Bone or Cartilage Invasion by Advanced Head and Neck Cancer

Intra-arterial Supradose Cisplatin Chemotherapy and Concomitant Radiotherapy for Organ Preservation

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**Background:** Invasion of bony or cartilaginous structures by advanced upper aerodigestive tract cancer has been considered an indication for surgery on the basis of historic experience of poor responsiveness to radiation therapy. At University of Tennessee–Memphis, patients with advanced head and neck cancer have been treated on a protocol of concomitant intra-arterial (targeted) cisplatin and conventional radiation therapy.

**Objective:** To compare the efficacy, in terms of disease control and survival, of this protocol in patients with T4 squamous cell cancers and invasion of bony or cartilaginous structures (group 1; n=45) vs those with T4 disease but no bone or cartilage involvement (group 2; n=90).

**Design:** Subset analysis of protocol database and retrospective chart review.

**Methods:** Treatment consisted of 4 weekly intra-arterial infusions of cisplatin (150 mg/m² per week), with simultaneous systemic neutralization by intravenous sodium thiosulfate (9 mg/m²), and concurrent radiation therapy at 180 rad (1.8 Gy) or 200 rad (2 Gy) per fraction to a planned total of 6600 to 7400 rad (66-74 Gy) to the primary site or overt nodal disease. Presence of bone or cartilage invasion was established by review of tumor diagrams of clinical findings and computed tomography or magnetic resonance imaging reports.

**Results:** Of 135 patients who had T4 disease in a minimum follow-up of 9 months (median, 40 months), 45 had clinical or radiologic evidence of bone (n=29: mandible, 12; maxilla, 9; sphenoid, 3, hyoid, 6) and/or cartilage (n=18: thyroid, 16; cricoid, 4) invasion (some patients had involvement of more than 1 site). The rate of complete response in group 1 (66.7%) was not significantly different from that in group 2 (71.1%) (χ² test, P=.79). The 2-year overall actuarial survival for group 1 (46.3%; 95% confidence interval, 30.3%-62.3%) was not significantly different (generalized Wilcoxon test, P=.36) from that of group 2 (36.9%; 95% confidence interval, 25.5%-48.4%). A marked trend was noted for higher response rates in cases of cartilage invasion (81.2%) than in those with bone invasion (58.6%) (P=.15).

**Conclusion:** Equivalent efficacy of treatment in the 2 groups suggests that targeted chemoradiation can be a definitive therapeutic option in patients with advanced head and neck cancer invading bony or cartilaginous structures.


Surgery continues to be the mainstay of treatment for advanced cancers of the head and neck. The combination of chemotherapy and radiation, however, is increasingly recognized as a viable alternative to radical surgery for selected patients. The decision of choosing between these 2 alternatives remains highly subjective, based frequently on intuition and personal impressions. There is a general lack of information in the literature specifically addressing clinical prediction of responsiveness to chemoradiation. One such example of subjectivity, in our opinion, is the frequently cited argument that presence of bone or cartilage invasion by cancer is a contraindication for organ-preservation approaches. We wanted to examine whether this presenting characteristic of the tumor is truly a clinical predictor of poor responsiveness to chemoradiation therapy.

At the University of Tennessee Health Sciences Center, Memphis, patients with advanced head and neck cancer are treated with concomitant high-dose intra-arterial cisplatin chemotherapy and radiation. Both operable and inoperable cancers are treated with this regimen, and surgical salvage is performed 8 weeks later in patients with operable residual disease. We do not consider invasion of bone or cartilage a contraindication to this approach. In this report, we compare the oncologic results of a group of patients presenting with T4...
PATIENTS AND METHODS

Between August 1, 1993, and December 31, 1998, 293 patients with advanced squamous cell cancers of the head and neck region received treatment on our protocol of intraarterial cisplatin with concomitant radiation. Among these, 135 patients presented with a T4 primary cancer.2 These patients form the basis of this study. A review of clinical charts, computed tomography and magnetic resonance imaging reports, and information in the protocol databases was carried out to select patients whose tumor invaded bony or cartilaginous structures at the primary site. Forty-five such patients were identified (group 1), leaving 90 patients who had advanced (T4) disease at the primary site that did not involve bone or cartilage (group 2).

