# Sequential Chemotherapy for the Curative Treatment of Squamous Cell Cancer of the Head and Neck: A New Paradigm

By Marshall R. Posner, MD


## ABSTRACT

*The integration of chemotherapy into the combined modality treatment of squamous cell cancer of the head and neck (SCCHN) has remained controversial. There is compelling evidence from clinical trials and meta-analyses that chemotherapy increases survival and reduces morbidity by organ preservation. There are two distinct methods of delivering chemotherapy as part of the curative treatment for locally advanced disease—induction chemotherapy and chemoradiotherapy—and both are effective. Induction chemotherapy improves patient performance before definitive radiotherapy, allows high systemic exposure of chemotherapy, and permits intermediate assessment of prognosis and adjustment of subsequent therapy. Induction chemotherapy does not increase local/regional dose intensity and many failures are local/regional. Chemoradiotherapy increases local/regional dose intensity and increases local/regional control, but chemoradiotherapy regimens are associated with significant short- and long-term local/regional toxicity and poor long-term survival. Surgery, timed to be most effective after chemotherapy and radiotherapy, can eliminate some sites of bulk disease or persistent tumors.*

*Addition of taxanes (T) to the standard therapy, cisplatinum/5-fluorouracil (PF), may increase the effectiveness of induction chemotherapy. Phase II trials of docetaxel in combination with PF or PF plus leucovorin (L), TPF, and TPFL, respectively, have demonstrated significant response rates and long-term survival of patients with advanced disease. TPF, an intermediate-dose regimen, with toxicity comparable to PF, has entered phase III testing to compare it with standard PF. The design of the North American phase III trial of TPF vs PF, TAX 324, incorporates a new paradigm for treatment of locally advanced SCCHN-sequential chemotherapy. In TAX 324, sequential chemotherapy includes intensive induction chemotherapy, chemoradiotherapy with weekly carboplatinum, and planned surgery as the final stage. Two additional studies of sequential chemotherapy are being performed or have been completed. While TAX 324 includes carboplatinum in its chemoradiotherapy phase, other sequential chemotherapy plans either have more intensive chemoradiotherapy or are targeted at patients who have a poor prognosis after induction chemotherapy.*

*Sequential chemotherapy places induction chemotherapy and chemoradiotherapy into an integrated treatment plan and offers advantages over both forms of single treatment. Future studies may target more or less intensive chemoradiotherapy for patients with different prognoses and thus limit short-term toxicity and long-term morbidity.*


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## INTRODUCTION

The integration of chemotherapy into the curative treatment of locally advanced squamous cell cancer of the head and neck (SCCHN) has remained controversial. This is despite compelling evidence that, for patients with locally advanced disease, combined modality therapy can lead to organ preservation for those with resectable disease and improved survival for those with unresectable disease.[1-8] The results of multiple trials and meta-analyses support combined modality treatment plans; however, physician reluctance to engage in combined modality treatment plans that limit surgery and include chemotherapy continues at many levels. The difficulties in accepting and carrying out combined modality approaches are multiple: (1) SCCHN is widely heterogeneous and risk assessment can be difficult; (2) underlying patient morbidity is frequent, but not universal, and contributes to the difficulty in decision-making; (3) posttherapy morbidity from combined modality therapy

**TALKING POINTS** Physicians Pharmacy Formulary Cancer Nurses

*Sequential chemotherapy can adjust the intensity of the different phases of treatment to tumor response and patient tolerance. Side effects are still formidable, but cure rates in compliant patients are high.*

*Patients are taking continuous infusion therapy home with them and completing courses of therapy in the home setting. This may require an adjustment in chemotherapy preparation and delivery systems, and coordination with nursing services.*

*There will be increasing use of taxanes in head and neck cancer. Home therapy will require more use of third generation oral antiemetics and home fluid administration.*

*Nursing input in home delivery of chemotherapy and ancillary support, including fluids and antiemetics, is extensive and important in head and neck cancer. Because side effects are formidable, patient education and follow-up in the early stages of treatment should be intensive.*

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is considerable, recovery is prolonged, and considerable physician input and patient care is required; (4) it is difficult to effectively coordinate combined modality treatment plans; (5) because of the proliferation of different treatment regimens with different levels of toxicity and complexity, it is difficult to determine the most appropriate and effective combined modality approach.

