Multimodal Intensification Regimens for Advanced, Resectable, Previously Untreated Squamous Cell Cancer of the Oral Cavity, Oropharynx, or Hypopharynx

A 12-Year Experience

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Objective: To determine the feasibility of, compliance with, and long-term survival with intensification treatment regimens for patients with advanced, resectable, previously untreated head and neck squamous cell carcinoma.

Design: Prospective phase 2 clinical trial (3 similar, consecutively evolved trials).

Setting: Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University.

Patients: One hundred twenty-three patients (median age, 60 years; range, 30-78 years) with previously untreated, resectable, advanced squamous cell carcinomas of the oral cavity, oropharynx, or hypopharynx.

Interventions: Perioperative cisplatin chemoradiotherapy, surgical resection with intraoperative radiotherapy, and postoperative paclitaxel and cisplatin chemoradiotherapy.

Main Outcome Measures: The feasibility, compliance, and long-term survival associated with the 3 intensification regimens.

Results: Compliance with all 3 intensification regimens averaged 61% (75/123). Patient-directed noncompliance occurred in 16 patients (13%). The average locoregional (112/123, 91%) and systemic (106/123, 86%) disease control rates were excellent. Overall long-term disease-specific survival was 73%. Median time at risk was 62.5 months (range, 1 day to 100.4 months).

Conclusions: The intensification regimens result in excellent disease control rates and long-term survival in this particular patient population. Future evolution of these regimens will include some modifications to further decrease toxic effects followed by phase 2 multi-institutional trials to determine whether the single-institutional experience can be duplicated. The results of these studies will determine whether phase 3 trials can be proposed.

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EAD AND NECK CANCER composes approximately 6% to 7% of all human malignancies. More than 40,000 new cases of head and neck cancer are diagnosed each year in the United States, and 500,000 new cases are diagnosed worldwide. In the United States, head and neck cancer results in 12,000 deaths per year. In contrast to advanced stage laryngeal cancer, survival rates for the most common disease sites in the head and neck have not improved in the past 40 years. The standard therapy regimen of surgery and postoperative radiotherapy for previously untreated advanced stage resectable cancers arising in the oral cavity, oropharynx, and hypopharynx produces 4-year survival of only 38%.

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Frequent distant metastases and overall poor prognosis in this patient population have stimulated researchers to find more effective systemic cytotoxic therapy that could be used in a neoadjuvant or adjuvant setting. A phase 3 trial in the
United States for previously untreated advanced stage resectable disease of the oral cavity, oropharynx, and hypopharynx was sponsored by the National Cancer Institute Head and Neck Intergroup. Although not showing survival improvement, the study demonstrated a statistically significant decrease in the frequency of distant metastases in the experimental arm using chemotherapy. However, the combination of locoregional and systemic therapy still produced high failure rates for primary tumors (15.3%), neck nodes (9.5%), and distant metastases (14.9%) and no improvement in the poor compliance rate for this patient population.

The efficacy of intensive chemoradiotherapy as a primary modality for organ preservation in patients with advanced squamous cell carcinoma of the head and neck in short-term follow-up was shown by Hanna et al. Despite the improvement in overall 3-year survival (57%), the rate of distant metastases was still high (14%) and accounted for almost 40% of all treatment failures. Furthermore, the high rate of severe long-term complications after intensive chemoradiotherapy demonstrated that nonsurgical organ preservation does not necessarily result in functional preservation. No substantial differences have been found in the overall quality of life of patients with advanced laryngeal cancer treated with total laryngectomy or laryngeal preservation.

Some additional clinical studies have also provided encouraging results demonstrating enhanced ability to control locoregional disease with concurrent chemoradiotherapy. Not only have these studies demonstrated improvement in locoregional control but some have demonstrated survival improvement for certain head and neck cancer subpopulations. Another recent phase 2 trial by Urba et al using induction chemotherapy followed by definitive chemoradiotherapy achieved organ preservation, with 3-year overall survival of 64% in advanced stage tongue base and hypopharynx carcinomas.

