Recurrent Advanced (T3 or T4) Head and Neck Squamous Cell Carcinoma

Is Salvage Possible?

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Background: Salvage surgery is often the only curative option for recurrent cancer. In patients whose initial tumor is stage T3 or T4, the primary therapy often makes salvage even more difficult. We therefore analyzed the outcome in patients who were originally treated for T3 or T4 squamous cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx and who then had a recurrence and chose to undergo further therapy for cure.

Patients and Methods: From 1980 to 2000, a total of 940 patients were treated for stage T3 or T4 cancer. Forty-eight patients underwent salvage therapy for recurrence: 24 for primary site recurrence, 20 for regional recurrence, and 4 for locoregional recurrence.

Results: The mean time to recurrence was 14.0 months, and the mean survival time was 26.2 months. Among the 28 patients treated for primary site recurrence, the mean time to recurrence was 12.6 months, and the mean survival time was 27.3 months. Only 5 of the 28 patients had prolonged survival. The stage of the recurrent disease did not influence outcome. Among the 20 patients treated for neck recurrence, the mean time to recurrence was 14.0 months, and the mean survival time was 25.0 months. Six of the 20 patients had prolonged survival, but none had a recurrence in a previously dissected and irradiated neck.

Conclusions: These results show the limited potential for survival in patients who have a recurrence after treatment for advanced primary site head and neck cancer. Patients who have not undergone all modalities of therapy have the potential for salvage, but even then the chances are limited. Given the morbidity of salvage therapy, and the limited chance for cure, physicians must cautiously counsel patients who are contemplating treatment of recurrent cancer after therapy for advanced disease.

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Cancer recurrence is all too common an outcome after treatment of advanced head and neck cancer. Salvage surgery often offers the only chance of survival for the patient; however, few studies have evaluated outcome after salvage surgery, and even within these studies, it is difficult to discern if those patients with initial advanced disease, who are most likely to have a recurrence, can be salvaged.

Goodwin1 reviewed the literature on salvage surgery and performed a meta-analysis. He identified 32 studies that evaluated the role of salvage surgery, 16 of which were from the United States. Based on the 12 studies that had sufficient data for analysis, a 5-year survival rate of 36% was calculated. Unfortunately, this rate included patients with cancer of the larynx whose recurrences were in an early stage, and their 2-year survival rate was 84%, thus skewing the data. Only 2 studies concentrated on advanced recurrences; both of them focused on the larynx and demonstrated a 5-year survival rate of 36%. Other studies have focused on surgical salvage after failed radiation therapy, particularly for stage III and IV laryngeal cancer,2,3 and, as expected, they generally demonstrated salvage survival rates that were higher than 60% at 2 years. The outcome for patients with recurrence after treatment for initial T4 disease, however, is poorer.

While these cited studies did evaluate outcome after salvage surgery, they did not specifically involve patients with tumors that were initially advanced (T3 or T4), whose options for salvage surgery may be more limited by prior therapy. A MEDLINE search found no studies involving recurrences of advanced primary site head and neck cancer that addressed the issue of salvage therapy. Reliable data concerning such cases are important, as the clinician is frequently confronted with...
METHODS

The head and neck cancer database of the Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati, Cincinnati, Ohio, was used to retrieve data on all patients treated for T3 or T4 squamous cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx from January 1, 1980, to December 31, 2000. A total of 940 cases were recorded in this category. Patients who had a recurrence after primary treatment and then chose to undergo salvage therapy for cure were included. Patients who developed second primary tumors or were treated palliatively were excluded. Of the 48 patients who had recurrences and underwent treatment for cure, 24 had a recurrence only at the primary site, 20 had a recurrence only in the neck, and 4 had both local and regional recurrences. We evaluated only those cases in which the initial therapy was performed at our institution for 2 reasons: (1) so that all of the records of the initial tumor were readily available and (2) to increase the likelihood that the initial therapy was thorough.

The study included 40 men and 8 women, with a mean age of 60 years (age range, 39-86 years). The site of the original tumor was the oral cavity in 20 patients, the oropharynx in 16 patients, the larynx in 7 patients, and the hypopharynx in 5 patients. The mean time to recurrence from initial therapy was 11.4 months (range, 2-45 months).

