Treatment Outcomes of T4 Locally Advanced Head and Neck Cancers With Soft Tissue Invasion or Bone and Cartilage Invasion

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Purpose/Objective(s): T4 locally advanced squamous cell cancers of the head and neck (SCCHN) with bone and cartilage invasion (BCI) traditionally have been treated with resection followed up with chemoradiotherapy (CRT). Because the organ preservation trials, more patients with BCI, as well as those with soft tissue invasion (STI), have been treated with definitive CRT. This is a review of our experience.

Materials/Methods: We performed a retrospective review of patients who underwent definitive CRT or radical resection followed up with postoperative CRT for T4N0-3M0 locally advanced SCCHN. We analyzed outcomes based on STI/BCI and types of treatment. Radiotherapy doses ranged from 59.4 to 72 Gy. Concurrent chemotherapy was platinum based in all CRT patients.

Results: From 1995 to 2006, 101 patients with locally advanced SCCHN were treated definitively. Of these, 51 had STI and 50 had BCI. Of the 51 patients with STI, 42 were treated with CRT, 5 patients were treated with resection followed by CRT, and 4 patients were treated with radiotherapy alone. Of the 50 patients with BCI, 26 patients were treated with CRT, 20 patients were treated with radical resection followed by radiotherapy or CRT, and 4 patients were treated with radiotherapy alone. Five-year local-regional control was 51% and 43% for STI and BCI patients treated with CRT, respectively, and 44% for BCI treated with radical resection. Five-year overall survival was 23%, 51%, and 28% for STI treated with CRT, BCI treated with CRT, and BCI treated with radical resection. Outcomes were not statistically different between these groups.

Conclusions: This study suggests similar outcomes for CRT or resection followed up with chemoradiotherapy for patients with locally advanced SCCHN with BCI. Concurrent CRT may be viable alternative to upfront resection in these patients. Further studies should be performed to validate these provocative findings.

Key Words: head and neck cancer, chemoradiation, resection, postoperative chemoradiation, locally advanced

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Bone or cartilage invasion (BCI) occurs in 12% to 43% of patients diagnosed with squamous cell carcinomas of the head and neck (SCCHN).[1–4] Traditionally, such patients were managed with resection secondary to low curability rates with radiation alone.[5] However, high recurrence rates and reduced outcomes were found in those with BCI treated with resection alone.[6–8] Often these patients are treated with postoperative radiotherapy, with or without chemotherapy.[2] This treatment resulted in substantial functional morbidity, including loss of natural voice and change in deglutination. However, the VA Laryngeal Cancer Study (VALCS)[9] revealed similar outcomes in locally advanced laryngeal cancers treated with either sequential chemoradiotherapy (CRT) or resection, followed by radiotherapy. However, the VALCS did not specifically address the outcomes of those with STI and/or BCI. Subsequently, RTOG 9111,[10] which excluded patients with BCI, revealed improved outcomes with concurrent CRT versus radiotherapy alone or sequential CRT. In an effort to extend those outcomes to patients with BCI, Samant et al[11] revealed similar outcomes in patients with T4 locally advanced SCCHN caused by BCI or soft tissue invasion (STI) treated with CRT. Soo et al[12] reported their phase III trial evaluating those with III/IV SCCHN treated with surgery, followed by radiotherapy versus CRT. They revealed similar outcomes between the 2 treatment regimens. This study included a variety of primary sites, including oral cavity, oropharynx, laryngeal, and hypopharyngeal sites, but did not specifically address outcomes associated with BCI or STI.

Because these studies, our institutions have used CRT as definitive treatment for patients with head and neck cancers with BCI and STI with increased frequency. Surgical salvage, when feasible, was performed for local relapse after definitive CRT. Primary surgery still remained a treatment option followed by postoperative CRT. This is a retrospective report on our multi-institutional experience exploring the outcomes of patients with T4 locally advanced SCCHN with BCI and STI treated with definitive CRT or resection followed up with radiotherapy, with or without chemotherapy. To our knowledge, this is the first publication exploring these outcomes of T4 head and neck cancers, with BCI/STI treated with definitive CRT or resection followed by radiotherapy.

