SALVAGE SURGERY AFTER RADICAL ACCELERATED RADIOTHERAPY WITH CONCOMITANT BOOST TECHNIQUE FOR HEAD AND NECK CARCINOMAS

Daniel Taussky, MD,[1] Pavel Dulguerov, MD,[2] Abdelkarim S. Allal, MD[1]

[1] Division of Radiation Oncology, University Hospital of Geneva, Geneva, Switzerland; Hopital Notre Dame, 1560 Sherbrooke Est, Montreal H2L 4M1, Canada. E-mail: daniel.taussky.chum@ssss.gouv.qc.ca
[2] Head and Neck Surgery, University Hospital of Geneva, Geneva, Switzerland

Accepted 19 August 2004
Published online 30 December 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20139

Abstract: *Background.* Definitive radiotherapy (RT) for head and neck cancer is increasingly used to preserve organ function, whereas surgery is reserved for treatment failure. However, data are sparse regarding the feasibility of salvage surgery, particularly for unselected patients after accelerated RT.

Methods. From 1991 to 2001, 297 patients, most with stage III to IV cancer (Union Internationale Contre le Cancer) were treated with concomitant boost RT (median dose, 69.9 Gy in 41 fractions) with or without chemotherapy (in 33%, usually cisplatin with or without 5-fluorouracil). The 75 patients seen with local and/or regional failure were studied. We analyzed the factors influencing the decision to attempt surgical salvage, the oncologic outcome, and the associated complications.

Results. Seventeen (23%) of the 75 patients had a salvage operation. This included all five patients with laryngeal cancers but only 16% to 20% of patients with tumors in other locations. Most patients could not be operated on because of disease extension (40%) and poor general condition/advanced age (30%). Patients with low initial primary T and N classification were more likely to undergo surgery (p = .002 and .014, respectively). Median post-recurrence survival was significantly better for patients who had salvage operations than for those without surgical salvage treatment (44 vs 11 months, p = .0001). Thirteen patients were initially seen with postoperative complications (mostly delayed wound healing and fistula formation).

Conclusions. After definitive accelerated RT with the concomitant boost technique, only a minority of patients with local or regional recurrence underwent salvage surgery. Disease stage, tumor location, and patient's general condition at the initial diagnosis seemed to be the main factors influencing the decision to attempt surgical salvage. For patients with initially resectable disease who undergo radical nonsurgical treatment, more effective follow-up is needed to favor early detection of treatment failure, which may lead to a timely and effective salvage surgery. © 2004 Wiley Periodicals, Inc. *Head Neck* **27:** 182–186, 2005

Keywords: head and neck cancer; recurrence; salvage surgery

Correspondence to: D. Taussky

In head and neck squamous cell carcinomas (HNSCCs), radiotherapy (RT) with or without chemotherapy is increasingly used to preserve organ function, with surgery held as a second-line treatment modality for salvage of locoregional failures. This treatment strategy has been shown to be effective in selected patients, particularly for laryngeal[1] and hypopharyngeal carcinoma[2–5] or isolated neck recurrence.[6] On the other hand, altered RT fractionation schedules, either used alone or combined with chemotherapy, have

become a frequently prescribed treatment option in advanced HNSCC.[7] In our experience, however, salvage surgery is uncommonly performed in this setting, despite the potential for increasing ultimate cure rates. The literature provides little insight into the proportion of failures amenable to salvage surgery,[8] the value of salvage surgery,[9] or the reasons surgical management of recurrences is not attempted.

Since 1991, we have routinely treated patients with HNSCC with accelerated RT by use of a concomitant boost technique.[10] This study was undertaken to analyze how patients whose accelerated RT was unsuccessful were managed, with a special emphasis on factors influencing the decision for salvage surgery and the associated morbidity.

PATIENTS AND METHODS

Patient Characteristics. From February 1991 to June 2001, 297 patients were treated with radical accelerated RT with or without chemotherapy. Pretreatment evaluation consisted of medical history and physical examination, panendoscopy, chest x-ray, and CT or MRI of the head and neck region. The characteristics of patients seen with local or regional failure are detailed in Table 1.

Therapy and Follow-up. The RT schedule has been described previously.[10] The planned total dose was 69.9 Gy delivered in 41 fractions over 38 days. A technique combining lateral opposing 6-MV beams to the primary tumor and the cervical lymph nodes and a single anterior field to the supraclavicular and inferior neck nodes was used in most cases. Chemotherapy (usually cisplatin with or without 5-fluorouracil) was administered in 97 patients (33%) initially seen generally with T3 to T4 or N2 to N3 tumors; of these patients, 82 (85%) had at least one cycle concomitantly with RT. Forty-two patients (14%) underwent a neck dissection before RT, but no patients had primary surgical treatment of the primary tumor or a planned neck dissection after radiotherapy. Patients were scheduled to have a monthly clinical examination for the first 2 years and every 2 to 4 months thereafter without a planned routine imaging, except for patients enrolled in prospective trials.

