Intensification Regimen for Advanced-Stage Resectable Hypopharyngeal Carcinoma

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Objective: To determine feasibility, compliance, long-term survival, and disease control rates in the intensification regimen for advanced resectable hypopharyngeal carcinoma.

Design: Prospective, nonrandomized, controlled phase 2 trial with a median follow-up period of 89 months (range, 3.4-140.0 months).

Setting: Cancer center at a state university.

Patients: Thirty-two patients (age range, 44-79 years; median age, 59 years) with advanced (69% stage IV, 31% stage III) resectable hypopharyngeal carcinoma.

Interventions: Combination of surgery, radiation therapy, and chemotherapy (cisplatin and paclitaxel) along with intraoperative radiation therapy.

Main Outcome Measures: Compliance, long-term survival, and locoregional and systemic disease control rates and functional outcome.

Results: The protocol compliance rate was 62% (20 of 32 patients), and the overall 5-year survival rate was 56%. Local recurrence occurred in 3 patients (9%). The systemic disease control rate was 91% (29 of 32 patients). Total laryngectomy was required in 15 patients (47%); preservation of the larynx was possible in 17 patients (53%). Only 3 (13%) of 6 patients were percutaneous endoscopic gastrostomy tube dependent in the long-term follow-up.

Conclusions: The intensification regimen described in this study accomplished excellent long-term survival and disease control rates in patients with advanced resectable hypopharyngeal carcinoma. The future plan is to proceed with a phase 3 trial if the single-institutional experience at The Ohio State University can be duplicated in a multi-institutional phase 2 study.

A combination of surgery, radiation therapy, and chemotherapy together with intraoperative radiation therapy (IORT) was designed as a regimen with the intent to intensify therapy at the primary tumor site, regional neck nodes, and distant sites, while improving patient compliance. A series of articles reported the results of modifications in the regimen to achieve the stated goals. The present article summarizes the long-term disease control, survival, and functional outcome results after multimodal treatment for resectable advanced-stage HPC.

**METHODS**

The patients were recruited from the Department of Otolaryngology–Head and Neck Surgery, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Comprehensive Cancer Center, The Ohio State University, Columbus. The investigational protocol was reviewed and approved by the institutional review board of The Ohio State University and the Scientific Review Committee of the Comprehensive Cancer Center. Eligible patients had previously untreated resectable SCC of the hypopharynx. The patients with resectable disease included those whose preoperative assessment determined the probability of all clinically detectable disease being surgically removed with negative histologic margins of resection. Eligible patients also must have had stage III or stage IV disease according to the American Joint Committee on Cancer (1997) and no distant metastases. A Karnofsky performance index of 60 or higher; adequate bone marrow function (platelet count >100 × 10^9/L and absolute neutrophil count >2.0 × 10^9/L); creatinine clearance greater than 1.0 mL/s (>60 mL/min); and adequate hepatic function (bilirubin <1.8 mg/dL [<31 µmol/L] and serum transaminase values 4 times the upper limit) were required. Written informed consent was obtained from all patients before the initiation of therapy. Patients with prior malignant neoplasms were excluded unless they were disease free for 5 years, had adequately treated basal or squamous cell skin cancers, or had in situ cervical cancer (because of the excellent prognosis associated with these limited cancers). Patients with a history of cardiac disease were cleared for treatment by the medical oncologist. In general, patients with prior bradyarrhythmias, atrioventricular conduction defects, or marginal cardiac function were eligible but underwent cardiac monitoring during treatment. During the course of 3 phase 2 trials evaluating the intensification regimen, there were 32 patients with hypopharyngeal primary tumors.

The most recently applied intensification regimen (Table 1) is as follows: Perioperatively (days 1–4), the patients were given a slightly accelerated hyperfractionated boost of external beam radiotherapy consisting of 9.1 Gy with 6-MV x-rays delivered to the primary tumor and clinically involved nodes (excluding the spinal cord). The external beam radiotherapy was divided into 7 twice-daily treatments of 1.3 Gy, with an interfraction interval of at least 6 hours. Concurrent cisplatin chemotherapy (30 mg/m² per day) was delivered intravenously on days 1 to 3. Patients were hydrated intravenously...
with 1 L of 0.45% sodium chloride with 10 mEq of potassium chloride, 3 g of magnesium sulfate, and 40 g of mannitol for 2 hours before cisplatin therapy. Surgical resection and IORT to the site of closest surgical margin were performed on day 4. For patients with negative surgical margins (as determined by intraoperative frozen-section pathologic analysis), an intraoperative dose of 7.5 Gy was delivered with 6-MeV electrons (prescribed to the 90% isodose).

