

Salvage Surgery for Locoregional Failure after Definitive Radiotherapy for Base of Tongue Cancer

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Abstract. *In this study, the results of definitive radiotherapy (RT) and salvage surgery treatment of base of tongue cancer were evaluated. A total of 94 consecutive patients (16 female and 78 male) with T1-4, N0-3 and M0 disease underwent definitive RT between 1992 and 2005. External beam RT alone (mean dose, 63 Gy) or external beam RT (mean dose 61 Gy) with brachytherapy boost (mean dose, 17 Gy) was given for 50 and 44 patients, respectively. Eight patients were subjected to neck node dissection, generally at the time of brachytherapy. At a median follow-up time of 95 months, 37 (39%) patients had no residual disease or locoregional recurrence, 34 (36%) patients had locoregional residual disease and 23 (25%) patients developed locoregional recurrence. The 5-year cause-specific survival for all patients was 45% (43 of 94). In multivariate analysis, N2-3 stage and histological grade 3 proved to be independent negative predictors of cause-specific survival (relative risk: 2.2 and 3.1, respectively). The overall number of patients with locoregional failure was 57. Salvage surgery was possible in 18 (32%) patients; more than half of the patients (31 of 57) with locoregional failure were not suitable for salvage surgery due to unresectable disease, poor health status or distant metastasis. Salvage surgery was successful in 10 (56%) patients, while 8 patients developed a second locoregional recurrence. For patients undergoing definitive RT, more effective follow-up and care is needed to increase the rate of salvage surgery.*

Numerous prospective and randomized trials conducted over the past 10 years have highlighted the central role of radiotherapy (RT) in the management of head and neck cancer

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(1-4). In base of tongue cancer, definitive RT is increasingly used to preserve organ function, with surgery held as a second-line treatment modality for salvage of locoregional failures (5-8). Primary surgical treatment is not recommended because both functional outcome and survival are poor after mutilating resection of advanced lesions (9).

In 1992, we designed a phase II trial to establish the feasibility of treating patients with base of tongue cancer using external beam RT with or without brachytherapy (BT) boost. The 5-year results of definitive RT alone for cancer of tongue base were published elsewhere (10, 11). Although surgery is not intended as part of the definitive RT or chemoradiation plan, salvage surgery may be carried out in an attempt to cure those with an incomplete response or recurrent disease. Publications provide little insight into the proportion of the local failures amenable to salvage surgery following definitive RT for head and neck cancer (12-13). This study was undertaken to evaluate the outcome of salvage surgery for patient with locoregional residual disease or recurrence following definitive RT for base of tongue cancer.

Patients and Methods

Between 1992 and 2005, 94 patients with T1-4, N0-3 and M0 carcinoma of the tongue base underwent definitive RT in the Department of Radiotherapy of the National Institute of Oncology, Budapest, Hungary. Pretreatment evaluation consisted of physical examination, panendoscopy, chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck region, and routine hematology. Pathological diagnosis was confirmed with tissue biopsies. However, 8 patients underwent neck dissection at the time of brachytherapy (n=5) or 1 month later (n=3). Radiotherapy treatment planning and dosimetry are described elsewhere (10, 11). For 44 patients, external beam RT (mean dose, 61 Gy; range, 50-66 Gy) with BT (mean dose, 17 Gy; range, 12-30 Gy; fraction number, 1-8) and for 50 patients, external beam RT alone (mean dose, 63 Gy; range, 60-72 Gy) was given. Patients were scheduled to have a 2-monthly clinical examination for the first 2 years and every 3 to 6 months thereafter, with planned routine imaging (CT or MRI) every 6 months. Response to RT was assessed at 2 to 3 months after completion of RT. Local or regional disease persistence (patients not obtaining a complete response) was counted as a failure. Patients with

resectable locoregional failure (stage that allows R0 resection) were considered for salvage surgery. Before surgery, restaging investigations were carried out to exclude extensive local extension or distant metastases. Salvage surgery consisted of wide excision, resection of the tongue base and lateral wall of the pharynx, resection of the tongue base with partial glossectomy or glossectomy, and/or neck node dissection. Reconstruction was accomplished at the time of the salvage surgery.

Survival analysis was carried out using the Kaplan-Meier method (14). The log-rank test was used to compare survival curves. The risk of cancer-specific death was estimated in proportional hazards regression models described by Cox (15). The estimates of the models are given as relative risk (RR) with 95% confidence intervals (95% CI). The chi-squared test (two-tailed) was used to evaluate differences in proportions. A difference with a *p*-value of 0.05 or less was considered significant.