Statistical Analysis. The chi-square test (two-tailed) and Fisher exact test were used to evaluate differences in proportions, whereas the log-rank test was used to compare survival curves. The actuarial overall survival rate was calculated with the Kaplan-Meier method, and the Cox regression model was used for multi-

Table 1. Characteristics of patients with local and/or regional failure (n = 75).

Characteristic	All patients (n = 75)	Patients with salvage surgery (n = 17)	Patients without salvage surgery (n = 58)	p value
Median age (range), y	58 (20–88)	59 (47–80)	58 (20–88)	.41
Sex: male	79%*	82%†	78%†	.48
WHO performance status	49%*	41%†	53%†	.42
Tumor location				.001
Oral cavity	13%*	20%†	80†	
Oropharynx	51%*	16%†	84%†	
Hypopharynx	23%*	18%†	82%†	
Larynx	7%*	100%†	0%†	
Nasopharynx	7%*	20%†	80%†	
T classification at presentation				.002
T1–2	29%	36%†	64%†	
T3–T4	71%	17%†	83%†	
N classification at presentation				.014
N0–1	45%*	35%†	65%†	
N2–N3	55%*	12%†	88%†	
UICC stage at presentation				.002
I–II	15%*	54%†	46%†	
III–IV	85%*	17%†	83%†	
Median RT dose (range)	69.9 Gy (62.5–70.4)	69.9 Gy (65.5–70.4)	69.9 Gy (62.5–69.9)	NS

Abbreviations: WHO, World Health Organization; UICC, Union Internationale Contre le Cancer; RT, radiotherapy; NS, not significant.
**% of patients with recurrence.*
†% of patients presenting with this location/stage.

Table 2. Reasons for not operating (n = 58, multiple answers possible).

Reasons for not undergoing salvage surgery	No. (%)
Unresectable disease	25 (43%)
Poor health status/age	21 (30%)
Patient refusal	6 (8%)
Metastasis and simultaneous local recurrence	6 (8%)
Rapid disease progression/intercurrent death	3 (5%)
Not clear	8 (11%)

variate analysis. A difference with a p value of .05 or less was considered significant. All the analyses were done with SPSS software.

RESULTS

Seventy-five patients (25%) had local and/or regional failure. Fifty-nine patients had both local and regional recurrence, 12 had neck metastasis, and four had primary tumor recurrence only. Included in this analysis are 12 patients (16%) initially seen with disease persistence, defined as disease progression occurring within 3 months of the end of RT. Seventeen patients (23%) had salvage surgery. The mean time from the end of RT to salvage surgery was 16 months (range, 3.3–53.4 months). Seven patients had palliative chemotherapy only, and one patient had RT and chemotherapy. Besides patients initially seen with locoregional recurrences, 25 patients were initially seen with distant metastasis alone. Thus, for all patients, the actuarial disease-free survival (DFS) rate was 61% at 5 years.

Factors Correlated with Treatment Decision. Table 1 compares the characteristics of patients undergoing salvage surgery with those of patients for whom surgical treatment was not carried out. Although all patients with recurrent laryngeal cancers (five of five) were operated on (all had N1 disease and three had T1 disease), salvage surgery was attempted in only 16% to 20% of patients with the other tumor locations (p = .001). Moreover, patients with low T and N classifications at the time of the initial diagnosis were more likely to have salvage surgery (p = .002 and .014, respectively). There was no difference between the two groups in terms of initial performance status, sex, and age. Table 2 displays the reasons patients did not have salvage surgery. More than half of the reasons (60%) were related to the extent of the recurrence and to the compromised general health of the patients.