On day 10, the patients began receiving weekly 3-hour infusions of paclitaxel (45 mg/m²). All patients were premedicated with dexamethasone (20 mg administered orally at 12 and 6 hours before the beginning of paclitaxel infusion or 20 mg administered intravenously 30 minutes before paclitaxel infusion). The patients received 300 mg of cimetidine hydrochloride intravenously and 50 mg of diphenhydramine hydrochloride intravenously 30 minutes before paclitaxel therapy. Subsequent courses of the same dose of paclitaxel were given weekly on an outpatient basis on days 17, 24, 31, 38, 45, 52, 59, and 66, for a total of 9 courses of paclitaxel therapy.

On day 31, after intravenous hydration, patients received a second course of cisplatin (30 mg/m² daily for 3 days). On day 32, patients underwent external beam radiotherapy with 6-MeV x-rays (an additional 40 Gy delivered in 20 treatments to the primary tumor site and regional draining lymph nodes and 45 Gy delivered in 20 treatments to the lower neck and bilateral supraclavicular areas). Parallel opposed upper neck fields were prescribed to the midline, and the lower neck/supraclavicular field was prescribed to the 100% isodose. If a histologically positive node larger than 3 cm was present, bilateral posterior neck electron boosts of 10 Gy (at 100% isodose) were delivered in 5 treatments. The electron energy was chosen to limit the spinal cord dose to less than 45 Gy (total dose). On day 52, the third course of cisplatin (30 mg/m² daily for 3 days) was administered (with hydration as previously described).

Recombinant human granulocyte-colony–stimulating factor was administered at the discretion of the medical oncologist (eg, for neutropenic fever). Prophylactic antibiotic and antifungal therapy consisting of oral ciprofloxacin (500 mg twice daily) and oral fluconazole (100 mg/d) was administered to patients who developed an absolute neutrophil count of less than 0.5 × 10⁹/L and continued until the absolute neutrophil count was above 1.5 × 10⁹/L. Radiotherapy was delayed when the absolute neutrophil count was less than 0.5 × 10⁹/L and continued when it was greater than 0.5 × 10⁹/L. If the absolute neutrophil count was less than 1.5 × 10⁹/L, then chemotherapy was delayed until it rose above 1.5 × 10⁹/L. If the delay in granulocyte recovery was 7 days or longer or if the patient had neutropenic fever, subsequent doses of paclitaxel were reduced to 30 mg/m² (33% dose reduction). Paclitaxel is used to improve the control of distant metastases and is administered as a 3-hour infusion at a dose of 45 mg/m² for 9 weeks.

RESULTS

The study population included 27 men and 5 women with squamous cell carcinoma of the hypopharynx (Table 2). Three of the male patients and 1 of the female patients were African American. The remaining patients were white. Their ages ranged from 44 to 79 years, with a median of 59 years. Twenty-eight patients had cancer of the pyriform sinus; 3 had cancer of the posterior pharyngeal wall; and 1 had cancer of the postcricoid region. Although 1 patient in the study group had T1 disease and 8 patients had T2 disease, overall 10 patients (31%) had stage III disease at presentation and the rest (22 [69%]) had stage IV disease (Table 3).

Resection of the primary tumor site ranged from partial pharyngectomy to total laryngopharyngectomy. Total pharyngectomy together with partial cervical esophagectomy, subtotal pharyngectomy, and partial pharyngectomy techniques were used in 3 patients (9%), 3 patients (9%), and 26 patients (82%), respectively. Total laryngectomy and partial laryngectomy was required in 15 patients (47%) and 11 patients (34%), respectively. The overall total or partial preservation of the larynx was achieved in 17 patients (53%). Thirty-two neck dissections were performed in 29 patients. The types of neck dissection included modified radical (n=12), radical (n=10), and extended radical (n=8). Carotid artery invasion requiring carotid artery resection and replacement occurred in 2 patients.