Results

Patient pretreatment characteristics are shown in Table I. The median follow-up time for surviving patients was 95 months (range, 24-169 months). The 5-year overall or cause-specific actuarial survival rate for all patients was 39% (32 of 94) and 45% (43 of 94), respectively. No patient experienced disease progression during RT. Initial evaluation after RT showed that overall locoregional tumor response was complete in 60 patients (64%). At a median follow-up time of 95 months, 37 (39%) patients had no residual disease or locoregional recurrence. Of these patients, 24 (65%) are still alive without distant metastasis, the others died of distant relapse (n=1), internal disease (n=6) and other malignancies (n=6). After RT, 34 patients (36%) had locoregional residual disease and 23 (25%) patients developed locoregional recurrence. Thirty patients had both local and regional failures, 7 had neck metastasis only, and 20 had local failure only. Eighteen (32%) of the patients with locoregional failure underwent salvage surgery. Reasons for salvage surgery were: residual local disease (n=3), local recurrence (n=12), residual regional disease (n=5), and regional recurrence (n=3). Salvage surgery consisted of wide excision (n=6), resection of tongue base and lateral wall of the pharynx (n=3), resection of tongue base with partial glossectomy (n=5) or glossectomy (n=1), and neck node dissection (n=11). Eight patients underwent both local and regional salvage surgeries.

Table I compares the characteristics of operated failure patients with unoperated failure patients. The rates of T4 and N2 stages were higher in the no salvage surgery group, and the rate of initial N0/1 lymph node stage for patients with locoregional failure with or without salvage surgery was 72% and 41%, respectively (*p*=0.0523). Patients eligible for salvage surgery generally had better T and N stage at the time of initial diagnosis (Table I). The size and extent of the primary tumor had an impact on local tumor control. The 5-year actuarial local (primary site) control rates by T status were: T1 100%, T2 75%, T3 48%, T4 33% (*p*=0.0062).

Table I. Characteristics of patients with and without local and/or regional failure (n=94).

Characteristic	Patients without failure (n=37)	Patients with failure (n=57)		P-value
		With salvage surgery (n=18)	Without salvage surgery (n=39)	
Mean age (range), years	55.6 (38-73)	57.1 (44-72)	57.4 (36-77)	NS
Gender				
Male	27	17	34	NS
Female	10	1	5	-
Initial tumor size				
T1	4	0	0	-
T2	6	0	2	-
T3	12	8	9	NS
T4	15	10	28	0.0763
Initial nodal status				
N0	16	6	5	NS
N1	15	7	11	NS
N2	6	4	19	0.0435
N3	0	1	4	NS
AJCC stage				
I-II	6	0	0	-
III-IV	31	18	39	NS
Histological grade ^a				
1	11	5	11	NS
2	19	9	15	NS
3	7	4	13	NS
Clinical appearance				
Exophytic	3	0	2	-
Infiltrating	19	4	15	NS
Ulcerative	15	14	22	NS

NS, not significant; ^aone adenocystic, all the others squamous cell carcinoma.

In univariate analysis, initial nodal status (N0-1 vs. N2-3: RR, 2.95; 95% CI, 1.69-5.15; *p*=0.0001) and histological grade (1-2 vs. 3: RR, 2.08; 95% CI, 1.18-3.65; *p*=0.0114) significantly increased the risk of cause-specific death, but initial tumor status (T1-2-3 vs. T4: *p*=0.1315) and clinical appearance of the primary tumor (exophytic/infiltrating vs. ulcerative: *p*=0.3937) did not. Gender (female vs. male) and age (≤ 50 vs. > 50 years) of the patients showed borderline significance (*p*=0.0526 and 0.0979, respectively). In multivariate analysis, both nodal status (RR, 2.24; 95% CI, 1.27-3.96; *p*=0.0053) and histological grade (RR, 3.11; 95% CI, 1.76-5.49; *p*=0.0001) remained independent predictors of cause-specific survival. The combination of the two independent predictors strengthened their prognostic value.

The 5-year cause-specific survival rate with N0-1 with grade 1-2 (n=44) or with N2-3 with grade 3 (n=8) disease was 69% and 0% (13% at 2 years), respectively (*p*=0.0003). Figure 1 shows the cause-specific survival curves of patients without locoregional failure, and with locoregional failure with or without salvage surgery. Patients without locoregional failure

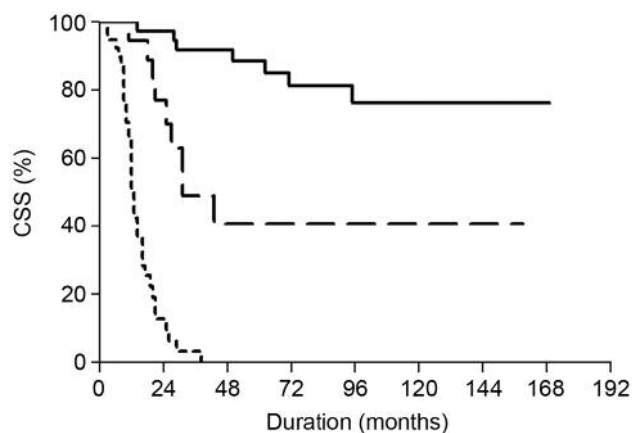


Figure 1. Kaplan-Meier cancer-specific survival curves. — Patients without locoregional failure ($n = 37$), - - patients treated with salvage surgery for locoregional failure ($n = 18$), . . patients with locoregional failure without salvage surgery ($n = 39$). The 5-year cancer-specific survival (CSS) was 88%, 41% and 0% (12% at 2 years), respectively. All p -values are <0.02 by two-group non-parametric test.