All patients were treated with concomitant intraarterial cisplatin along with conventional radiation therapy. Chemotherapy, delivered on days 1, 8, 15, and 22 of radiation therapy, consisted of cisplatin, 150 mg/m2, infused directly into the main arterial supply of the location of primary tumor via superselective catheterization. The infusion was given during a period of 3 to 5 minutes and was preceded by prehydration with 1 L of 5% dextrose with 0.5N isotonic sodium chloride solution containing 20 meq of potassium chloride and 2 g of magnesium sulfate administered during the preceding 2 hours. Sodium thiosulfate (9 g/m2 in 200 mL of distilled water) was given by intravenous push during 15 to 20 minutes, concurrently with intra-arterial cisplatin. This was followed by a continuous intravenous infusion of sodium thiosulfate, 12 g/m2, during 6 hours (the 12 g/m2 is dissolved in 1 L of distilled water and infused at 167 mL/h). Posttreatment hydration was achieved with 1 L of 3% dextrose with 0.35N isotonic sodium chloride solution containing 20 meq of potassium chloride and 2 g of magnesium sulfate during the next 6 hours.

RESULTS

PATIENT CHARACTERISTICS AND TREATMENT DELIVERY

Table 1 shows the age, sex, site, and nodal-stage distribution in the 2 groups. Both groups evenly represented site and nodal involvement except for a somewhat higher proportion of patients in group 2 with oropharyngeal cancers.

Among patients with bone and/or cartilage invasion (group 1), there were 27 patients with bone invasion, 16 patients with cartilage invasion, and 2 patients with invasion of both bone and cartilage (hyoid and thyroid in one and hyoid and cricoid in the other). The 2 patients with bone and cartilage invasion were included in the category of bone invasion for all response and survival calculations in this article. Structures involved were the mandible (n=12), maxilla (n=9), hyoid (n=6), and sphenoid (n=3) bones, and thyroid (n=16) and cricoid (n=4) cartilages.

Thirty-one (69%) of 45 patients with bone or cartilage invasion received all 4 cisplatin infusions. Nine patients received 3 infusions, 2 patients received 2 infusions, and 3 patients received a single cisplatin infusion because of advanced age, toxic effects, or poor compliance. Thirty-eight patients (84%) received a radiation dose of 6500 rad (65 Gy) or more. Two patients received 5000 and 5400 rad (50 and 54 Gy), respectively, and 5 received less than 5000 rad (50 Gy).

TREATMENT RESPONSE

Fourteen patients in the bone invasion category had a complete histologic response (Figure 1), which was determined with a biopsy in 13 patients and on surgical resection in 1 patient. Three additional patients had a clinical complete response (no biopsy was performed). In the cartilage invasion category (Figure 2), 12 patients were proved by biopsy to have a complete histologic response; one other patient had a clinical complete response. None of these patients underwent surgery to the squamous cell cancers of the head and neck with clinically and/or radiologically documented bone or cartilage invasion with those of another group with T4 squamous cell cancers of the head and neck with clinically and/or radiologically documented bone or cartilage invasion.
primary site. Nine patients (of the 45 in group 1) had a neck dissection at the time of restaging.

Table 2 lists the responses achieved after chemoradiation in groups 1 and 2. While 26 patients achieved a histologically proved complete response, 4 additional patients were deemed to have a complete response on the basis of clinical and radiologic findings. Combining the 2 categories, a complete response rate of 66.7% (30/45) was achieved. In comparison, the complete response rate for group 2 (no bone or cartilage invasion group) was 71.1% (64/90). This difference was not statistically significant ($\chi^2$ test, $P = .79$).

Table 3 lists the responses obtained when patients in group 1 were separated by presence of bone or cartilage invasion. Two patients who had both bone and cartilage invasion were included in the category of bone invasion for this analysis. The difference in response rates approaches significance ($\chi^2$ test, $P = .15$), with cartilage invasion showing a higher response rate (81.2%) than bone invasion (58.6%).