The pectoralis major musculocutaneous flap, which was the most common pharyngeal and laryngopharyngeal reconstruction technique, was used 20 times in 18 patients (56%) (Table 4), including 16 patients with a total or partial laryngopharyngectomy and 2 with pharyngectomy defects. Carotid artery coverage in appropriate patients was accomplished with 10 dermal grafts, and acellular human dermis (Alloderm) was used in 1 patient.

The rate of protocol compliance (receiving all courses of treatment per protocol) was 62% (20 of 32 patients). Noncompliance occurred in 12 cases, 5 of which were patient directed. Four patients could not receive further chemotherapy because of heart attack, elevated levels of serum urea nitrogen and/or creatinine (2 patients), and peripheral neuropathy. Two patients experienced stroke, and 1 patient died of sepsis during the treatment.

The median overall follow-up period was 89 months (range, 34–140.0 months). The overall 5-year survival rate was 56% (Figure). Only 4 (12%) of the 32 patients died of disease. The 5-year disease-free survival rate was 53%. Two patients died of primary lung cancer during the 12th and the 96th month of follow-up. The other causes of the

Table 2. Patient Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value*</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (84)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Race</td>
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</tr>
<tr>
<td>White</td>
<td>28 (88)</td>
</tr>
<tr>
<td>African American</td>
<td>4 (12)</td>
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<tr>
<td>Age, y</td>
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</tr>
<tr>
<td>Range</td>
<td>44-79</td>
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<tr>
<td>Median</td>
<td>59</td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
</tr>
<tr>
<td>Pyriform sinus</td>
<td>28 (88)</td>
</tr>
<tr>
<td>Posterior pharyngeal wall</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Postcricoid region</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Overall stage</td>
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</tr>
<tr>
<td>III</td>
<td>10 (31)</td>
</tr>
<tr>
<td>IV</td>
<td>22 (69)</td>
</tr>
<tr>
<td>Grade</td>
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</tr>
<tr>
<td>Poorly differentiated</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>2 (6)</td>
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*Values other than age are expressed as number (percentage).
deaths among the patients without disease were acute renal failure, respiratory failure, cerebrovascular accident, gall bladder surgery complication, ruptured abdominal aortic aneurysm, and unknown etiology.

The locoregional and systemic disease control rates were both 91% (29 of 32 patients). All 3 distant metastases involved the lungs. Local recurrence occurred simultaneously with distant metastasis in 1 patient who had refused IORT and postoperative chemoradiotherapy.

Preservation of the larynx was possible in 17 patients (53%). Tracheoesophageal puncture and voice prosthesis were used in 13 (87%) of the 15 patients who underwent total laryngectomy. Six (26%) of 23 patients with the minimum follow-up period of 24 months experienced dysphagia, and only 3 (13%) of these 6 patients needed a permanent percutaneous endoscopic gastrostomy tube. All the patients who underwent surgical procedures for larynx preservation could successfully be decannulated, and none of them needed a permanent tracheostomy tube.

**COMMENT**

Hypopharyngeal carcinoma is a rare disease, representing only 4.3% of all malignant neoplasms in the head and neck. It still produces the worst prognosis among head and neck cancers. Regardless of treatment modality, the prognosis for advanced HPC is extremely poor. Surgery, radiation therapy, or a combination of both has been the treatment of choice for HPC in the last decades. With standard primary radiation therapy and salvage surgery, the overall 5-year survival rate is approximately 20%. Chemo-therapy was added to the treatment regimen in only 18% of HPC cases. The results of a large, well-conducted meta-analysis by Pignon et al, who looked at the effects of chemotherapy added to locoregional treatment in head and neck cancers, suggested that a significant survival benefit (8%) was associated with concomitant chemoradiation schedules. On the other hand, in a recent study, even with combined definitive chemoradiotherapy, the overall 5-year survival rate was still 15% in cases of HPC.