METHODS

From 1995 to 2006, 101 patients with T4aN0-3M0 locally advanced SCCHN were treated at Long Beach Memorial Medical Center (LBMMC), Long Beach Veteran's Hospital (LBVA), and the City of Hope National Cancer Center (COHNCC). Patients with oral cavity, oropharyngeal, laryngeal, and hypopharyngeal squamous cell carcinomas were included in this study. Nasopharyngeal, salivary gland, and paranasal sinus squamous cell carcinomas were excluded. Pretreatment workup included CT scans, MRI scans, PET/CT scans, examination under anesthesia, triple endoscopy with biopsies, CXR, and associated labs. BCI was determined by findings from imaging studies and confirmed on pathologic specimens whether the patient underwent primary resection. Cartilaginous sites of invasion included the thyroid, cricoid, and tracheal cartilages. Bony sites of invasion included the mandible, hyoid, hard palate, and retromolar trigone. Patients with T4 locally advanced SCCHN secondary to STI were also included to compare with patients with BCI to evaluate whether BCI conferred a worse prognosis. T4 patients with STI were staged according to the AJCC staging manual[13] and included deep muscle invasion of the tongue, strap muscles, or central compartment soft tissue.

Patients were treated with definitive resection followed by radiotherapy, with or without chemotherapy, or definitive CRT. Patients with STI were treated with CRT, although 5 of the patients with STI were treated with resection followed by radiotherapy. Patients with BCI were treated with resection followed by CRT or

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radiotherapy. However, patients deemed unresectable and/or inoperable and those who refused surgery underwent CRT. Records were reviewed retrospectively, and data regarding age, gender, primary diagnosis, nodal disease, treatment selection, and treatment outcome were recorded. This retrospective review was approved by the Institutional Review Boards of the institutions involved in this study.

Treatment Techniques

Surgery

Surgery included a wide resection of the tumor with comprehensive neck dissection. Comprehensive neck dissection for node-positive disease involved removal of levels I–V lymph nodes. Resections performed included partial and total laryngectomies, partial or total glossectomies and pharyngo laryngectomies. Adjuvant radiotherapy was given to the tumor bed and bilateral neck in all surgical cases. Radiotherapy was given via parallel opposed fields with a single AP field, helical tomotherapy, or intensity-modulated radiotherapy. Patients were immobilized by aquaplast masks followed by CT simulation. Doses were generally 1.8 to 2 Gy per fraction, 5 days a week to a total of 59.4 to 70 Gy. Gross residual disease received 70 Gy. Volumes at high risk for recurrence received 60 Gy. Areas at low risk for microscopic disease received 50 Gy. Early in the study period, patients were treated with adjuvant radiotherapy alone. Because the RTOG and EORTC, studies revealed improved outcomes of adjuvant CRT over radiotherapy alone,[14,15] institutional policies were to treat these patients with adjuvant CRT. Chemotherapy consisted of cisplatin and 5-fluorouracil (5-FU) based regimens given every 3 weeks. Cisplatin was given intravenously at 100 mg/m^2 and 5-FU was administered as a continuous 24 hour infusion for 5 days at 1000 mg/m^2 per day.

Concurrent Chemoradiotherapy

Definitive radiotherapy consisted of 59.4 to 74 Gy to the primary tumor site. Median radiotherapy dose was 66 Gy. Radiotherapy was delivered by conventional opposed laterals with single AP field, helical tomotherapy, or intensity modulated radiotherapy. Patients were immobilized by aquaplast masks followed by CT simulation. Daily doses of 1.8 to 2 Gy per fraction, 5 days a week were used. The primary tumor site and involved nodes received 70 Gy. Volumes at high risk for recurrence received 60 Gy. Areas at low risk for microscopic disease received 50 Gy. Chemotherapy was given concurrently and consisted of cisplatin and 5-FU-based regimens every 3 weeks. Cisplatin was given intravenously at 100 mg/m^2 and 5-FU was administered as a continuous 24-hour infusion for 5 days at 1000 mg/m^2 per day. Surgical salvage of the neck and primary was performed when documented recurrence occurred and the patient was fit for surgery.

Assessments/Outcomes and Statistical Analysis

After completion of treatment, patients were followed every 2 months for the first 2 years, every 3 months for the next year, and every 6 months thereafter. At each visit, a thorough physical examination including bimanual examination and nasopharyngolaryngoscopy was performed. Tumor responses were assessed by clinical evaluation and imaging studies. Overall survival, local recurrence free survival, locoregional failure-free survival, and metastases-free survival were calculated from the date of diagnoses to the time of death or failure. Kaplan-Meier life table analyses were used, with statistical inferences on the actuarial curves made using log rank tests. *P* values were considered significant at the 5% level. Multivariate analysis was performed to determine the significance of clinical parameters such as gender, age, nodal status, primary site, BCI, STI, or treatment approach. The statistical method used in multivariate actuarial analysis was by the Cox Proportional Hazards model.