Table 4 shows the response rates as analyzed for individual bony or cartilaginous structures involved.
TOXIC EFFECTS

Acute toxic effects observed in our protocol have been described earlier.1 For this study, we reviewed the acute toxic effects that occurred in the group with bone and cartilage invasion (group 1). Three patients died during treatment, 1 of neutropenic sepsis and 2 of causes related to general debility and electrolyte loss. In addition, a grade 3 hematologic toxic reaction developed in 4 patients and a grade 3 mucosal toxic reaction in 13 patients. One patient developed a cerebrovascular event.

There were no instances of delayed radiation-induced toxic effects that were severe enough to warrant hyperbaric oxygen treatment or surgery. Long-term laryngeal function and tracheostomy and feeding tube requirements were not evaluated for this study but have been reported elsewhere.1,3,4

LONG-TERM DISEASE CONTROL AND SURVIVAL

Follow-up ranged from 9 to 76 months, with a median of 40 months.

Figure 1 depicts the patterns of failure observed in the subset of patients presenting with invasion of bony structures. Among those with histologic complete response (n=14) at the primary site, only 1 patient underwent surgical resection of the primary site at the time of restaging. No tumor was found in the specimen (resection of floor of mouth and segmental mandibullectomy) in this patient. The defect was repaired with a fibula free flap. Despite an excellent postoperative recovery, the patient died 6 weeks later of a myocardial infarction. No conclusions about long-term disease control are therefore possible in this patient.

No recurrence developed at the site of primary cancer in any of the other 13 patients in this category, although 4 developed distant metastasis and 1 a nodal recurrence in the opposite side of the neck. Among the 3 patients with clinical complete response, 1 had local failure; in the other 2, disease remained controlled in the primary site and neck but appeared later as distant metastasis. Among the partial responders (histologic, 3; clinical, 2), 4 had unresectable residual disease and 1 was treated with salvage surgery. This last patient had local recurrence a year later, at which time no salvage surgery could be performed due to the unresectable nature of the disease. One patient with no response was switched to intravenous palliative chemotherapy for progression of disease. In 6 patients response was unevaluable for various reasons (poor medical status, detection of distant metastasis, and death before restaging).

Figure 2 shows the failure pattern of 16 patients with cartilage invasion. There were 13 complete responders (histologic, 12; clinical, 1), only 1 of whom had local failure. This was a patient with a supraglottic cancer who developed extensive recurrence in the oropharynx and nasopharynx. Three patients had un evaluable results because they died before restaging.

The 2-year overall actuarial survival for group 1 (46.3%; 95% confidence interval, 30.3%-62.3%) was not significantly different (generalized Wilcoxon test, P=.36) from that of group 2 (36.9%; 95% confidence interval, 25.5%-48.4%). Figure 3 depicts the overall survival of patients in groups 1 and 2. Figure 4 shows the overall survival for the categories of bone invasion and cartilage invasion. While there is a trend toward better survival in those with cartilage invasion, this was not found to be statistically significant (generalized Wilcoxon test, P=.36).

Table 4. Response Rates According to Individual Structures Involved*

<table>
<thead>
<tr>
<th>Structure</th>
<th>Response at Primary Site (CR + CCR)/Total</th>
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<tbody>
<tr>
<td>Mandible</td>
<td>CR 5, CCR 2, PR 1, NR 1, UE 3 7/12</td>
</tr>
<tr>
<td>Maxilla</td>
<td>CR 3, CCR 1, PR 2, CPR 2, UE 1 4/9</td>
</tr>
<tr>
<td>Sphenoid</td>
<td>CCR 1, PR 1, UE 1 1/3</td>
</tr>
<tr>
<td>Hyoid</td>
<td>CR 6 6/6</td>
</tr>
<tr>
<td>Thyroid</td>
<td>CR 12, CCR 1, UE 3 13/16</td>
</tr>
<tr>
<td>Cricoid</td>
<td>CR 3, CCR 1 4/4</td>
</tr>
</tbody>
</table>

*CR indicates complete response; CCR, clinical complete response; PR, partial response; CPR, clinical partial response; NR, no response; and UE, unevaluable.