Recently, Cooper et al found that concurrent postoperative chemoradiotherapy significantly improves the rates 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, although the combination of chemotherapy was associated with a substantial increase in adverse effects.

In another study, long-term survival and local disease control rates for advanced resectable hypopharyngeal cancer were shown to be significantly improved in the treatment arm using neoadjuvant chemotherapy-surgery-radiotherapy compared with the treatment arm of neoadjuvant chemotherapy and radiotherapy alone without surgery. This survival improvement was associated with the surgical treatment arm, which produced better local control rates (63% vs 39%).

These encouraging results of multimodal treatments motivated us to initiate a series of pilot studies evaluating therapeutic regimens designed to improve the survival rate while limiting the toxic effects related to primary intensive chemoradiotherapy and achieving a high compliance rate for previously untreated, resectable, advanced stage squamous cell cancer arising in the oral cavity, oropharynx, and hypopharynx.

The goal of these regimens is to intensify the therapy at the primary tumor site, regional neck nodes, and distant sites while minimizing the treatment-limiting toxic effects. The results and minor modifications of the intensification regimens (IRs) have been partially reported previously. This study reports the overall toxic effects, compliance, long-term systemic and local disease control rates, and survival analysis associated with all 3 IRs completed in the past 12 years.

**METHODS**

The patients originated from the Department of Otolaryngology–Head and Neck Surgery at the Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute of The Ohio State University. The investigational protocol was reviewed and approved by The Ohio State University's institutional review board and the Comprehensive Cancer Center's scientific review committee. Eligible patients had previously untreated, resectable squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx. The patients must have had stage III or IV disease of the oral cavity and oropharynx and stage II, III, or IV disease of the hypopharynx according to the American Joint Committee on Cancer, with no distant metastases. A Karnofsky performance index of 60 and greater, adequate bone marrow function (platelet count $>100 \times 10^9/L$ and absolute neutrophil count $>2.0 \times 10^9/L$), creatinine clearance greater than 1.0 mL/s (>60 mL/min), adequate hepatic function (bilirubin level $<1.8 \mathrm{mg/dL}$ [<31 $\mu\text{mol/L}$]), and serum transaminase levels less than 4 times the upper limit were required. Written informed consent was obtained from all the patients before the initiation of therapy. Patients with previous 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 previous bradycardiac, atrioventricular conduction defects, or marginal cardiac function were eligible but underwent cardiac monitoring during treatment. One hundred twenty-three patients were registered into 3 consecutive intensification trials (patient populations for IR1, IR2, and IR3 were 37, 43, and 43, respectively) between February 1, 1993, and December 9, 2000.

The most recent IR schema (Table 1) is as follows: perioperatively (days 1-4), patients were administered 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/m$^2$ 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 intraoperative radiotherapy to the site of the closest surgical margin were performed on day 4. For patients with negative surgical margins (as determined by intraoperative frozen-section pathological analysis), an intraoperative dose of 7.5 Gy was delivered with 6-MeV electrons (prescribed to the 90% isodose). A dose of 10 Gy was used with positive surgical resection margins.

On day 10, patients began receiving weekly 3-hour infusions of paclitaxel, 45 mg/m$^2$. All the patients were premedicated with dexamethasone, 20 mg orally 12 and 6 hours before...
For the beginning of paclitaxel infusion or 20 mg 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 on an outpatient basis weekly 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-MV x-rays, with 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 given (with hydration as previously described).

Recombinant human granulocyte colony-stimulating factor was administered at the discretion of the medical oncologist (ie, for neutropenic fever). Prophylactic antibiotic and antifungal coverage consisting of oral ciprofloxacin, 500 mg twice daily, and oral fluconazole, 100 mg daily, was given to patients who developed an absolute neutrophil count less than 0.5×10⁹/L and was continued until the absolute neutrophil count was greater than 1.5×10⁹/L. Radiotherapy was delayed when the absolute neutrophil count was less than 0.5×10⁹/L and was continued when the count 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).