RESULTS

Patients Characteristics

Fifty-four patients were treated at LBMMC, 27 patients at LBVA, and 20 patients at COHNCC. There were 51 patients with T4 disease caused by STI and 50 patients with BCI. Radiotherapy alone was administered to 8 patients. Of the 68 patients treated with CRT, 42 had STI and 26 had BCI. Of the 25 patients who underwent primary resection, 5 had STI and 20 had BCI. The remaining 8 patients underwent radiotherapy alone, 4 with STI and 4 with BCI. Overall patient characteristics are listed in Table 1. Patient characteristics for patients who received only radiotherapy alone are in Table 2.

Local Control

For patients treated with XRT alone, 5-year local recurrence-free survival was 33%. Overall, 5-year local control was 54% and 48% for patients who received CRT or surgery followed by radiotherapy, respectively ($P = 0.81$). Five-year local control was 56% for patients with STI treated with CRT, 50% for patients with BCI who were treated with CRT, and 45% for BCI patients treated with resection followed up with CRT/radiotherapy (Fig 1). There was no significant difference between patients with STI treated with CRT or patients with BCI treated with CRT or resection. In addition, treatment at different institutions did not result in any significant different local control outcomes.

Locoregional Control

For patients treated with XRT alone, 5-year locoregional control was 33%. Overall, 5-year locoregional control was 47% for

TABLE 1. Patient Characteristics Treated With Definitive CRT or Surgery Followed by RT/CRT

	Chemoradiotherapy (68)		Resection (25)	
	Soft Tissue (%)	BCI (%)	Soft Tissue (%)	BCI (%)
Median age (yrs)	63	63	60	62
Men	30 (71)	21 (81)	4 (80)	16 (80)
Women	12 (29)	5 (19)	1 (20)	4 (20)
Site of disease				
Oral cavity	2 (5)	10 (38)	2 (40)	10 (50)
Oropharynx	25 (60)	9 (35)	3 (60)	6 (30)
Laryngeal	6 (14)	6 (23)	0 (0)	3 (15)
Hypopharynx	9 (21)	1 (4)	0 (0)	1 (5)
N0	13 (30)	9 (35)	3 (60)	7 (35)
N1	7 (17)	6 (23)	1 (20)	8 (40)
N2	20 (48)	11 (42)	1 (20)	5 (25)
N3	2 (5)	0 (0)	0 (0)	0 (0)

TABLE 2. Radiotherapy Alone

Patient Characteristics	(%)
Median age	73
Male	6 (75)
Female	2 (25)
BCI	4 (50)
STI	4 (50)
Primary site	
Oropharynx	4 (50)
Laryngeal	3 (37.5)
Oral cavity	1 (12.5)

