Salvage Therapy for Recurrent Carcinoma of the Nasopharynx

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Introduction

Recurrent carcinomas of the nasopharynx are particularly challenging to treat. For most head and neck sites when the initial form of therapy is either surgery or radiation therapy, the other modality can be used, often with good results, to salvage failures of the first method of treatment. This is not generally the case for tumors of the nasopharynx when they recur at the primary site. The anatomical location of the nasopharynx dictates that radiation therapy must be the mainstay of treatment for both *de novo* and recurrent tumors with salvage surgery being reserved for failures in the treated neck. While it is true that carcinomas of the nasopharynx have a propensity towards distant metastases, approximately 30–50% of first failures are local/regional in nature and aggressive therapy may be currative in some percentage of these patients.

In this paper I will first discuss the determinants of local/regional control and then the expected outcomes with "classical" salvage radiotherapy. I will then review the complications of this form of treatment and areas where new approaches may yield improved results. These approaches include the use of concomitant chemotherapy along with radiotherapy in the manner of the Intergroup Study 0099 for de novo lesions, the use of intensity modulated radiotherapy to improve dose localization, and the use of stereotactic radiotherapy with either a linear accelerator or a Gamma Knife to treat tumor extensions through the skull base.

Determinants of Local Regional Control with Primary Treatment

Before considering how to salvage radiation failures, let us first consider the prognostic factors that make a failure more likely. Patients with such factors may be candidates for more aggressive, first line forms of treatment.

In a classic paper, Wang notes that with radiation alone, a patient with an early-stage carcinoma of the nasopharyx can expect a cure rate of approximately 80%[1]. However, recurrences become much more likely in the setting of an initially-extensive primary lesion, too low of a radiation dose, insufficient tumor coverage due to the use of too small of radiation ports or a simple "geographic miss". In addition, there also can be second primary tumors arising in the previously irradiated nasopharynx.

Sanguineti et al report on the MD Anderson experience for 348 patients with nasopharyngeal carcinoma treated with radiation alone[2]. While the overall 5-year actuarial local control rate was 71% at the primary site, they found that on both univariate and multivariate analysis, advanced T-stage (T4 vs. other), N-stage (N2/N3 vs. N0/N1), squamous histology, and presence of cranial nerve deficets were adverse prognositic factors. In particular, they found an 84% 5-year actuarial local control rate for lumphoepitheliomas vs 60% for squamous cell tumors and this improved local control was demonstrated out to 25 years on actuarial plots. In their series squamous cell tumors accounted for 51% of cases but the prevalence of this histology would most likely be lower in Asian countries.

Teo et al found a dose response relationship for local control for early stage tumors[3]. They analyzed 509 patients with T1 or T2 lesions and found a significantly-improved local control rate if brachytherapy was used following the delivery of external beam irradiation. This was not a randomized study but the authors compared the outcome for 346 patients treated with external beam alone (median dose 60Gy in 6 weeks with a range of 60–71.2Gy) to the outcome for 163 patients treated with a similar dose of external beam irradiation but followed with an HDR intracavitary implant delivering either 24Gy/3 fractions/15 days for documented locally-persistent tumor or 18Gy/3 fractions/15 days for apparent complete responders to the external beam treatment. The 5-year actuarial local failure rate was 5.4% in the group receiving the implant compared to 10.3% in the group treated with external beam alone (p=0.016). There was an increase in local mucosal ulceration and/or necrosis in the group receiving the implant but these complications were felt to be manageable. The authors conclude that there is a dose response curve which exists above the dose level that is normally considered to be tumorcidal.

Classical Salvage Therapy for Recurrent Tumors

Wang has reported on 51 patients with recurrent nasopharyngeal carcinomas who were treated with curative intent at the Massachussetts General Hospital between 1950−1981[1]. While the average time to developing the local recurrence was 18 months following the original treatment, 12% of the patients exhibited their first recurrence more than 5 years following the initial treatment. The time between the intial therapy and the recurrence was an important prognostic factor for outcome. If the time interval was >24 months, the 5 year actuarial survival was 66% compared to only 13% if the interval was ≤24 months (p=0.005). Wang also noted that it was important to give high doses of radiation even in the retreatment setting. If a high dose (≥60Gy) of re-irradiation was delivered, the 5-year survival rate was 45% compared to 0% for patients who received <60Gy (p=0.0001). It was also noted that reirradiation to high dose levels could cause complications such as soft tissue ulceration, breakdown of bone and cartilage, and cranial nerve damage. For tumors not involving the skull base, Wang recommends giving 40Gy external beam in 2Gy increments using carefully designed portals to be followed by 2 intracavitary ^{137}Cs applications giving 10Gy each with a 1 week interval between applications. If the recurrent tumor invades the skull base, the intracavitary application would not deliver an adequate radiation dose to the superior extent of tumor and in this setting Wang recommends giving 66Gy external beam irradiation in 2Gy increments.