**"…chemoradiotherapy-alone regimens lose intermediate assessment opportunities, lead to enhanced local toxicity, and reduce systemic drug exposure."**

Currently there are two generally accepted approaches to the treatment of locally advanced SCCHN: induction chemotherapy and chemoradiotherapy. In treatment plans that are based on induction chemotherapy, patients are generally treated with three or four cycles of chemotherapy and then receive definitive therapy that includes radiation therapy with or without surgery.[1-3] Chemoradiotherapy approaches combine chemotherapy directly with radiotherapy to increase local/regional dose intensity.[4,5] Both approaches have been validated by phase III trials and meta-analyses. Induction chemotherapy has been primarily used in resectable disease as a means of organ preservation, and chemoradiotherapy has been used primarily in patients with unresectable disease. These differences are somewhat arbitrary but have a profound impact on the integration of surgery in treatment plans.

Our past preference has been to use induction chemotherapy, as opposed to chemoradiotherapy, as our standard approach. More recently we have approached patients with a sequential treatment plan—a combination of induction chemotherapy, chemoradiotherapy, and surgery.[9] Chemotherapy, in a sequential approach, offers a number of tactical advantages over either singular approach. By giving induction chemotherapy, primary sites can be assessed independently at the end of the induction cycles, prior to radiotherapy, using an examination under anesthesia and biopsy. A postchemotherapy, preradiotherapy biopsy has prognostic value in determining how closely a primary site might be monitored and the risk of local/regional relapse.[10] Response assessment after chemotherapy can then guide the intensity of subsequent radiation therapy or chemoradiotherapy in the sequential approach; it also affects decisions to evaluate the primary site after completion of the radiotherapy phase of treatment. This supports primary-site preservation and dose-intensity adjustments based on the tumor's biologic behavior. Unfortunately, during chemoradiotherapy intermediate assessments and dose intensity adjustments are more difficult. Thus, chemoradiotherapy-alone regimens lose intermediate assessment opportunities, lead to enhanced local toxicity, and reduce systemic drug exposure. Finally, the long-term toxicity and efficacy of chemoradiotherapy have not been adequately assessed, in part because patient survival has been so poor.

Surgery also has an important role in a sequential treatment plan. In many patients the bulk of cancer cells are located outside the primary site within lymph nodes in the neck. It is within these large N2 or N3 neck lymph nodes that residual viable tumor cells reside after chemotherapy and radiation. It is here, after systemic chemotherapy and radiotherapy have been completed, that surgical treatment of the neck, as part of a sequential treatment plan, can make a major contribution to local control.

## *THE BIOLOGY OF SCCHN*

As a direct result of the evolving understanding of the biology of SCCHN, the timing and sequencing of chemotherapy, surgery, and radiotherapy have been identified as critically important elements in combined modality therapy for the curative treatment of locally advanced SCCHN. When model tumors are treated by radiotherapy, the tumor cells remaining after treatment begin to repopulate the tumor bed. These cells grow from spared, quiescent, or partially resistant populations that were not eliminated.[11-13] The theoretical repopulation of tumors with cells that may be partially resistant to subsequent therapy may lead in vivo to the clinical observations that protracted radiotherapy and delays between surgery and start of radiotherapy reduce local and regional control rates.[12]

Another factor that may influence repopulation and local cure rate is tumor potential doubling time. Potential doubling times for tumors in SCCHN patients are very rapid, on the order of 48 hours.[13] Rapid tumor potential doubling time accelerates tumor repopulation, as a greater fraction of remaining cells are capable of cycling and expanding after each cycle of therapy. Altered fractionation treatments, which give radiation therapy at a higher dose rate in shorter intervals, are designed to have increased efficacy because of a greater impact on rapidly repopulating tumor cells. Accelerated fractionation schedules are superior to standard fractionation therapies.[14]