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The 2-year actuarial disease control above the clavicles (absence of disease at the primary site or in the neck) for group 1 (64.3%; 95% confidence interval, 50.2%-78.3%) was also not different statistically (generalized Wilcoxon test, \( P = .55 \)) from that in group 2 (68.3%; 95% confidence interval, 58.5%-78.0%). Figure 5 shows the actuarial control of disease above the clavicles in groups 1 and 2. The sharp drop at 3 months reflects the patients who had incomplete response (histologic partial response, clinical partial response, and no response categories) who could not be cleared of their disease surgically, as well as the patients in the unevaluable category.

**COMMENT**

Selecting between surgical and nonsurgical treatment for a given patient depends on several factors: performance status and comorbidities, which determine the patient’s ability to tolerate chemotherapy; family and social history, which predicts the patient’s ability to complete intensive protocol-based treatment; and the morphologic, radiologic, and pathologic characteristics of the tumor, which influence the physician’s judgment regarding the likelihood of success with nonsurgical therapy. In this last category, invasion of bony and cartilaginous structures by cancer has often been cited as reason to treat the patient surgically.

There are 2 principal reasons why cancers invading bone and cartilage are considered unsuitable for treatment with radiation therapy. First, these cancers are considered less likely to respond to radiation.2-13 This impression is based on the observation of relatively poor results obtained when patients with T4 cancers of the oral cavity and larynx are treated with radiation as the primary modality. An extensive review of the literature by Parsons et al11 showed that only 50% of T4 cancers of the larynx are controlled locally with radical radiotherapy. Similarly, in a series of oral cavity cancers treated with radiotherapy at Christie Hospital in Manchester, England, control at the primary site was found to be inversely related to increasing T stage, node positivity, and bone involvement at presentation.12 Studies reporting the results of curative radiation for advanced (T4) soft palate and tonsillar cancers show that less than 50% of these cancers are expected to respond completely.5-7,13

The second reason for preferring surgical treatment for advanced cancers of the head and neck that invade bony and cartilaginous structures is a concern for a higher incidence of radiation-induced complications in these patients. In Parsons and coworkers’ series of T4 laryngeal carcinomas, complications were graded as mild (soft tissue necrosis or bone exposure lasting 3 months or less), moderate (permanent tracheostomy or gastrostomy but retained laryngeal speech), or severe (total laryngectomy).11 Five percent, 7%, and 5% of their patients developed mild, moderate, and severe complications, respectively. Osteoradionecrosis of the mandible has been noted to occur in 5% to 10% of individuals treated with radiation for oral cavity cancers.12,14

As stated previously, involvement of bone or cartilage is not considered a contraindication for chemoradiation at our institution. As a result, many patients with this characteristic have been treated with our protocol of intraarterial chemotherapy and radiation. In particular, these are patients who would otherwise require a total laryngectomy or a resection of a large portion of their tongue if treated surgically.1,14 In addition, a few patients with paranasal sinus and nasopharyngeal cancers invading the bones of the skull base are also included in this series. While group 1 contains T4 cancers invading bony and cartilaginous structures, group 2 consists of individuals with advanced tumors displaying extensive mucosal or soft tissue extension of disease resulting in their categorization as T4 cancers. Given the fact that both resectable and unresectable cancers are included in this study, we believe that a complete response rate of 66.7% represents a substantial improvement over the historical response rates observed with radiation therapy alone. Furthermore, a complete response rate of 71.1% obtained in group 2 is not statistically significantly different from that obtained in group 1. Hence, with our protocol, presence of bone or cartilage invasion does not adversely affect the likelihood of disease control.