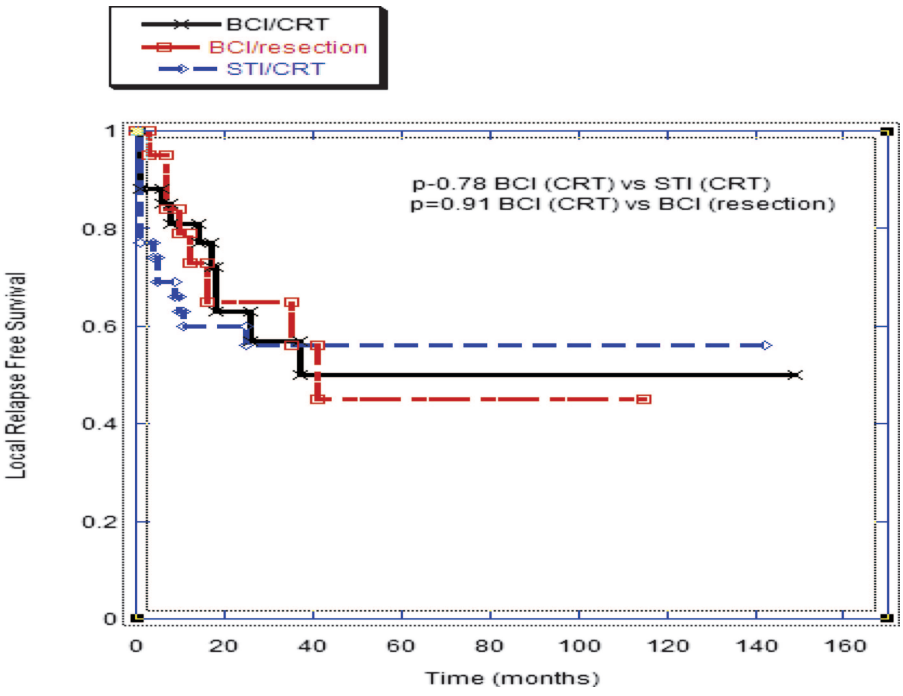

FIGURE 1. Kaplan-Meier local control. Five-year local control for patients with STI with CRT was 56%, BCI with CRT was 50%, and BCI with resection followed by CRT/RT was 45%. RT indicates radiotherapy.

patients treated with CRT or resection followed by radiotherapy/CRT ($P = 0.74$). Five-year locoregional control was 51% for patients with STI treated with CRT, 43% for patients with BCI treated with CRT, and 44% for patients with BCI treated with resection, followed up with CRT/radiotherapy (Fig. 2). There was no significant difference between patients with STI treated with CRT or patients with BCI treated with CRT or resection. In addition, treatment at different institutions did not result in any significant different locoregional control outcomes.

Distant Metastases-Free Survival

For patients treated with XRT alone, 5-year distant metastases-free survival was 80%. Five-year distant metastases-free survival was 79% if treated with CRT and 73% if treated with resection ($P = 0.30$). Five-year distant metastases-free survival was 66% for patients with STI treated with CRT, 89% for patients with BCI treated with CRT, and 81% for patients with BCI treated with resection, followed up with CRT/radiotherapy (Fig. 3). There was no significant difference between patients with STI treated with CRT or patients with BCI treated with CRT or resection. In addition, treatment at different institutions did not result in any significant different distant metastases-free survival outcomes.

Overall Survival

No patients treated with XRT alone survived at 5 years. Five-year overall survival for all patients treated with CRT was 33% and with resection was 27% ($P = 0.81$). Five-year overall survival was 23% for patients with STI treated with CRT, 51% for patients with BCI treated with CRT, and 28% for patients with BCI treated with resection, followed by CRT/radiotherapy (Fig. 4). There was a trend toward improved overall survival ($P = 0.07$) in favor of BCI over those with STI if treated with CRT. However, there was no significant difference in overall survival between patients with BCI treated with CRT or resection followed up with radiotherapy. In addition, treatment at different institutions did not result in any significant different overall survival outcomes. CT images of a patient with cartilage invasion treated with definitive chemoradiotherapy is shown in Figure 5.

Postoperative Chemoradiotherapy Versus Postoperative Radiotherapy

Eleven of the 25 patients who underwent resection as their definitive treatment received postoperative CRT. The other 14 patients received postoperative radiotherapy alone. There was no statistically significant difference in local control, locoregional control, distant metastases-free survival, or overall survival in patients who received either postoperative CRT or postoperative radiotherapy alone.

Prognostic Factors

On multivariate analysis, the only prognostic factor for overall survival was extent of nodal disease. Primary site, BCI, STI, age, gender, or hospitals of treatment were not prognostic for any outcome measurement.

Toxicity

There were 4 patients with long term dysphagia, 4 patients with osteoradionecrosis, 2 patients with xerostomia, 3 patients who were feeding tube dependent, and 2 patients with hoarse voice in the STI group treated with CRT. There were 4 patients with dysphagia, 5 patients with xerostomia, and 1 patient with stricture requiring dilatation in the patients with BCI treated with CRT. There were no cases of osteoradionecrosis in this group of patients. There were 4 patients with xerostomia, 1 patient with osteoradionecrosis, 1 patient who was feeding and was tube dependent, and 1 patient with trismus in the patients treated with resection followed up with radiotherapy.

Salvage Treatment

There were 4 patients who underwent salvage neck dissection and 1 patient who underwent salvage resection of the primary site in the STI patients treated with CRT. There were 3 patients who underwent salvage neck dissection and 4 patients who underwent salvage resection of the primary site in the BCI patients treated with CRT.