These data, taken together with clinical studies, strongly support the notion that when

chemotherapy is given before radiation, then radiation should follow as quickly as possible to prevent tumor repopulation. In addition, surgery is not capable of sterilizing the tumor bed when performed immediately after induction chemotherapy. Surgery immediately after induction chemotherapy delays the onset of radiotherapy. This is important because, in many patients, tumor cells remain outside the surgically removed tissues. These cells have been perturbed by chemotherapy, may be partially resistant to radiotherapy, and are, theoretically, more capable of rapid growth than the parental tumor cells within the residual tumor bed and underlying tissues. As opposed to chemoradiotherapy programs, where surgery follows chemoradiotherapy and thus timing is less of an issue, surgery after induction chemotherapy should follow radiation rather than be interposed between chemo- and radiotherapy. Based on our current understanding of the biology of SCCHN, we propose that a sequential approach that integrates induction chemotherapy and chemoradiotherapy offers an effective and rational choice for patients with locally advanced disease and should be explored for suitable patients.

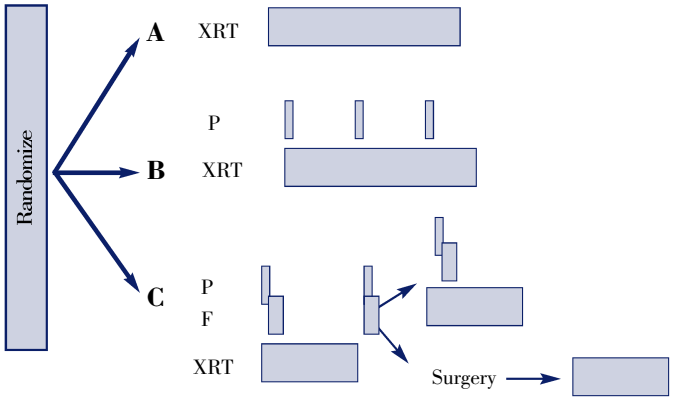
This proposal might be considered a radical departure in the treatment of locally advanced SCCHN. This is because neither induction chemotherapy nor chemoradiotherapy, as noted above, is readily accepted by many physicians as a standard of care for either organ preservation or improving survival. This is despite ample evidence from phase III trials and meta-analyses that support these as standard curative treatment for patients with SCCHN. Before we can move forward to a new paradigm for treatment of locally advanced SCCHN, it is important to review the evidence supporting combined modality therapy as a standard of care.

### *EVIDENCE FOR INDUCTION CHEMOTHERAPY AND CHEMORADIOTHERAPY:*

Data supporting the integration of chemotherapy into the combined modality treatment of SCCHN derive from recently reported randomized clinical trials and from three published meta-analyses.[6-8] All three meta-analyses reviewed trials performed over prolonged intervals; they included studies, published up to 1993, with a no-chemotherapy control arm and concluded that chemotherapy provided a statistically significant, but quantitatively low, survival advantage. All three meta-analyses also found that chemoradiotherapy gave superior results in the aggregate, although induction chemotherapy significantly improved survival in only one analysis. While meta-analyses have been taken to suggest that chemoradiotherapy is superior to induction chemotherapy, there are limits to the interpretation that can be applied. For example, only a small fraction of trials in the published studies used the current standard for induction chemotherapy, cisplatinum and 5-fluorouracil (PF), at acceptable doses.[3] In addition, patients were not identified as unresectable or resectable. In a setting of resectable disease, the combination of primary site surgery, radiotherapy, and induction chemotherapy may not be additive. Finally, in resectable and unresectable disease, the timing and extent of surgical intervention may also be critically important.

As described above, we now believe that the timing of surgery in combined modality regimens that include chemotherapy has a profound effect on local and regional control. Surgical interventions in the majority of induction chemotherapy trials and chemoradiotherapy trials were not based on our present understanding of tumor biology. Suboptimal surgical timing may well have reduced tumor control rates. Two randomized trials illustrate this.[1,15] In INT-026, a cooperative group trial of chemoradiotherapy, patients with unresectable disease were treated with radiotherapy alone, chemoradiotherapy with platinum, or split-course intensive chemoradiotherapy with PF and a protocol-driven

**FIGURE 1. TREATMENT SCHEME FOR THE NT-026 TRIAL**




XRT=radiotherapy; P= cisplatinum; F=5-fluorouracil.