Chua et al. have reported on 140 patients with recurrent nasopharyngeal tumors who were restaged with CT scanning[4]. Twelve highly-selected patients were treated with a surgical resection, 97 were reirradiated with curative intent, and 31 were treated only palliatively. I will consider further only those patients treated with curative intent. In the group treated for cure with reirradiation, 91 had relapsed only at the primary site and 6 had relapsed at both the primary site and in the neck nodes. External beam radiation alone (60Gy) was used to treat 62 patients, a gold seed (^{198}Au) permanent implant delivering 50Gy was used to treat 34 patients, and one patient was treated using a combination of external beam radiotherapy and a gold seed implant. For the reirradiated patients, the median overall survival was 33.6 months with a 5-year overall survival rate of 36%. For the patients treated with surgical resection, the median overall survival was 34.1 months and the 5-year overall survival was about 38%. Thus, the group treated with radiotherapy did as well as the group treated with salvage surgery. Only thirteen percent of patients treated with curative intent ultimately developed distant metastases. The time interval between the initial treatment and the development of the recurrence was not found to be an significant prognostic factor in overall survival, but it must be noted that Chua et al used a 12 month rather than a 24 month cutoff. Only older patient age (>40 years) and T-stage at recurrence (T3/T4 vs. T1/T2) were found to be important predictors of survival in the curatively treated group. A significant number of patients developed complications after reirradiation with severe trismus occurring in 30% of patients and neurological complications occurring in 34% of patients. The authors note that these high complication rates are not unexpected given that the majority of patients had received >100Gy cummulative dose with the two courses of treatment.

Potential Areas for Improvement

One potential area for improvement is to retreat patients using concomitant chemotherapy and radiotherapy rather than just with radiation alone. The Intergroup Study 0099 for patients with *de novo* nasopharyngeal tumors demonstrated improved local control and survival when chemotherapy was added to radiotherapy[5]. In the experimental arm patients were given concomitant chemotherapy consisting of cis-platinum at 100mg/m^2 every three weeks along with radiotherapy followed by 4 cycles of consolidation chemotherapy with cis-platinum and 5-fluorouracil (5FU) and in the control arm patients were treated with standard fractionated radiotherapy. This study was stopped early when an interim analysis showed a statistically-significant advantage for the experimental arm. At the time of closure, the median progressionfree survival was 52 months on the experimental arm vs. 13 months ($p<0.0001$) on the control arm and respective absolute survivals were "median not yet reached" vs. 30 months ($p=0.0007$). While this approach has not been tested in the setting of locally-recurrent tumors, there is reason to think that the dose response curves of the recurrent tumors would shift in the same manner as the dose response curves of the *de novo* lesions with this change in treatment regimen.

If the radiation dose to the muscles of mastication could be reduced during the retreatment process, this should reduce the incidence of servere trismus. Intensity modulated radiotherapy (IMRT) offers a method of accomplishing this[6)7)]. Hsiung et al[6)] also studied the impact of IMRT in reducing the dose to the brain stem in patients with nasopharyngeal tumors. They compared the treatment plans for 14 consecutive patients who were treated with three dimentsional conformal radiotherapy (3D-CRT) with 5- and 7-field IMRT plans. In terms of the prescribed tumor dose, the dose delivered to 5% of the brainstem was 30.9% with 3D-CRT compared to 15.3% with 5-field IMRT and 14.7% with 7-field IMRT. Note that after a certain degree of complexity, there are diminishing returns to adding more IMRT fields. Hsiung et al[6)] identified the following features as predicting for the greatest improvement with IMRT : 1) vertical length of target >7cm, 2) minimal distance between target and brain stem <0.1cm, 3) maximal overlap between the target and brain stem on AP projection >0.6cm, 4) maximal overlap of target and spinal cord >1cm on AP projection, and 5) any degree of vertical overlap between the target and the eyes.

While IMRT can greatly reduce the dose delivered to the brain stem and optic structures, stereotactic radiotherapy methods offer even greater precision. These techniques require a rigid frame immobilization to "fix" the patient in the same position in the planning scans as in the treatment itself. Quoted accuracies of beam delivery are fractions of a millimeter. Either a specially-modified linear accelerator or a special device untilizing a large number of ^{60}Co sources, eg. a Gamma Knife, can be used to deliver the radiation. At the University of Washington in situations where prior radiotherapy to the optic nerves and brain stem limits the ability to treat portions of tumor extending through the skull base, we use the Gamma Knife to "boost" the superior extent of tumor after giving the maximal amount of external beam irradiation using IMRT or other precision techniques. We have performed this treatment on 14 patients with either recurrent nasopharyngeal carcinomas or minor salivary gland tumors of the paranasal sinuses and have demonstrated the safety of this technique. We do not as yet have sufficient followup to determine whether this boost to the skull base portion of the tumor yields improved local control.

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