following definitive RT had an excellent survival rate, 88% at 5 years. Patients with locoregional failure without salvage surgery had very poor outcome: all of them died within 5 years. The cause of tongue cancer-specific death was locoregional tumor progression in the majority of cases ($n=45$). The crude rate of total distant metastasis was 5% (5 of 94). Table II displays the reasons for patients not undergoing salvage surgery. The majority of reasons ($n=39$) were related to the extent of recurrence and to the compromised general health status of the patients.

Of 18 patients operated on, 10 patients had one or more salvage surgery complications (Table III). After salvage surgery, eight patients (44%) developed second local ($n=6$) or regional ($n=2$) recurrence. The median time to second locoregional recurrence was 8 months (range: 6-13 months). The actuarial cause-specific survival at 5-years following salvage surgery was 40% (8 of 18).

Discussion

Radical RT with or without chemotherapy is a well-established primary treatment for locally advanced (stage III/IV) head and neck cancer (6, 8, 16, 17). Salvage surgery remains a treatment modality for patients with operable residual disease and for those who experienced resectable locoregional recurrence (4, 6, 12). In our series, the rate of clinical complete response to RT was 64%. Pletcher *et al.* treated 45 patients with stage III/IV tongue base cancer with RT alone and 25 (56%) achieved a complete response (18). In a taxane-based concurrent chemoradiation phase II trial, 41% of the evaluable patients had complete response (19). In the Southwest Oncology Group Trial, after concurrent cisplatin-based chemoradiation, the clinical and histological complete

Table II. Reasons for no salvage surgery.

Reason	No. of patients (%)
Unresectable disease	12 (30.8)
Poor health status	15 (38.5)
Patient refusal	8 (20.5)
Distant metastasis	4 (10.2)
Total	39 (100)

Table III. Post-salvage surgery complication in 10 patients^a.

Complications	No. of patients
Delayed healing	5
Fistula formation	2
Bleeding	0
Seroma formation	3
Dysphagia	2
Wound infection	1
Flap necrosis	0
Pneumonia	1
Death	0
Total	14

^aEight out of 18 patients had no complication.

response rate was 69% and 54%, respectively (6). In another taxane-based chemoradiation phase II study, the clinical complete response rate was very high, 90% (17). In our series, 57 patients (61%) had residual locoregional disease after RT or developed locoregional failure during the follow-up time.

Salvage surgery provides the best chance of long-term disease control and possible cure for patients with operable head and neck cancer with resectable locoregional failure (12). In our series, 32% (18 of 57) of patients with locoregional failure were subjected to salvage surgery and the 5-year cause-specific survival was 41%. In the study of the Aarhus University Hospital (20), salvage surgery was possible in 30% (52 of 173) of the patients and 24 treatments (46%) were successful. The feasibility of salvage surgery depends on the anatomical location and extent of recurrence, as well as on the general condition of the patients. The main reasons for no salvage surgery for our patients were unresectable locoregional disease (31%) and poor general condition (39%). In the study of Tausky *et al.*, 23% (17 of 75) of the patients with locoregional failure underwent salvage surgery. In the no salvage resection group, 43% of the failures were unresectable and 30% of the patients had poor health status (13). The proportion of patients with recurrent oropharyngeal cancer eligible for salvage surgery is about 30% (13, 20). Poor general health status and malnutrition preclude major surgery. In order to detect candidates for salvage surgery as early as possible, patients should be followed up carefully (3, 12, 20).

Distant metastasis is relatively uncommon in head and neck cancer, occurring in approximately 10% of patients treated for

oropharyngeal cancer (12, 16, 20). In our series, the crude rate of distant metastasis was 5% and locoregional tumor progression was the main cause of death. The 5-year cause-specific survival for patients without locoregional failure was excellent, 88% .

In our cases, advanced initial nodal status (N2-3) or high histological grade of the primary tumor increased the risk of cause-specific death. The 5-year cause-specific survival rate for patients with N0 to 1 status with low histological grade was 69% , but all patients with N2 to 3 status with high histological grade died within 5 years. In other studies, the initial N stage and histological grade were also independent predictors of cause-specific survival (20-22).

In our series, significant postsalvage surgery complication occurred in a total of 10 patients (78%). In the study of Taussky *et al.*, 13 out of 17 patients (76%) had postsalvage surgery complication (13). After definitive RT, delayed wound healing is the most common complication (12, 13).

In conclusion, patients without locoregional failure after definitive RT for base of tongue cancer have a good prognosis. Salvage surgery after definitive RT is feasible and is found to result in a favorable success rate in patients suitable for relapse treatment. However, many patients are medically unfit for salvage surgery or have extensive locoregional recurrence.

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