Posner MR. *Oncology Spectrums.* Vol 2. No 3. 2001.

surgical intervention before completion of chemoradiotherapy for patients who became resectable during chemoradiotherapy (Figure 1A). Unresectable patients and postsurgical patients in this last group then completed their chemoradiotherapy. The pure chemoradiotherapy arm did significantly better, while the interventional surgery arm fared worse. Chemoradiotherapy, without intervening surgery, was significantly better than radiotherapy alone for survival. It appears that surgical intervention, interrupting the course of chemoradiotherapy, reduced local/regional control.

**"...the meta-analyses support the notion that an integrated approach that includes chemotherapy improves survival in patients with SCCHN."**

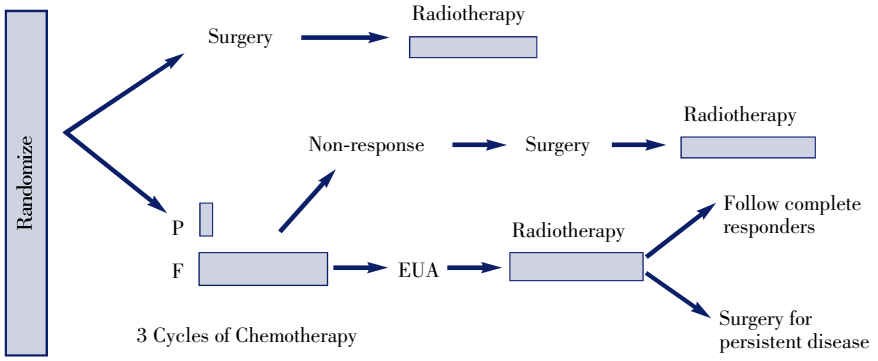
The STUDIO trial explored the use of induction chemotherapy in a broader population of patients who were stratified into resectable and unresectable groups. Patients were treated with four cycles of PF and resectable patients then underwent surgery followed by radiotherapy. Unresectable patients underwent immediate definitive radiotherapy. If, after radiotherapy, the primary site was disease free, a neck dissection was performed for prior nodal disease. Resectable patients had statistically equivalent overall survival and disease-free survival in both arms. In unresectable patients, the chemotherapy arm had almost 2-fold better overall and disease-free survival, and they also had significantly better overall survival than the standard radiation group. Thus, a planned intervening surgical resection for resectable patients may have reduced the impact of induction chemotherapy on local/regional tumor control and obviated the value of induction chemotherapy on organ preservation, while a postchemotherapy and postradiotherapy neck dissection contributed to improved survival in unresectable patients. The data with respect to unresectable patients are consistent with the additive effect of induction chemotherapy to radiation therapy on local/regional control, and they reaffirm the importance of the timing of surgery in management of SCCHN.

In keeping with this concept, if there were also delays in movement of patients from induction chemotherapy to radiotherapy, then local/regional control rates may well have been compromised.[12] This pertains more to induction therapy since there is no interval between chemo- and radiotherapy in chemoradiotherapy protocols. Finally, with regard to the trials included in the meta-analyses, surgical and radiotherapy decision-making was generally not protocol-driven and may have varied considerably or been compromised or delayed.

Despite the qualifications and difficulties in analyzing disparate trials performed, literally, over decades, the meta-analyses support the notion that an integrated approach that includes chemotherapy improves survival in patients with SCCHN. They do not address the issues of organ preservation or the current state of knowledge about SCCHN biology. There are several relatively recent randomized trials of induction chemotherapy and chemoradiotherapy that support the use of these treatments over standard surgical or radiotherapy approaches.

The VA Larynx Trial and the European Organization for Research and Therapy of Cancer (EORTC) Hypopharynx Trial were designed as organ preservation studies (Figure 2).[2,3] The VA Larynx Trial, originally published in 1991, included stage III or stage

**FIGURE 2. TREATMENT SCHEME FOR THE VA LARYNX TRIAL**




P=cisplatinum; F=5-fluorouracil; EUA=examination under anesthesia.

Posner MR. *Oncology Spectrums.* Vol 2. No 3. 2001.