Oncologic Outcome. At the time of analysis, only four patients (5%) were still alive, two in each group. The median survival for all patients initially seen with locoregional failure was 15 months, 11 months (range, 2–67 months) for patients without salvage surgery and 44 months (range, 7–135 months) for patients who underwent salvage surgery (p = .0001). Although 96%

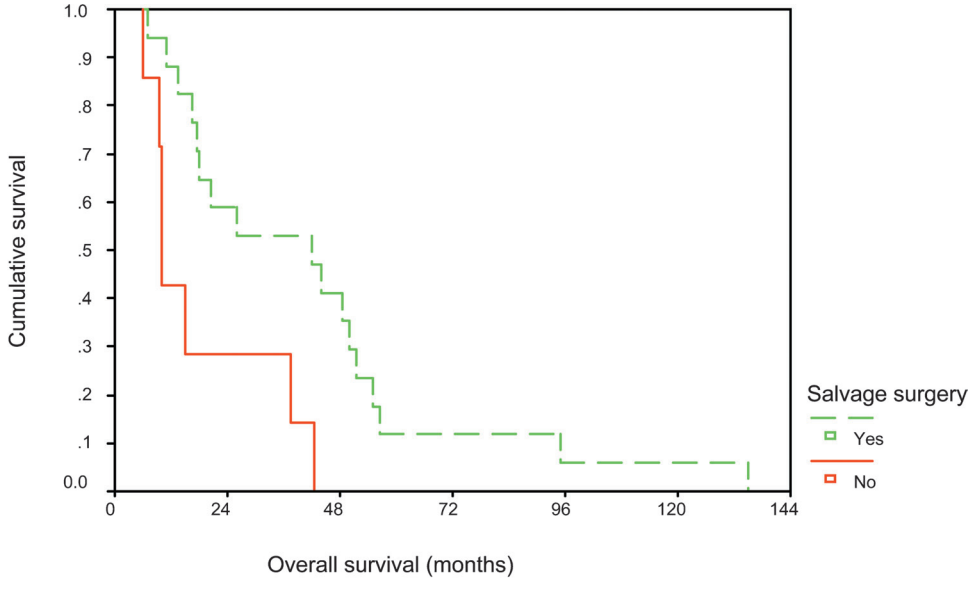

FIGURE 1. Cumulative overall survival curve for patients who had surgery (n = 17;) versus patients without surgery (n = 58, p = .005). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 3. Postoperative complications in 13 patients (multiple per patient possible).

Complications	No.
Delayed healing	4
Fistula formation	4
Severe dysphagia*	1
Bleeding	1
Seroma formation	2
Tracheostomy needed†	3
Death	1
Unknown	1
Total	17

**After buccopharyngectomy, necessitating a gastrostomy.*
†After laryngectomy for respiratory problems.

(n = 55) of patients who had no salvage surgery died from their cancer, only 60% (n = 10) of patients who had surgery died from their cancer. The corresponding 3-year post-recurrence overall actuarial survival rates were 16% and 46%, respectively, and 53% (n = 9) of patients who underwent surgery were free of disease at last follow-up or death.

In a univariate analysis, T classification (p = .0021), surgery (p = .005, Figure 1), and the Union Internationale Contre le Cancer (UICC) stage (p = .0061) were significant factors influencing overall survival. Chemotherapy (p = .25), World Health Organization (WHO) performance status (p = .26), N classification (p = .25), and sex (p = .85) were all not significant. In a multivariate analysis including the preceding significant factors, only the UICC stage retained its significance (p = .035), whereas surgery was of borderline significance (p = .063). Because of small sample size, all analyses are considered exploratory only, and appropriate caution must be taken in interpreting results.

Complications of Salvage Surgery. Of 17 patients operated on, 13 patients were initially seen with one or more complications, whereas four had none (Table 3). The most frequently encountered complications were related to neck wound healing or its subsequent leakage, as well as fistula formation. Moreover, one patient died from a hemorrhage after composite resection.

DISCUSSION

Radical RT with or without chemotherapy is a well-established primary treatment for head and neck cancers. Implicit in the acceptance of this treatment approach is the potential availability of radical surgery as second-line therapy for locoregional failures. However, there are few studies addressing the feasibility of salvage operations in unselected patients treated with the more aggressive nonsurgical treatment schedules and few data to shed light on the reasons why only a minority of patients are able to undergo surgical salvage.

The feasibility of salvage surgery depends on not only the location of the recurrence but also its extent and the type of surgery that can be attempted. Previous studies reported that the proportion of patients eligible for salvage surgery ranged between 34% and 75%, with patients with laryngeal cancers being the most often and most successfully salvaged.[3–5,11–13] In our series, all patients with laryngeal recurrences were operated on, whereas less than one quarter of the patients with recurrences in other locations were able to have salvage surgery. Although in some reports salvage surgery in patients with glottic carcinoma has been reported to yield an ultimate tumor control of more than 80%,[4] in our series, locoregional disease progression remained the main cause of death. In line with the literature finding, in our series most patients who were not selected for surgical salvage either were initially seen with disease that was judged too extensive or were medically inoperable because of poor general condition. Other authors predominantly reported concurrent metastatic disease, patient refusal,[11,12] and unresectable disease[6,11] as reasons for not having surgery.