DISCUSSION

Current treatment strategies for locally advanced SCCHN have included primary resection followed by radiotherapy, CRT

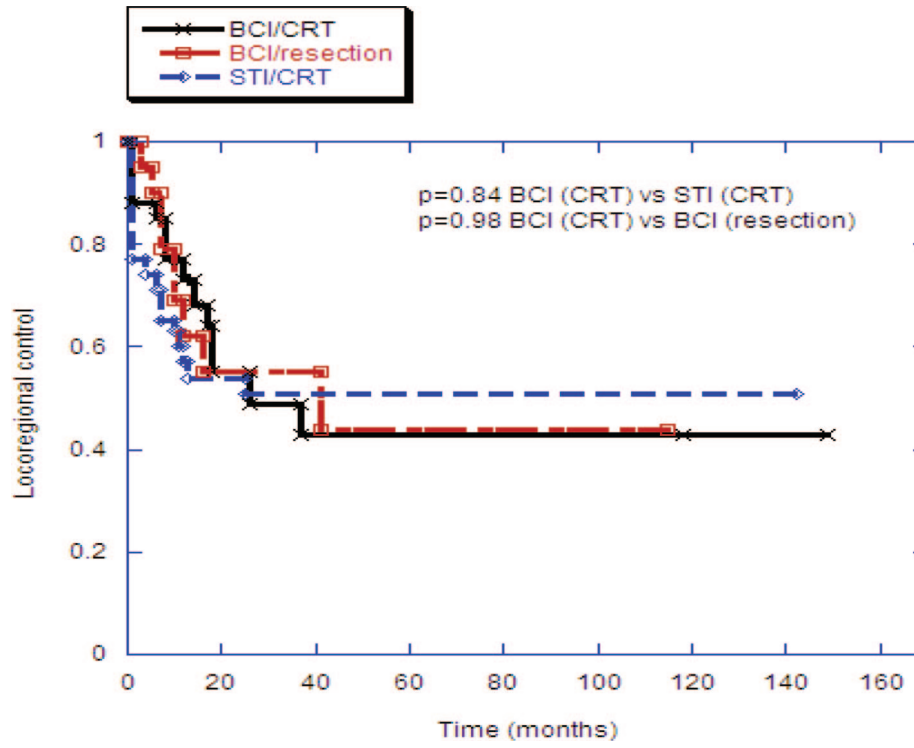

FIGURE 2. Kaplan-Meier locoregional control. Five-year locoregional control of STI with CRT was 51%, BCI with CRT was 43%, and BCI with resection followed by CRT/RT was 44%.

