Table 3 shows the overall survival within the first 5 years following salvage surgery.

Table 2 Causes of death in 162 patients

	Frequency	%
Local disease only	35	21.6
Regional disease only	16	9.9
Locoregional disease	29	17.9
Distant metastasis only	7	4.3
Local and distant disease	3	2.5
Regional and distant disease	2	1.2
Locoregional and distant disease	4	1.9
Treatment complications	7	4.3
New primary tumor	18	11.1
Other causes	24	14.8
Unknown causes	17	10.5

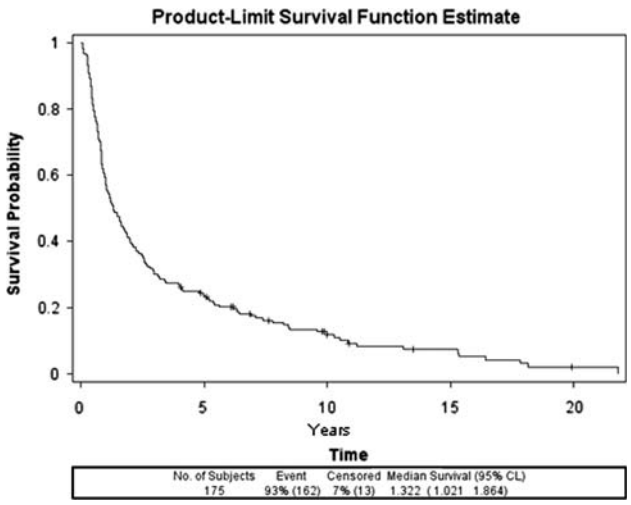

Fig. 1 Overall survival following salvage surgery

The 5-year cause-specific survival was 40%. The probability of death due to disease was higher than the probability of death due to other causes (Table 4; Fig. 2). The median time to death due to disease was approximately 2 years. The probability of death due to disease increased quickly within the first year and continued to increase for the first 5 years following surgery. In contrast, the probability of death due to other causes increased steadily, but at a slower rate, over 15 years following surgery. The 2-year overall survival for patients with local, regional and locoregional recurrence was 48, 35, and 28%, respectively. The prognosis of patients with locoregional recurrence was significantly worse ($p = 0.008$).

Both N-classification and T-classification were found to be significant predictors of time to death ($p = 0.0006$, and $p = 0.02$, respectively). The increasing hazard ratio for the clinical stage suggests that increased stage of disease is associated with increased probability of death. Table 5 shows the overall significance of clinical staging in predicting time to death controlling for T and N classification,

Table 3 Survival rates for the first 5 years following salvage surgery

# Years following surgery	Survival (%)	95% CI
1	58	(51–65)
2	40	(33–47)
3	30	(23–37)
4	26	(20–33)
5	23	(17–30)

Table 4 Probability of cause-specific death for the first 5 years following salvage surgery

# Years following surgery	Cause of death	Probability of death (%)	95% CI (N–A var)
1	Disease	35	(27–43)
	Other cause	9	(5–13)
2	Disease	50	(42–58)
	Other cause	13	(8–18)
3	Disease	55	(47–63)
	Other cause	18	(12–24)
4	Disease	57	(49–65)
	Other cause	20	(14–26)
5	Disease	60	(52–68)
	Other cause	20	(14–26)

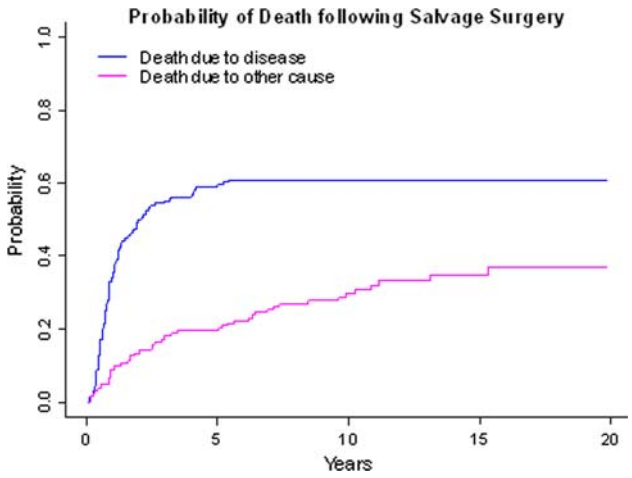

Fig. 2 Probability of death following salvage surgery

Table 5 Cox Proportional Hazards model estimates

Parameter	*p*-value	HR	95% CI for HR
Time to recurrence	0.0980	1.1	(0.9–1.3)
T stage			
T2	0.718	2.1	(0.9–4.8)
T3	0.0345	2.4	(1.1–5.5)
T4	0.0048	3.4	(1.5–8.0)
Ref: T1			
N stage			
N1	0.0654	1.4	(1.0–2.1)
N2	0.0483	1.5	(1.0–2.4)
N3	<0.0001	6.6	(2.8–15.5)
Ref: N0			

with both T and N stage being significant predictors of time to death. There did not appear to be evidence of an association between time to first recurrence and time to death following salvage surgery ($p = 0.28$).