The most recently completed trial (IR3) was modified from the first and second IRs by adding paclitaxel and then decreasing the individual paclitaxel doses and increasing the frequency of administration so that the total dose was identical to that of the second trial. Paclitaxel was given as a 3-hour infusion at a dose of 45 mg/m² for 9 weeks in IR3.

Table 1. Intensification Treatment Schema*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prestudy</th>
<th>Days 1-3</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 31</th>
<th>Day 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Triple endoscopy and biopsy, gastrostomy tube placement</td>
<td></td>
<td>Surgical resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IORT</td>
<td>Boost to area of close (7.5 Gy) of positive margins (10.0 Gy) with 6-MV electrons (90% isodose) or HDRB at 0.5 cm deep</td>
<td></td>
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<tr>
<td>EBRT</td>
<td>Off-cord boost, 9.2 Gy over 9 treatments (1.3-Gy fractions with 6-MV photons)</td>
<td>Off cord boost, 9.2 Gy over 7 twice-daily treatments (1.3-Gy fractions with 6-MV photons)</td>
<td>Begin 40 Gy/20 fractions, 6-MV photons to primary and nodal area, and 45 Gy/20 fractions, 6-MV photons to lower neck and bilateral supraclavicular areas. If (+) node &gt;3 cm, bilateral posterior neck electron boosts 10 Gy/5 fractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>30 mg/m² daily for 3 d</td>
<td></td>
<td>30 mg/m² daily for 3 d every 3 wk, 2 cycles total</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td>45 mg/m² in 3 h weekly, 9 cycles total</td>
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</table>

Table 2. Demographic Characteristics of the 123 Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No (%)</td>
<td>M 93 (75.6) F 30 (24.4)</td>
</tr>
<tr>
<td>Race, No (%)</td>
<td>White 112 (91.0) African American 10 (8.1) Asian 1 (0.9)</td>
</tr>
<tr>
<td>Age, median, range, y</td>
<td>60 (30-78)</td>
</tr>
<tr>
<td>Tumor site, No (%)</td>
<td>Oral cavity 37 (30.0) Oropharynx 54 (43.9) Hypopharynx 32 (26.1)</td>
</tr>
<tr>
<td>Overall stage, No (%)</td>
<td>Stage III 28 (22.8) Stage IV 95 (77.2)</td>
</tr>
</tbody>
</table>

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 32, the third course of cisplatin, 30 mg/m² daily for 3 days, was given (with hydration as previously described).

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Table 2 lists the demographics of the study population, which included 93 men and 30 women. Ages ranged from 30 to 78 years, with a median of 60 years. Thirty-seven patients (30.0%) had oral cavity primary cancers, 54 (43.9%) had oro-
pharyngeal cancers, and 32 (26.0%) had hypopharyngeal tu-
mors. Most patients (77.2%) had stage IV disease. Survival was
defined as the period from the first day of preoperative radio-
therapy to the last date of follow-up or death. Data were ana-
lyzed using Kaplan-Meier techniques.

The median time at risk in the IRs was 62.5 months (range,
1 day to 100.4 months). Total protocol compliance, de-
fin ed as patients receiving the full dose of chemotherapy
and radiation within the prescribed time without delay or
dose reduction and receiving all courses of treatment per
protocol, was 60.9% (75 of 123 patients). Sixteen (13.0%)
of 123 patients had patient-directed noncompliance, de-
fin ed as the patient deciding against continuing treatment
per the protocol (Table 3). The compliance differ-
ences between IRs were not significant (P = .07).