IV larynx cancer patients who were randomly assigned to receive chemotherapy for three cycles with PF followed by radiation therapy or to undergo laryngectomy and radiation therapy. Chemotherapy-treated patients who achieved at least a partial response (PR) after two cycles received a third cycle and went on to radiation therapy, and patients with persistent disease after radiotherapy had surgical excision. Patients whose disease did not respond to PF chemotherapy had laryngectomy before radiotherapy. In the EORTC Hypopharynx Trial, patients with locally advanced disease were also treated with three cycles of PF chemotherapy. Patients who achieved a complete response (CR) to chemotherapy went on to definitive radiotherapy, while patients with PR or nonresponders had surgery followed by radiotherapy.

These trials demonstrated that chemotherapy could replace surgery without reducing survival, and that 35–60% of surviving chemotherapy patients retained laryngeal function. Survival data are now complete for more than 8 years in the VA Larynx Trial. Patients treated in both the surgical and chemotherapy arms have identical survival rates.[16] It is notable that neither trial included a large number of patients with N2 or N3 nodal disease, a very poor prognosis group. Also, neither trial specified the maximum time interval between chemotherapy and initiation of radiotherapy. Despite these caveats, both trials demonstrated that chemotherapy could replace surgery for patients in whom organ preservation was the therapeutic goal and both demonstrated that, in this context, survival was identical.

In the VA Larynx Trial, over 100 patients in the chemotherapy group had biopsies taken after chemotherapy and before radiotherapy, and 88% of CRs as well as 45% of PRs were pathologically disease-free at the primary site.[10] Local/regional control was highly correlated with complete pathologic response. Thus, primary site histology after chemotherapy can be an important guidepost to further therapeutic decisions. This is an important consideration if one has a series of options of varying intensity for postchemotherapy treatment.

Two important randomized trials of chemoradiotherapy, the Duke and Calais studies, have recently been published.[4,5] Both studies included a small fraction of resectable patients. In the Duke study, patients were randomized to fractionated radiation twice a day or radiation twice a day plus two cycles of concurrent, modified PF chemotherapy and two cycles of adjuvant PF chemotherapy. Disease-free survival was significantly better in the chemoradiotherapy arm; however, overall survival was very poor and not significantly different between the two arms. Morbidity from treatment was considerable as well.

The Calais study compared chemoradiotherapy with three cycles of carboplatinum and 5-FU to standard daily, fractionated radiotherapy in patients with locally advanced oropharyngeal carcinoma. Both disease-free and overall survivals were significantly improved in the chemoradiotherapy arm. Overall survival at 3 years in the chemoradiotherapy arm was 51% vs 31% in the radiotherapy arm and disease-free survival was 42% vs 20%, respectively. Importantly, the Calais study, as opposed to the Duke study, demonstrated better overall survival than disease-free survival in both treatment arms. While this may reflect many things, including the number of resectable patients, the focused disease site, and the planned integration of surgery, it may be that the Calais study patient population had less underlying morbidity from noncancer causes. When patients are lost to noncancer causes early in a study, it becomes difficult, if not impossible, to interpret study results.

While randomized trials comparing chemoradiotherapy and induction chemotherapy have been performed, they were not optimally designed and none showed a benefit to induction chemotherapy.[17-22] Most were small; in some, patient entry was not well controlled and included patients with significant preexisting morbid illness; others did not use the standard PF; and many included a surgical intervention between chemo- and radiotherapy or after radiotherapy for

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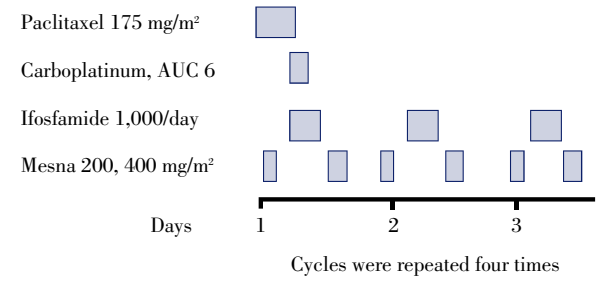
**FIGURE 3. TREATMENT SCHEME FOR THE TIC REGIMEN**




TIC=paclitaxel-ifosfamide-carboplatinum; AUC=area under the curve.