Of the 28 patients with a recurrence at the primary site (24 at the primary site alone and 4 at the primary site and the neck), 25 were treated with salvage surgery, 2 of whom also received postoperative radiation therapy, and 3 were treated with radiation therapy alone. The sites of tumor in the 25 patients who underwent surgical salvage were the oral cavity (n=12), the oropharynx (n=8), the larynx (n=2), and the hypopharynx (n=3). Wide tumor margins were attempted during salvage surgery whenever feasible. The therapies that were initiated for the original tumors in these 25 patients were surgical resection followed by postoperative radiation therapy (n=11), surgical resection alone (n=5), and radiation therapy and/or chemotherapy (n=9). Seventeen tumors were stage T3 and 8 were stage T4. Three patients who had a recurrence at the primary site were treated with radiation therapy alone; 1 patient was initially treated with surgery followed by postoperative radiation therapy; 1 patient was treated with surgery alone; and 1 patient was treated with radiation therapy alone.

Of the 20 patients who had a recurrence only in the neck, 16 were treated with salvage neck dissection and 4 were treated with radiation therapy. The original tumor was stage T3 in 11 patients and stage T4 in 9 patients, and the original N stage was N0 in 10 patients, N1 in 6 patients, N2 in 3 patients, and N3 in 1 patient. Eleven of the 16 patients who underwent neck dissection had never received radiation therapy and underwent irradiation after the neck dissection. Ten of the 16 patients had undergone prior neck dissection; 8 had a recurrence in the dissected area of the neck, and 2 had a recurrence in an undissected area of the neck. Salvage surgery was attempted in only 1 patient who had a recurrence in the neck and who had previously undergone dissection and irradiation of the neck.

The recurrent primary tumors were staged as either early (T1 or T2) or advanced (T3 or T4) disease, as some authors have suggested that the stage of the recurrence is predictive.1 Seven of the recurrent primary tumors were at an early stage of disease and 21 were advanced. All 7 patients with early-stage recurrent tumors underwent salvage surgery.

The Kaplan-Meier method was used to evaluate time to recurrence and patient survival. Two patients who died of cardiopulmonary collapse in the immediate postoperative period after undergoing a neck dissection were excluded from the recurrence and survival analysis.

RESULTS

Only 4 of the 48 study patients remain alive. Among the 42 who died, the cause of death was as follows: locoregional disease (n=24), distant metastases (n=8), and intercurrent disease (n=10). The mean time to recurrence among the 46 evaluable patients was 14.0 months (median, 7 months) (Figure 1), and the mean survival time was 26.2 months (median, 13 months) (Figure 2). The 2-year survival rate was 31%, and the 5-year survival rate was 15%.

The 28 patients with primary site recurrence had a mean time to recurrence of 12.6 months (median, 7 months) (Figure 3) and a mean survival time of 27.3 months (median, 12 months) (Figure 4). The 2-year survival rate was 29%, and the 5-year survival rate was 16%. When the 3 patients whose recurrence was treated with radiation therapy alone were excluded, the mean time to recurrence among the remaining 25 surgically treated patients was 12.7 months (median, 7 months) and the mean survival time was 28.4 months (median, 13 months). There was no relation between the time from initial treatment to recurrence and survival.

Of the patients treated for primary site recurrence, only 2 are alive and only 3 remained without disease for
more than 2 years. An attempt was made to analyze these 5 cases to determine what made them successful. The stage of the recurrent cancer was advanced in 4 patients and early in 1. The stage of the recurrence therefore did not predict success, as 6 of 7 patients with early recurrences, all of whom underwent salvage surgery, had recurrences. Two patients with oropharyngeal tumors who were treated with radiation therapy alone were salvaged with surgery at 9 and 18 months: one is alive and without cancer at 52 months, and the other one had a recurrence in the neck at 32 months and died. Two patients, including the patient who had an early-stage recurrence, had their original oral cavity and oropharyngeal tumors resected but not irradiated and were salvaged with reresection and postoperative radiation therapy at 2 and 4 months: one is alive and without cancer at 21 months, and the other died of a myocardial infarction at 80 months. One patient who underwent resection of an original oral cavity tumor, followed by postoperative radiation therapy, was salvaged with reresection at 7 months and lived an additional 140 months without cancer. This patient represents the only successful case of salvage among the 12 patients who underwent prior tumor resection and radiation therapy.