Discussion

In early stage tonsil carcinoma, similar outcomes have been reported with either radiation or surgery [2]. Tumor control rates for primary radiotherapy are of 87% for T1, 70% for T2, 71% for T3, and 44% for T4 lesions [9], this is similar to other studies [6, 11]. The use of radiotherapy or chemoradiation as primary treatment modalities for advanced carcinoma of the tonsil has been well described in the literature [3, 7, 8]. Concomitant chemotherapy and radiotherapy were found to be superior to radiotherapy with improved locoregional control and survival outcome [3]. Unfortunately, a proportion of these patients will fail in spite of adequate treatment.

Recurrences are typically managed with salvage surgery whenever possible. Although the use of re-irradiation with or without chemotherapy for salvage has been reported [12, 13], surgery remains the mainstay of salvage treatment. There is relatively limited data on outcomes of salvage surgery for recurrent tonsil carcinoma following radiation. The objective of the current study was to report outcomes following salvage surgery for recurrent tonsil carcinoma following standard fractionation radiation therapy. The long follow-up in this relatively large study group demonstrated the high mortality rate in patients with recurrent disease despite undergoing salvage surgery. Only 13 of 175 patients who underwent salvage surgery were alive at last follow-up, with the majority of patients dying within the first year after salvage surgery. The median time to death following salvage surgery was short at 1.3 years. The majority of patients died from their disease or from a second primary tumor. The probability of death due to disease was much higher than the probability of death due to other causes. Both T stage and N stage at presentation were significant predictors of time to death. There was no evidence, however, of an association between time to first recurrence and time to death following salvage surgery. Kesler et al. [14] evaluated the results of definitive radiotherapy and salvage surgery for oropharyngeal cancer. Patients were initially treated with external beam RT alone or combined with brachytherapy. Salvage surgery was possible in 32% patients and was successful in 56% of them. Others reported [15] poor survival rates in patients undergoing salvage surgery of recurrent cancer with 1- and 2-year overall survival rates of 60 and 27%, respectively. Wu et al. [16] evaluated the benefit of salvage surgery following radical radiotherapy (60–70 Gy) as compared to preoperative RT (40–50 Gy) with planned surgery. The salvage surgery arm recurred locally in 28% and regionally in 9.6%, with a 5-year survival rate of 59%. The authors stated that a salvage surgery approach avoided 60% of composite resection surgeries compared with radiation with surgery reserved for salvage. The Gustave–Roussy Institute reported on their

10 year experience with salvage surgery for locally recurrent tonsillar carcinoma following primary radiation. Overall survival after salvage surgery was 34% at 3 years and 23% at 5 years [17]. Similarly, we demonstrated high local and locoregional recurrence after salvage surgery.

One specific concern with salvage surgery is the potential morbidity associated with surgery following radiation or chemoradiation. Suzuki et al. [18] found that while salvage surgery was effective in some patients, the post-surgical complication rate was significantly higher in patients who underwent surgical reconstruction and those who received chemotherapy. Lee et al. [19] noted that salvage surgery after chemoradiation carries a higher complication rate than either primary surgery or salvage surgery after radiation alone. Gehanno et al. [4] noted a higher mortality rate of 8% (4 out of 50) in patients undergoing salvage surgery compared to 1.4% (1 out of 70) in those treated primarily with surgery [4]. Other authors reported rates of post-operative complications as high as 45% of cases, however, frequently these are minor complications [17]. On the other hand, Perez et al. did not find any difference in the mortality rate, whether the patients were treated with pre-operative or postoperative radiation; the rates being 5.3% (7 out of 133) and 5.6% (2 out of 36), respectively [6]. The post-operative major complication rate in our series was 4.3% which is comparable to that of other series [17, 20]. It is noteworthy that 6 out of the 7 postoperative deaths occurred prior to 1984. The use of more advanced reconstructive modalities with the liberal use of either pedicled or free tissue transfer may account for the reduction in the incidence of complications associated with surgery in previously irradiated wounds. Reported surgical complication following chemoradiation includes wound infection, orocutaneous fistulas, flap necrosis [21], hypothyroidism, weight loss and osteoradionecrosis [22].