Posner MR. *Oncology Spectrums.* Vol 2. No 3. 2001.

**TABLE 1. DOCETAXEL-BASED MODIFICATIONS OF PF AND PFL**

| Drugs* | TPFL5 | TPFL4 | OpTPFL | TPF |
|---|---|---|---|---|
| Docetaxel | 60 | 60 | 90 | 75 |
| Cisplatinum | 125 IVCI over 5 days | 125 IVCI over 4 days | 100 bolus day 1 | 100 bolus day 1 |
| 5-fluorouracil | 700 x 4 days | 700 x 4 days | 700 x 4 days | 1000 x 4 days |
| Leucovorin | 500 x 5 days | 500 x 4 days | 500 x 4 days | None |
| G-CSF | Yes | Yes | Yes | No |
| Antibiotics | Yes | Yes | Yes | Yes |
| Postinduction radiotherapy | Bid | Bid | Bid | Institutional choice |

* Doses are in mg/m².
P=cisplatinum; F=5-fluorouracil; L=leucovorin; T=docetaxel; Op=outpatient; IVCI=intravenous continuous infusion; G-CSF=granulocyte colony stimulating factor.

Posner MR. *Oncology Spectrums.* Vol 2. No 3. 2001.

responding patients, including those considered unresectable at treatment onset.

Unfortunately, a well-controlled randomized trial comparing induction chemotherapy with standard PF to a chemoradiotherapy program in resectable and unresectable patients has not been completed. Future randomized comparisons of induction chemotherapy and chemoradiotherapy should pay special attention to the timing between radio- and chemoradiotherapy in the induction arms; include stratification between resectable and unresectable disease; and manage the appropriate integration of surgery in the postradiotherapy setting. Because of the recent identification of taxanes as effective agents in the treatment of SCCHN, new trials may compare newer combination therapies for induction chemotherapy. Integrated induction and chemoradiotherapy sequential treatment plans have also been developed and may supplant PF as a standard in such trials.

**"Integrated induction and chemotherapy sequential treatment plans have also been developed and may supplant PF as a standard in such trials."**

## *PHASE II TRIALS OF TAXANE-BASED COMBINATION CHEMOTHERAPY*

Phase II studies of the taxanes, paclitaxel and docetaxel, have shown them to be highly active single agents to treat recurrent SCCHN.[23-26] To improve on the therapeutic result of PF, we and others have added taxanes to P or PF, or have developed entirely new regimens, such as paclitaxel-ifosfamide-carboplatinum (TIC) (Figure 3).[27-31] In our own studies we have chosen to work with docetaxel and the standard PF chemotherapy regimen. Docetaxel lacks significant neurotoxicity, is associated with minimal mucositis, and can be added to PF-based induction regimens, with minimal added toxicity, primarily myelotoxicity. The taxanes work by mechanisms of action distinct from P or F and would be expected to add to PF therapy.

We have completed four studies with docetaxel specifically to address its use in the induction setting (Table 1).[28-31] Three single-center trials investigated use of docetaxel in high-dose PFL (leucovorin) regimens (TPFL).[32] PFL is highly active but associated with considerable toxicity. A fourth multicenter trial was performed to define the dose of cisplatinum to be used in phase III trials incorporating docetaxel in PF chemotherapy (TPF).

All four trials delivered three cycles of chemotherapy before definitive therapy. Nonresponding patients after two cycles and patients with progressive disease could be taken off protocol treatment. TPFL5, TPFL4, and outpatient TPFL (opTPFL) consisted of docetaxel, PF, and leucovorin. TPFL5 was given on a 28-day schedule; however, all further therapeutic trials specified a 21-day cycle. TPFL5 and opTPFL were dose-escalation trials for docetaxel. For TPFL-5, a maximal tolerated dose (MTD) of 60 mg/m² of docetaxel was reached. Cisplatinum was given as 125 mg/m² over 5 days with 5-FU, 700 mg/m² for 4 days, and leucovorin for 5 days. For opTPFL, docetaxel MTD was 90 mg/m² and cisplatinum was given as a 100 mg/m² bolus on day 1. TPFL4 was a phase II study, with docetaxel at 60 mg/m² and a compressed version of TPFL5 given. All the TPFL regimens required growth factor support and antibiotics for predictable neutropenia.