Pinheiro et al evaluated the use of IORT as an adjuvant modality in the treatment of advanced cancer of the head and neck and skull base and found that it is safe at a dose of 12.5 Gy and that it improves tumor control and survival for patients who are likely to have microscopic residual disease in sites that are difficult to resect, such as the skull base. The safety and effectiveness of IORT have also been demonstrated in the management of advanced cervical metastasis. Although IORT is still not easily found in all tertiary medical centers, part of the success in disease control and survival in the intensification regimen is contributed by IORT.

The effectiveness of both paclitaxel and cisplatin therapy for head and neck cancer is very well known. Eckardt et al demonstrated impressive clinical and pathologic response rates (38% complete pathologic response) with concurrent weekly paclitaxel-carboplatin therapy and radiotherapy as a preoperative treatment modality in advanced oral and oropharyngeal cancer. In the intensification regimen, along with weekly preoperative chemoradiotherapy with cisplatin, 9 weeks of paclitaxel therapy was added to 2 more postoperative cycles of cisplatin.
Although Cooper et al.\textsuperscript{13} found that concurrent postoperative chemoradiotherapy significantly improves the rate of local and regional control (82\% in 2 years) and disease-free survival (78\% in 2 years) in high-risk patients with resected head and neck cancer, the combination of chemotherapy was associated with a substantial increase in adverse effects. Bernier et al.\textsuperscript{18} also supported these findings in a recent study of advanced-stage head and neck cancer, even though the overall 5-year survival rates among the patients who received postoperative adjuvant chemoradiotherapy and radiotherapy alone were 53\% and 40\%, respectively. The intensification regimen in our study resulted in a protocol compliance rate (ie, patients receiving all courses of treatment per protocol) of 62\%, and only 1 patient died (of sepsis) during the treatment, while achieving overall survival rates of 67\% at 3 years and 56\% at 5 years.

Beauvillain et al.\textsuperscript{19} compared long-term survival and local disease control rates in cases of advanced resectable HPC in the treatment arm of neoadjuvant chemotherapy-surgery-radiotherapy (arm A) and neoadjuvant chemotherapy and radiotherapy alone without surgery (arm B). After a mean follow-up of 92 months, survival was statistically better in arm A (overall 5-year survival rate, 37\%; median survival, 40 months) than in arm B (overall 5-year survival rate, 19\%; median survival, 20 months) because of a better local control rate (63\% vs 39\%). On the other hand, the same successful results could not be demonstrated in other studies,\textsuperscript{20} and the 5-year survival rates were similar in the nonsurgical and the surgical groups. Also, the larynx preservation rate was only 35\%.\textsuperscript{21} The larynx preservation rate in our study was 53\%, and 17 (87\%) of the patients who underwent laryngectomy were successfully treated with a voice prosthesis. Only 3 (26\%) of the patients experienced dysphagia, and 6 (13\%) needed a permanent percutaneous endoscopic gastrostomy tube.

Distant metastases remain a major cause of death in patients with advanced HPC.\textsuperscript{22} The local and distant disease control rates in our patient population were excellent: 91\%. All 3 distant metastasis sites were the lungs. Unfortunately, 2 other patients developed a second primary cancer: 1 patient died (of pulmonary metastasis) because of a better local control rate (63\% vs 39\%). On the other hand, the same successful results could not be demonstrated in other studies,\textsuperscript{20} and the 5-year survival rates were similar in the nonsurgical and the surgical groups. Also, the larynx preservation rate was only 35\%.\textsuperscript{21} The larynx preservation rate in our study was 53\%, and 17 (87\%) of the patients who underwent laryngectomy were successfully treated with a voice prosthesis. Only 3 (26\%) of the patients experienced dysphagia, and 6 (13\%) needed a permanent percutaneous endoscopic gastrostomy tube.

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The intensification regimen described herein has been successfully used in the treatment of advanced resectable head and neck cancers for 12 years. Although it requires interdisciplinary cooperation and specialized radiotherapeutic technologies such as IORT, our goal is to duplicate these encouraging single-institutional phase 2 results in multi-institutional cooperative studies and then to proceed with a phase 3 trial if the single-institutional experience at The Ohio State University can be duplicated in a multi-institutional phase 2 study.

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REFERENCES