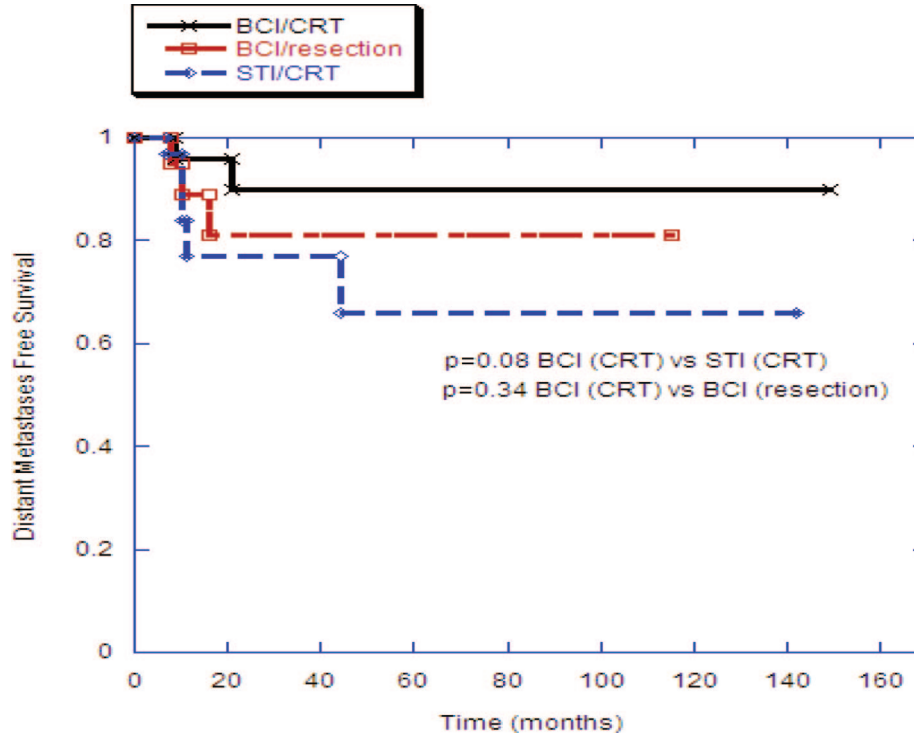

FIGURE 3. Kaplan-Meier distant metastases-free survival. Five-year distant metastases-free survival of STI treated with CRT was 66%, BCI treated with CRT was 89%, and BCI with resection followed by CRT/RT was 81%.

alone, or neoadjuvant chemotherapy followed by CRT. However, surgeries to remove these tumors often entail large resections followed by extensive reconstruction. The morbidity from these resections have a negative impact on the quality of life and self image of these patients.[16] In addition, postoperative radiotherapy with or without chemotherapy is often needed to improve outcomes in these patients.[14,15] In an effort to perform organ preserving treatment, the VALCS compared patients with locally advanced laryngeal cancer treated with sequential CRT against laryngectomy, followed by radiotherapy.[9] No difference in outcomes was found between the 2

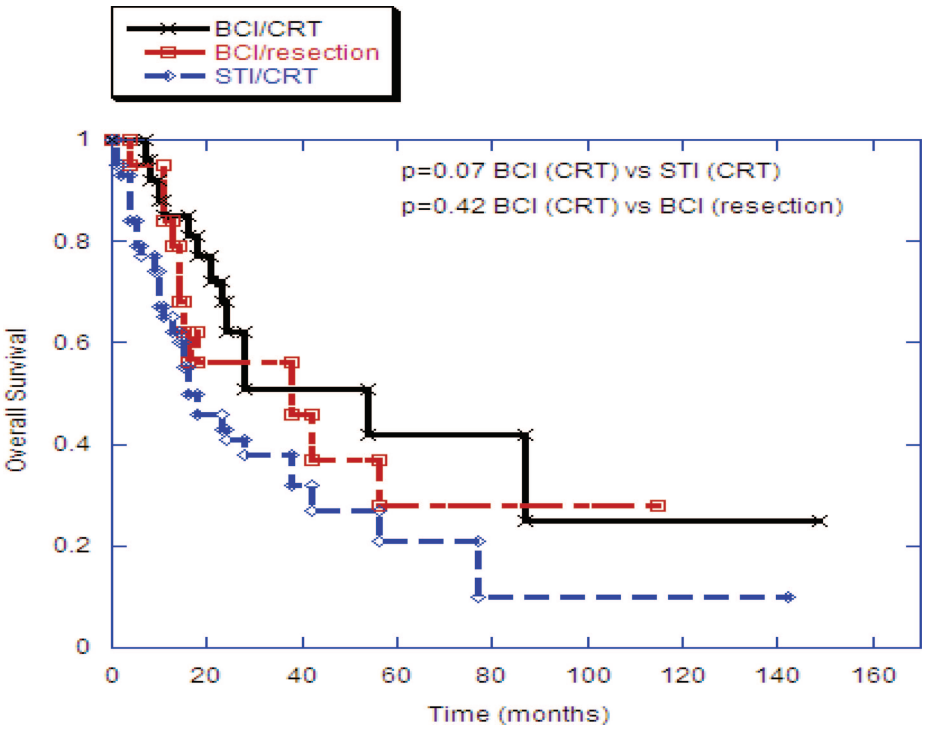

FIGURE 4. Kaplan-Meier overall survival. Five-year overall survival of STI treated with CRT was 23%, BCI treated with CRT was 51%, BCI treated with resection followed by CRT/RT was 28%.

FIGURE 5. CT scans of a patient with cartilage invasion (A) before chemoradiotherapy and (B) after chemoradiotherapy. This patient had long-term control of his primary site and remained alive with no evidence of disease.

treatment groups. The EORTC also compared sequential CRT with resection followed by radiotherapy for patients with hypopharyngeal tumors.[17] Again, the 2 treatment arms revealed no statistically significant difference in outcomes. This was followed by RTOG 9111, which compared patients with locally advanced laryngeal tumors treated with sequential CRT versus concurrent CRT or radiotherapy alone.[10] The patients treated with concurrent CRT had the highest rate of larynx preservation and locoregional control. This trial set concurrent CRT as a new standard of care in patients with locally advanced laryngeal cancers. However, patients with BCI were not included in this study.