In the multicenter TPF trial, docetaxel was given at 75 mg/m² and two different cisplatinum doses, 75 mg/m² and 100 mg/m², were studied. TPF was given as 1,000 mg/m²/day for 4 days by continuous infusion, resulting in a total per cycle dose of 4,000 mg/m². In all four trials, we asked that patients undergo an examination under anesthesia after the last cycle to assess response. All TPFL protocols required that patients initiate definitive radiotherapy within 6 weeks of starting the final cycle. They received radiation twice a day and patients with PRs after chemotherapy in nodal disease sites underwent protocol-defined, planned postradiation neck surgery. All patients given TPF received standard antibiotic support for 10 days during each cycle.

All four trials included patients with locally advanced, potentially curable SCCHN

involving the larynx, hypopharynx, oropharynx, and oral cavity. The multicenter TPF trial did not include patients with tumors of the nasopharynx, nasal cavity, and paranasal sinuses, or unknown primaries. Other important patient characteristics are summarized in Table 2, with data for both dose levels of TPF combined. As noted before, nodal disease is a major predictor of response and local/regional control, and few patients with N2/N3 nodal disease were included in the two major trials of organ preservation reported in the literature. All four trials included a majority of N2/N3 patients and, across all four trials, comprised of 130 patients, 87 or 67% had N2 or N3 disease. Further, oropharynx cancer, which was primarily the tongue base, accounted for 43% of primary sites. Organ preservation in this group is particularly important.

Table 3 shows an analysis of response data. The CR rate for all four studies was high. Responses can be evaluated in the primary site and the nodal sites separately in these trials. This is particularly important when primary site preservation is a consideration because the neck can receive additional therapy as a separate site. The clinical primary site CR rate in TPFL5, TPFL4, and opTPFL was 86%, 71%, and 72%, respectively. For TPF, 58% of patients had a clinical primary site CR. A pathology-documented CR was achieved in an additional 9 of 15 patients with a clinical PR or stable disease who were evaluated by postchemotherapy biopsy. One of 10 patients with a clinical CR was biopsy-positive. These data show, as expected, that the pathology-documented CR rate of the primary site is much higher than the clinical CR rate. The pathologic CR rate in biopsied patients is 72%. That is higher than that seen in the VA Larynx Trial. This trial did not require postchemotherapy biopsies, and only a fraction of patients had them. Thus, the full pathology-documented CR rate is not known for this trial. The lower clinical CR rate in TPF vs TPFL5 may reflect the use of computerized tomography or magnetic resonance imaging, rather than physical exam, for response determination in some cases. These imaging techniques are inferior to clinical examination in assessing response in SCCHN. Alternatively, this difference may result from lesser intensity of treatment in these patients, age, or distribution of cases vs the high-dose trials, or a combination of all these factors.

**TABLE 2. PATIENT CHARACTERISTICS**

| | TPFL5 | TPFL4 | OpTPFL | TPF |
|---|---|---|---|---|
| Entered (n) | 23 | 30 | 34 | 43 |
| Median age (year) | 49 | 50 | 55 | 57 |
| Oropharynx | 11 | 9 | 14 | 22 |
| Larynx | 2 | 7 | 5 | 7 |
| Hypopharynx | 2 | 1 | 0 | 8 |
| Oral cavity | 4 | 2 | 6 | 6 |
| Nasopharynx | 4 | 7 | 6 | Excluded |
| Maxillary sinus | 0 | 2 | 0 | Excluded |
| Unknown | 1 | 2 | 3 | Excluded |
| N2+N3 | 17 (76%) | 16 (54%) | 26 (76%) | 28 (65%) |

T=paclitaxel; P=cisplatinum; F=5-fluorouracil; L=leucovorin; Op=outpatient; N2+N3=N2 and N3 nodal involvement.

Posner MR. *Oncology Spectrums.* Vol 2. No 3. 2001.