A marked trend of improved responsiveness to our protocol was noted with cancers invading cartilage compared with those invading bone (81.2% vs 58.6%). This has important implications on the treatment of patients with cancers of the larynx and hypopharynx. Our results with these cancers have been discussed in detail in other reports.14 Of the 17 patients displaying complete response (among 29 with bone invasion), only 1 developed a local recurrence (Figure 1). Similarly, only 1 patient, among 13 complete responders in the cartilage invasion category, developed a local recurrence (Figure 2). Hence, despite the presence of bone and cartilage invasion at presentation, disease remained controlled in the long run in most complete responders.

There were 5 partial responders in the bone invasion category (Figure 1). Only 1 of these cases was amenable to surgical salvage. This patient had local failure a year later, and the extent of disease precluded surgical salvage. There were no partial responders in the cartilage invasion category (Figure 2). Since only 1 patient in the category of bone and cartilage invasion under-
went surgery at the primary site, it is not possible to comment adequately about wound complication rates in this group of patients.

Despite the impressive control of disease above the clavicle, which remained stable over time (Figure 5), survival remained modest (46.3% in group 1 and 36.9% in group 2). In large measure, this is a reflection of a significantly high incidence of distant metastases on follow-up. However, this is not entirely surprising given the advanced nature of the cancers in this study population. The lack of any difference in the 2-year overall survival between the 2 groups again suggests that presence of bone or cartilage invasion does not affect the curability of these cancers with our treatment protocol.

The objective of this study was limited to describing the oncologic results. Assessment of long-term function, morbidity, and quality of life would on its own have constituted a detailed investigation that was outside the scope of this article. While such studies are currently ongoing at our institution, we have previously undertaken some limited analyses of functional outcome. In a group of 47 patients with advanced head and neck cancer available for follow-up at 18 months, 13% were found to be dependent on tube feeding. In another evaluation, 5 of 15 patients with advanced pyriform sinus cancer surviving at 12 months were still dependent on tube feedings. Additional information on the long-term adverse effects of radiation, such as the development of osteoradionecrosis of the mandible in patients with oral cavity or oropharyngeal cancers, could be gathered by prospective assessment of pain scores and with radiologic imaging. Although such information is obviously not available in this study, there were no instances of any patients requiring hyperbaric oxygen or surgery for osteoradionecrosis. It is possible that longer follow-up and larger numbers of surviving patients with continued use of this approach may result in some patients developing this complication.

Because of the retrospective nature of this analysis, the magnitude of bone or cartilage invasion could not be accurately ascertained. It may be intuitively assumed that presence of massive destruction of bony or cartilaginous framework, such as in the mandible or the larynx, would diminish the likelihood of retained function and increase the chance of long-term adverse effects. Patients with such findings are usually treated surgically at our institution. While this study cannot clarify exactly how much bony or cartilaginous destruction may be safely treated with an organ-preserving regimen, it does establish the oncologic efficacy of targeted chemoradiation in certain selected patients with this finding.

Whether targeted chemoradiation can be as efficacious as surgery for patients with bone or cartilage invasion could only be truly determined if such patients were to be randomly assigned between these 2 treatments. However, the ethical difficulty of conducting such a trial leaves us with only the option of judging this regimen on its own in a phase 2 trial format. This communication argues that targeted chemoradiation could be a viable treatment alternative in patients with bone and cartilage invasion if the oncologic results are not inferior to those obtained with similarly staged cancers where such invasion is absent. In other words, if it is appropriate to treat advanced cancers not invading bone or cartilage with the organ-preservation approach, then it is also appropriate to treat cancers that invade these structures in a similar fashion.

In conclusion, several factors must be considered in selecting the appropriate line of therapy for advanced head and neck cancers. Concerns for long-term adverse complications of radiation must be balanced against the prospect of organ preservation. For the same stage of disease (T4), the results obtained with and without bone or cartilage invasion were comparable in this study. Hence, with our protocol of concomitant high-dose intraarterial cisplatin and radiation therapy, presence of bone or cartilage invasion by the primary cancer does not constitute an absolute contraindication to adopting an organ-preservation approach.

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