For most patients with advanced head and neck cancers with BCI, treatment involved resection secondary to the low curability rates with radiation alone.[5] However, it has been shown that for locally advanced SCHHN, CRT is superior to radiotherapy alone.[10,18–20] Denis et al[18] compared concurrent CRT with radiotherapy alone for locally advanced oropharyngeal cancer. Five-year overall survival, specific disease-free survival, and locoregional control were all improved with concomitant CRT. Our results of a 5-year locoregional control of 54% in patients treated with CRT were similar to these studies. In an effort to extend these results to patients with BCI, Samant et al[11] compared the results of concurrent intra-arterial cisplatin and radiotherapy in patients with either STI or BCI T4 disease. Similar to that study, our results revealed no statistically significant difference between patients with STI or BCI treated with chemoradiotherapy. These findings suggest that BCI does not confer a worse prognosis than patients with STI treated with CRT.

Despite the improvements of CRT over radiotherapy alone, many patients with BCI are still often treated with resection. However, recurrence rates with resection alone in these patients were still high.[1,4,6] Therefore, radiation was added adjuvantly in hopes of reducing the recurrence rates.[21] In our cohort of patients with BCI, treatment with CRT or upfront resection followed by radiotherapy yielded similar results. This finding is corroborated by the findings by Soo et al.[12] In that study, patients with stage III/IV SCCHN, but not specifically addressing those with BCI and/or STI, were randomized to upfront resection followed by radiotherapy or concurrent CRT. They found no difference in outcomes in these patients who were treated with CRT or resection followed by radiotherapy. However, 2 additional randomized phase III studies revealed a benefit to postoperative chemoradiotherapy over radiotherapy alone.[14,15] These studies included patients with high-risk characteristics found on pathology specimens of 2 or more involved lymph nodes, nodal extracapsular extension, positive margins, perineural spread, or the presence of vascular tumor emboli. Although patients with these findings benefit from CRT over radiotherapy alone, extension of this benefit to patients with BCI remains to be seen. Interestingly, when we compared patients who received adjuvant chemoradiotherapy or adjuvant radiotherapy alone, no difference was seen.

There has been a recent trend to treat patients with neoadjuvant chemotherapy followed by concurrent CRT.[22–25] Interestingly, Worden et al[26] reported on induction chemotherapy as the basis for organ preservation. In this study, patients were given 1 cycle of chemotherapy that consisted of cisplatin and 5-FU. If the patients had a greater than 50% response, they proceeded to concurrent CRT.

If less than 50% response was seen, laryngectomy was performed. Four-year overall survival and disease-free survival was 70% and 72%, respectively. Another promising treatment approach is the use of erbitux with radiation.[27] RTOG 0522 is currently investigating the role of erbitux with chemoradiotherapy. It remains to be seen whether these novel approaches can increase the outcomes of patients with BCI treated with CRT.

This study is limited to the selection bias inherent to any retrospective analysis. Comparisons to other studies should be done with caution. There were increased numbers of patients with advanced nodal disease in the STI group treated with CRT. This may explain the trend toward improved overall survival in patients with BCI treated with CRT. Indeed, nodal disease extent was the only significant prognostic variable for overall survival in our study. This finding has been corroborated by several other studies.[28,29] However, patients treated with CRT included those patients who were medically and technically unresectable, making this group less favorable. In addition, our treatment population is quite heterogenous and includes patients with oral cavity, oropharyngeal, laryngeal, and hypopharyngeal SCCAs. However, there have been increasing publications of similar heterogenous patient populations treated with CRT or radiotherapy with erbitux[22–25,27] as opposed to primary resection. Furthermore, primary site was not prognostic for any clinical outcome in our study. Lastly, our results may be a reflection of insufficient power in our series to detect a difference. Nevertheless, our results are highly provocative and certainly warrant additional confirmatory studies.

In conclusion, patients with BCI may be treated with upfront resection followed by CRT or concurrent CRT. This study suggests similar outcomes between these 2 treatment approaches. If treated with CRT, outcomes of patients with BCI seem similar to those achieved in patients with STI. In addition, salvage surgery can be performed when needed and when technically feasible. With new treatment approaches such as erbitux or neoadjuvant chemotherapy, organ preservation may be more achievable with acceptable outcomes. Further studies should be performed to validate these provocative findings.