When the 18 evaluable patients who had a recurrence only in the neck were evaluated, the mean time to recurrence was 14.0 months (median, 13 months) (Figure 5), and the mean survival time was 25.0 months (median, 15 months) (Figure 6). The 2-year survival rate was 35%, and the 5-year survival rate was 14%. The tumors in all 4 patients whose neck recurrence was treated with radiation therapy alone persisted or recurred within 6 months. The 14 evaluable patients who had a recurrence in the neck and who were treated with neck dissection had a mean time to recurrence of 17.7 months (median, 25 months) and a mean survival time of 31.1 months (median, 20 months). Among this group, 2 patients were alive and without recurrence at 10 and 15 months, and another 4 patients died without recurrence at 26, 55, 65, and 96 months after treatment. Three of these 6 patients had recurrences in a previously dissected neck but had never undergone radiation therapy. All three underwent removal of the neck mass followed by radiation therapy. The other 3 patients who had a recurrence in the neck had not undergone surgery, and only 1 of them had previously undergone radiation therapy. These 3 patients underwent neck dissection, and the 2 who had not undergone irradiation received postoperative radiation therapy. No patients who had a recurrence in a previously dissected neck that had been irradiated were salvaged.

**COMMENT**

The likelihood of cure for patients who have a recurrence after therapy for T3 and T4 head and neck cancer is remote, even with aggressive salvage surgery. While the majority of patients had another recurrence within 1 year, there were occasional patients in whom surgery did lead to prolonged survival. Analysis of these patients showed that neither the time to the original recurrence nor the stage of the recurrent tumor was important...
tant. Successful salvage was very unlikely if the patient had been initially treated with combination surgical resection and postoperative radiation therapy. Only one patient who had this “gold standard” type of therapy was successfully salvaged.

Our finding that early-stage recurrent tumors were no more likely to be successfully salvaged than advanced recurrent tumors is in contrast to the finding in Goodwin’s study in which recurrent tumor stage correlated with outcome. However, Goodwin’s study included all initial tumor stages, and in his patients the larynx was the most common site. Survival for patients with cancer of the larynx exceeded 30 months, while that of patients with cancer of the oral cavity was only 10.4 months. Other authors have found that for patients with recurrences of oral cavity tumors, the stage of the original tumor correlates with survival but that the stage of the recurrent tumor does not. In our study, tumors of the larynx represented a small minority, with only 7 laryngeal cancers, while there were 41 cancers of the oral cavity and pharynx.

The aggressiveness of prior treatment to the primary site influences the chance of salvage. Only 1 patient who had undergone prior resection and radiation therapy was successfully salvaged. Otherwise, salvage surgery was only successful in patients who had failed to complete their previously recommended radiation therapy and who were able to undergo resection and radiation therapy or in patients in whom radiation therapy alone had been administered and the first attempt at surgery was for salvage. Interestingly, because of our historic institutional and regional bias toward laryngectomy as initial therapy for advanced T-stage laryngeal cancer, none of our successful surgical salvages was for laryngeal tumors.

Treatment of recurrent neck disease is similarly problematic. Kowalski described 27 patients who had recurrences in the neck and who underwent radical neck dissection. Only 5 survived. It is generally accepted that surgical salvage of recurrence in a previously irradiated and surgically treated neck is highly unlikely, and, in fact, this was attempted in only 1 of our patients. We did have 6 patients, though, in whom surgical salvage did result in long-term survival; however, in none of these cases had the neck been previously dissected and irradiated.

Our study did not evaluate patient morbidity or quality of life but instead concentrated on recurrence and survival. Unfortunately, all salvage therapy, particularly after radiation therapy for cure, will result in significant morbidity and will significantly affect the quality of life of the patient. Before salvage therapy is considered, the morbidity of the therapy vs a realistic chance of cure must also be taken into consideration.

In addition to salvage surgery, reirradiation with or without chemotherapy is also an option for patients with recurrent cancer. Unfortunately, no patients in our study were successfully treated with reirradiation. Reirradiation treatments are highly toxic, and the cure rates as reported offer median survivals of less than 1 year. Studies are ongoing, however.

Our findings demonstrate the limited survival with salvage therapy in patients who had recurrent cancer after undergoing therapy for advanced disease. The study is flawed in that it evaluated patients with varied tumor sites and varied methods of initial therapy. However, this is consistent with other studies that have investigated this problem. When patients who underwent prior surgery and radiation therapy and then had a recurrence, the chance for cure with salvage surgery was minimal. However, if the patient received incomplete treatment or had undergone single-modality initial therapy, salvage surgery resulted in more of a chance for cure.

The data presented permit the physician to offer patients an informed choice before they make the decision to undergo salvage surgery after prior radical therapy for advanced cancer. Given the morbidity of salvage therapy, patients need to know the possibility, or, in many instances, the limited likelihood of successful salvage. Such knowledge is essential to prevent patients from undergoing morbid therapy with inappropriate expectations.

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REFERENCES