Acute toxic effects were defined as previously pub-
lished adverse results that occurred within 90 days of ini-
tiating perioperative treatment.18 Most commonly ob-
served nonoperative acute toxic effects were hematologic
(34.9%), infectious (22.7%), gastrointestinal (17.0%), and
mucosit ic (20.3%). Early operative complications were
pharyngocutaneous fistula (14.6%), hematoma (1.6%),
flap donor site dehiscence (0.8%), and flap failure (0.8%),
which are consistent with surgical complication frequen-
cies in the absence of perioperative chemoradiotherapy
(Table 4).

Late toxic effects were defined as adverse events oc-
curring more than 90 days after initiation of treatment.
Eleven patients (8.9%) experienced problems relating to
their mandibular hardware, including 10 who devel-
oped delayed plate exposure externally and 1 who ex-
perienced mandibular infection and loosening of her man-
dibular plate screws. Another patient had an exposed
mandible. One patient developed a prevertebral abscess
necessitating incision and drainage 4 months after comple-
tion of therapy that resulted in transient quadriplegia. This
patient subsequently recovered and underwent an addi-
tional workup that revealed no evidence of recurrent can-
cer. Two patients needed hyperbaric oxygen treatment
after experiencing osteoradionecrosis in months 14 and
27 of follow-up. Both patients were completely protocol
compliant. Myelodyplasia with anemia was detected 2.5
years after the regimen in 1 patient. Other late complica-
tions observed in the patients were a self-limited trans-
verse myelitis (Lhermitte syndrome) (0.8%), bilateral be-
nign pleural effusion (0.8%), esophageal and pharyngeal
strictures (1.6%), and chronic aspiration leading to total
laryngectomy (0.8%).

SURVIVAL

Long-term Kaplan-Meier survival analyses of the IR1, IR2,
and IR3 are seen in Figures 1, 2, and 3, respectively.
Whereas overall 5-year survival was 57% (IR1: 46%, IR2:
56%, and IR3: 68%), disease-specific 5-year survival was
73% (IR1: 60%, IR2: 78%, and IR3: 80%). Seven deaths
(5.6%) occurred during treatment. Of these 7 deaths, only
1 had disease (skull base recurrence after the resection
of vagus nerve with a positive margin); the other causes
included lung abscess, rupture of a cerebral aneurysm,
respiratory failure, lung cancer as the second primary, and 2 unknown.

DISEASE CONTROL

The overall locoregional disease control rate was 91% (112/123). The rate of distant metastases was 13.8% (17/123). The most common distant metastatic site was the lungs (70.5%), followed by the liver (17.6%), the brain (5.8%), and the mediastinum (5.8%). Four patients (3.2%) developed second primary lesions: 3 in the head and neck and 1 as a small cell lung carcinoma.

COMMENT

The Ohio State University experience with IRs in the past 12 years provides evidence that the evolved multimodal IRs with perioperative chemoradiotherapy, surgical resection, and intraoperative radiotherapy achieved excellent locoregional disease control and long-term survival rates with acceptable compliance in previously untreated, advanced, resectable oral cavity, oropharyngeal, and hypopharyngeal carcinomas.

Pinheiro et al23 evaluated the use of intraoperative electron beam radiotherapy (IORT) as an adjuvant modality in the treatment of advanced head and neck and skull base cancers and found that IORT at a dose of 12.5 Gy is safe and produces tumor control and survival for patients likely to have microscopic residual disease in sites difficult to resect, such as the skull base. The use of IORT is also reported in the management of advanced cervical metastasis.24 Although IORT is still not easily found in all the tertiary care medical centers, part of the success in disease control and survival in the IRs is attributed to IORT.

The effectiveness of paclitaxel and cisplatin in head and neck cancer is well known.25,26 Eckardt et al26 demonstrated impressive clinical and pathological response rates (58% complete pathological response) of concurrent weekly paclitaxel-carboplatin and radiotherapy as a preoperative treatment modality in advanced oral and oropharyngeal cancer. The IR uses preoperative chemoradiotherapy with cisplatin and 9 doses weekly of paclitaxel added to 2 more postoperative cisplatin cycles.