REFERENCES

1. De Vicente JC, Recio OR, Pendas SL. Oral squamous cell carcinoma of the mandibular region: a survival study. *Head Neck*. 2001;23:536.
2. Amdur RJ, Parsons JT, Mendenhall WM. Postoperative irradiation of for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. *Int J Radiat Oncol Biol Phys*. 1989;16:25.
3. Carter RL, Tanner NS, Clifford P. Direct bone invasion in squamous cell carcinomas of the head and neck: pathological and clinical implications. *Clin Otolaryngol*. 1980;5:107.
4. Dubner S, Heller KS. Local control of squamous cell carcinoma following marginal and segmental mandibulectomy. *Head Neck*. 1993;15:29.
5. Neal AJ, Habib F, Hope-Stone HF. Carcinoma of the maxillary antrum treated by pre-operative radiotherapy or radical radiotherapy alone. *J Laryngol Otol*. 1992;106:1063.
6. Overholt SM, Eicher SA, Wolf P. Prognostic factors affecting outcome in lower gingival carcinoma. *Laryngoscope*. 1996;106:1335–1339.
7. O'Brien CJ, Carter RL, Soo K. Invasion of the mandible by squamous carcinomas of the oral cavity and oropharynx. *Head Neck*. 1986;8:247–256.
8. Shingaki S, Nomura T, Takada M. Squamous cell carcinomas of the mandibular alveolus: analysis of prognostic factors. *Oncology*. 2002;62:17–24.
9. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991;324:1685–1690.
10. Forastiere AA, Goepfert H, Maor M. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091–2098.
11. Samant S, Robbins KT, Kumar P. Bone or cartilage invasion by advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2001;127:1451.
12. Soo KC, Tan EH, Wee J. Surgery and adjuvant radiotherapy vs. concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomized comparison. *Br J Cancer*. 2005;93:279–286.
13. American Joint Committee on Cancer. *AJCC Cancer Staging Handbook*. 6th ed. New York, NY: Springer-Verlag; 2002.
14. Bernier J, Domenge C, Ozsahin M. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350:1945.
15. Cooper JS, Pajak TF, Forastiere AA. Postoperative concurrent radiotherapy and chemotherapy for high risk squamous cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937.
16. Yousem DM, Gad K, Tufano RP. Resectability issues with head and neck cancer. *Am J Neuroradiol*. 2006;27:2024–2036.
17. Lefebvre JL, Chevalier D, Luboinski B. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer Phase III trial. *J Natl Cancer Inst*. 1996;88:890–899.
18. Denis F, Garaud P, Bardet E. Final results of the 94–01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced stage oropharynx carcinoma. *J Clin Oncol*. 2004;22:69–76.
19. Jeremic B, Shibamoto Y, Stanisavljevic B. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiother Oncol*. 1997;43:29–37.
20. Adelstein DJ, Saxton JP, Lavertu P. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in respectable stage III and IV squamous cell head and neck cancer. Preliminary results. *Head Neck*. 1997;19:567–575.
21. Ampil FL, Ghali GE, Caldito G. Treatment of head and neck cancer with bone or cartilage invasion by surgery and postoperative radiotherapy. *J Oral Maxillofac Surg*. 2004;62:408–411.
22. Hitt R, Lopez-Pousa A, Martinez-Trufero J. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol*. 2005;23:8636–8645.
23. Vermorken JB, Remenar E, van Herpen C. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357:1695–1704.
24. Posner MR, Hershock DM, Blajman CR. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357:1705–1715.
25. Cmelak AJ, Li S, Goldwasser MA. Phase II trial of chemoradiation for organ preservation in respectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: results of Eastern Cooperative Oncology Group Study E2399. *J Clin Oncol*. 2007;25:3971–3977.
26. Worden FP. T4 laryngeal squamous cell carcinoma: chemo-selection as an organ preservation strategy. *J Clin Oncol.* 2007;25. [Abstract 6005].
27. Bonner JA, Harari PM, Giralt J. Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567–578.
28. Perez CA, Patel M, Chao K. Cancer of the tonsillar fossa: prognostic factors and long term therapy outcome. *Int J Radiat Oncol Biol Phys*. 1998;42:1077.
29. 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.