Although patients with initially potentially operable cancers are often offered the choice between either surgery or RT, it would be of interest to know to what extent potentially operable patients remain eligible for surgery at the time of recurrence. In our series, only 54% of patients initially seen with stage I to II disease underwent salvage surgery, suggesting that the latter option became nonfeasible in many patients who were initially operable. However, the limitations of retrospective analyses preclude any definitive conclusion on this issue. Nevertheless, studies assessing the value of early recurrence detection with the different imaging tools should be encouraged, particularly for patients with initially resectable disease.

Acute and late toxicity are increased in accelerated RT regimens and concurrent chemotherapy, but both increase local control and overall survival when compared with standard regimens or radiotherapy alone.[7,14–16] Toxicity of

the primary treatment might well be an important factor in the treatment decision for a recurrence. Compared with monofractionated RT schedules, increased toxicity might be more likely to render patients medically unfit for surgery or might more often lead to an unwillingness of patients to undergo further treatment. In fact, little is known about the influence of the type of RT fractionation on operability and rate of surgical complications. It has been reported[17] that, after hyperfractionated accelerated RT, surgery becomes increasingly less difficult with increasing interval after RT. It is thought that the main surgical problem after RT is impaired healing because of disturbances in perfusion of irradiated tissue. But for most altered fractionated schemes, no higher incidence of surgical complications has been reported. From a randomized study, Davidson et al[11] compared the results of salvage surgery between patients treated with either a hyperfractionated or a hypofractionated RT schedule. Surgical complications were identical in both groups (27%). Generally, the rate of complication was higher when surgery was performed for the primary tumor or combined with neck dissection and lower when only a neck dissection was done. Parsons et al[12] did not find a higher surgical complication rate (37%) when comparing once-daily with twice-daily RT for supraglottic laryngeal cancer, whereas Johansen et al[4] reported a higher incidence of fistula after split-course RT.

In conclusion, in an unselected population treated with accelerated concomitant boost RT, with the exception of laryngeal cancers, salvage surgery is uncommonly used, because most patients are medically unfit or have extensive recurrences. In centers where nonsurgical approaches are favored for treatment of patients with initially resectable disease, an intensive and effective follow-up is needed to detect recurrences as early as possible to optimize the potential benefits of salvage surgery.

REFERENCES

1. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685–1690.
2. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–899.
3. Stoeckli SJ, Pawlik AB, Lipp M, Huber A, Schmid S. Salvage surgery after failure of nonsurgical therapy for carcinoma of the larynx and hypopharynx. Arch Otolaryngol Head Neck Surg 2000;126:1473–1477.
4. Johansen LV, Grau C, Overgaard J. Glottic carcinoma—patterns of failure and salvage treatment after curative radiotherapy in 861 consecutive patients. Radiother Oncol 2002;63:257–267.
5. Johansen LV, Grau C, Overgaard J. Squamous cell carcinoma of the oropharynx—an analysis of treatment results in 289 consecutive patients. Acta Oncol 2000;39:985–994.
6. Mabanta SR, Mendenhall WM, Stringer SP, Cassisi NJ. Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. Head Neck 1999;21:591–594.
7. Horiot JC, Bontemps P, van den Bogaert W, et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol 1997;44:111–121.
8. Parsons JT. In response to Dr. Karim [letter]. Int J Radiat Oncol Biol Phys 1996;34:971.
9. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 2000;110(Suppl 93):1–18.
10. Allal AS, de Pree C, Dulguerov P, Bieri S, Maire D, Kurtz JM. Avoidance of treatment interruption: an unrecognized benefit of accelerated radiotherapy in oropharyngeal carcinomas? Int J Radiat Oncol Biol Phys 1999;45:41–45.
11. Davidson J, Keane T, Brown D, et al. Surgical salvage after radiotherapy for advanced laryngopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 1997;123:420–424.
12. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million R. Salvage surgery following radiation failure in squamous cell carcinoma of the supraglottic larynx. Int J Radiat Oncol Biol Phys 1995;32:605–609.
13. Karim ABMF. Regarding Parsons et al [letter]. Int J Radiat Oncol Biol Phys 1996;34:970–971.
14. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7–16.
15. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol 1998;16:1318–1324.
16. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Nat Cancer Inst 1999;91:2081–2086.
17. Rugg T, Lartigau E, Sanders R, Glover G, Saunders MI, Dische S. The morbidity of salvage surgery following conventional radiotherapy and continuous, hyperfractionated accelerated radiotherapy (CHART). Int J Radiat Oncol Biol Phys 1991;20:581–586.