Although the literature describes 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.15 Bernier et al27 also support these findings in a recent study of advanced stage head and neck cancer, although their 5-year overall survival is 53% and 40% in postoperative adjuvant chemoradiotherapy and radiotherapy alone, respectively. Therefore, one of the primary challenges to be considered for the IRs is the tolerability and the subsequent improvement of the compliance rate. Toxic effects must be minimized while maintaining therapeutic effectiveness. Patient-directed noncompliance was substantially lower (13%) than what has been experienced in previously reported multimodal treatment programs for this identical patient population.9 Although the preexisting cardiac and vascular disease of this patient population affected the types of toxic effects, the IRs were tolerated well, with an overall protocol compliance of 61% (75/123), and the result is comparable with the previously mentioned studies.9,13,27

The protocol compliance differences among IR1, IR2,
and IR3 could be attributed to the addition of paclitaxel to the regimen.

To achieve better systemic disease control, paclitaxel was added to the previously administered IR1 chemotherapy regimen in IR2. As a result, 17.0% distant metastasis in IR1 was decreased to 7.9% in IR2; however, this regimen produced increased toxic effects of the systemic regimen, with 2 (4.6%) of the 43 patients experiencing grade 5 hematologic toxic effects, 16 (37.2%) grade 4, and 10 (23.2%) grade 3. These results prompted the modification of the regimen that is the basis for the last IR. To minimize the chemotherapy-related toxic effects, the most recently completed trial (IR3) was modified from the second IR by decreasing the individual paclitaxel doses and increasing the frequency of administration so that the total dose was identical to that of the second trial, where paclitaxel may have been responsible for decreased distant metastases in that study. Paclitaxel administration is started relatively early in the regimen as a means of decreasing the total time of treatment. The most recent regimen demonstrated continued high patient compliance and excellent locoregional control and infrequent pulmonary metastases.

Although most of the patient population in the intensification trials had stage IV cancer (77.2%), long-term survival (73%) and locoregional (91%) and systemic (86%) disease control rates were reassuring and encouraging. The IRs, using all 3 therapeutic modalities, produce not only favorable disease control but also excellent functional results. In another recent study, we found that of patients who completed the most recent IR and who were followed up for more than 12 months without evidence of disease, 71% were eating a regular diet, 20% were experiencing some swallowing difficulties but were ingesting a soft diet by mouth, and only 9% could not take anything by mouth. Percutaneous endoscopic gastrostomy dependence was observed in 11.4%. None of these patients required permanent tracheostomy tube placement. Total laryngectomy was required in only 5 (12%) of 43 patients, and voice prosthesis was applied successfully in all of them.

In conclusion, the combination of chemotherapy, radiotherapy, and surgery in these IRs is an intensive but tolerable treatment regimen with appropriate supportive interventions. It demonstrated good overall and disease-specific survival rates, with successful locoregional and systemic disease control rates. Future trials will assess modifications in these regimens intended to further reduce toxic effects, with the intention of improving protocol compliance. Expanding this trial to other institutions is also planned to determine whether the single-institutional results can be achieved in a multi-institutional setting. The ultimate goal is to validate the efficacy of these regimens by means of a phase 3 trial.

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Author Contributions: Drs Schuller, Ozer, Grecula, and Rhoades had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Schuller, Ozer, Agrawal, Grecula, Rhoades, and Young. Acquisition of data: Schuller, Ozer, Agrawal, Grecula, and Rhoades. Analysis and interpretation of data: Schuller, Ozer, Grecula, Rhoades, and Young. Drafting of the manuscript: Schuller, Ozer, Grecula, and Rhoades. Critical revision of the manuscript for important intellectual content: Schuller, Ozer, Agrawal, Rhoades, and Young. Statistical analysis: Young. Obtained funding: Schuller. Administrative, technical, and material support: Schuller, Agrawal, and Rhoades. Study supervision: Schuller, Agrawal, and Grecula.

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