Salvage surgery is not the only available modality. Re-irradiation with and without chemotherapy has also been used. Survival outcome following re-irradiation varied from 13% in unselected series to 93% in highly selected series [23, 24]. Lee et al. [25] have reported on their experience with salvage treatment using re-irradiation for recurrent head and neck cancer. The 2-year locoregional progression-free survival (LRPFS) and overall survival rates were 42 and 37%, respectively. Another re-irradiation study by Dawson et al. [26] reported a median survival following completion of re-irradiation of 12.5 months with 1- and 2-years survival rates of 51.1 and 32.6%, respectively. Re-irradiation with chemotherapy has also been used as salvage therapy in recurrent head and neck cancer. Nagar et al. [27] found that patients managed with external radiation alone benefited with subsequent chemo-reirradiation with a complete response rate of 54%. Other studies support these findings [28, 29]. Naidu et al. [30] evaluated the effect of targeted intra-arterial chemoradiation (RADPLAT) for advanced tonsil cancer and concluded that locoregional outcome is superior to the common protocols described in literature. The main outcome of the studies suggests although prognosis of patients with recurrent disease is poor, re-irradiation appears feasible and effective. IMRT reduces the treatment related toxicities and chemotherapy adds additional benefit to locoregional control and survival.

While we recognize that the radiation dose and fractionation schedule of the study population is different from what is currently being employed at the Princess Margret Hospital, the goal was to report on the long-term survival of patients developing recurrence following non-surgical therapy for tonsil cancer. While salvage surgery is possible in patients with surgically resectable disease, the outcome is poor with a 1- and 5-year overall survival rate of 58 and 23%, respectively. The best way to manage recurrences is to prevent it from occurring. More aggressive treatment protocols, such as altered fractionation radiation or concurrent chemoradiation, have been developed to try and improve locoregional control as well as survival. There is substantial evidence suggesting the advantage of hyperfractionated and accelerated radiation treatment in head and neck SCC [31]. In order to take advantage of the organ preservation of radiation and the improved control rates at the primary site with altered fractionation regimens, integration of planned neck dissection has been offered with improved regional control rates [32]. In recent years, induction chemotherapy with docetaxel plus cisplatin and fluorouracil (TPF) has been used in patients with advanced head and neck cancer and therefore it is available also for advanced tonsillar carcinoma. Posner et al. [33] demonstrated a longer survival with TPF compared to those who received cisplatin and fluorouracil induction chemotherapy. Vermorken et al. [34] investigated the role of induction chemotherapy with TPF in 177 locoregionally advanced unresectable head and neck SCC patients. They found that addition of docetaxel significantly improved progression-free and overall survival.

HPV DNA have been detected in approximately 20–72% of oropharyngeal cancer. Several studies [35, 36] have associated the presence of HPV with oropharyngeal cancer regardless of their tobacco and alcohol abuse. These findings suggest that HPV might contribute to the malignant transformation of normal epithelial cells to cancer, however, the presence of HPV correlates with better prognosis [37] and improved survival after treatment with concurrent chemoradiation [38]. The observed improved overall survival and disease free survival for HPV-positive HNSCC patients is unique to the oropharynx and may imply of a different etiology from other tumors of the head and neck [39]. At present, there is no data or research to suggest a change in treatment for these patients. Further studies are needed.

Conclusion

In conclusion, the reports on the outcome of tonsillar cancer patients who underwent salvage surgery are limited. The importance of the current study to the literature is based on the long follow-up of a large cohort of patients. In spite of the fact that the patients in this study had been treated prior to the widespread introduction of altered fractionation and concurrent chemoradiation for advanced tonsil carcinoma, it demonstrates the poor prognosis of recurrent disease. Although surgical salvage with a low complication rate is possible, the chance of curing disease is very low. Despite the poor prognosis, 20% of patients will be alive at 5 years and therefore should be considered when possible. While current organ preservation protocols improve the local and regional control rate, the survival of those who undergo salvage surgery needs to be evaluated. We believe that the current study provides a baseline from which to compare survival rates and complication rates following salvage surgery for these more aggressive treatment modalities.

Conflict of interest statement The authors have no conflict of interest. The study was not sponsored by any organization.

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