**TABLE 3. RESULTS OF CHEMOTHERAPY**

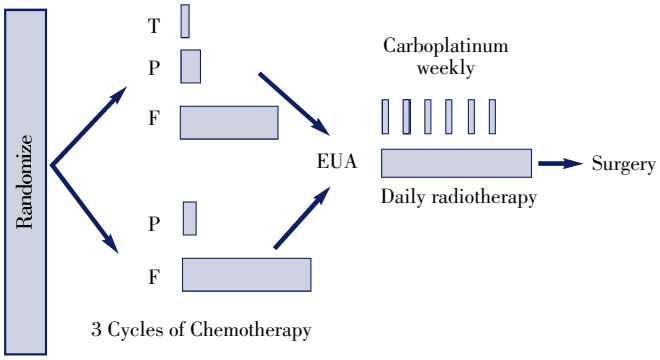
| | TPFL5 | TPFL4 | OpTPFL | TPF |
|---|---|---|---|---|
| Minimum follow-up (months) | 48 | 24 | 20 | 24 |
| Primary site | | | | |
| CR (%) | 86 | 71 | 67 | 56 |
| CR (%) | 61 | 63 | 44 | 42 |
| PR (%) | 39 | 30 | 50 | 51 |
| Response (%) | 100 | 93 | 93 | 93 |
| 2-year survival (%) | 83 | 80 | 71 | 82 |

T=paclitaxel; P=cisplatinum; F=5-fluorouracil; L=leucovorin; Op=outpatient; CR=complete response; PR=partial response.

Posner MR. *Oncology Spectrums.* Vol 2. No 3. 2001.

Toxicity in the high-dose trials was formidable. In TPFL-4, a single patient (3%) died during the second cycle of therapy due to prolonged neutropenia, stomatitis, and sepsis. Stomatitis remained a major toxicity in all TPFL trials, but the major toxicities associated with addition of docetaxel to PF- or PFL-based chemotherapy are neutropenia and febrile neutropenia. TPFL4 and opTPFL provided for early use of gram colony-stimulating factor and antibiotics to successfully reduce the incidence of febrile neutropenia For TPF, febrile neutropenia was rare, occurring in 16% of patients, but neutropenia was almost universal. No significant infections were documented in TPF patients. The incidence of grade 3 or 4 stomatitis was modest in the TPF protocol. In the high-dose studies mucositis was dose limiting and grade 3 or 4 mucositis

**FIGURE 4. TREATMENT SCHEME FOR THE NORTH AMERICAN TRIAL—TAX 324**




T=docetaxel; P=cisplatinum; F=5-fluorouracil; EUA=examination under anesthesia.

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**"Given the advantages and disadvantages of chemotherapy and chemoradiotherapy, sequential chemotherapy might represent the most biologically effective use of both schedules."**

occurred in up to 90%, as opposed to 25% of patients on the TPF trial.

The majority of morbidity from the high-dose trials resulted from a combination of neutropenia, mucositis, nausea, electrolyte disturbances, and dehydration, resulting in a 36%, 26%, and 15% hospitalization rate for all cycles for TPFL5, opTPFL at MTD, and TPFL4, respectively. Morbidity in the TPF trial was less, principally related to dehydration and febrile neutropenia, and consistent with toxicity observed in phase III trials of PF.[2,3]

The combined phase II data support the notion that docetaxel adds incrementally to the efficacy of PF and PFL. The multicenter TPF trial suggests that primary site response rates to TPF are higher then those observed historically for PF in North American patients with this extent of disease and consistent with those seen with PFL, without the excess toxicity. It is also noteworthy that the frequency of N2 and N3 nodal disease was substantially higher in the TPF trial than in the EORTC Hypopharynx and VA Larynx Trials.[2,3] Hence the high overall CR and PR rate of TPF is very encouraging. The phase II data suggest that TPF is more active then PF with equivalent or less toxicity. The TPF results and other taxane trial results have been used to establish TPF regimens as experimental arms in two phase III trials, one in Europe and one in North America, which will compare the European and North American TPF regimens to PF (Figure 4).

## *SEQUENTIAL COMBINED MODALITY THERAPY*

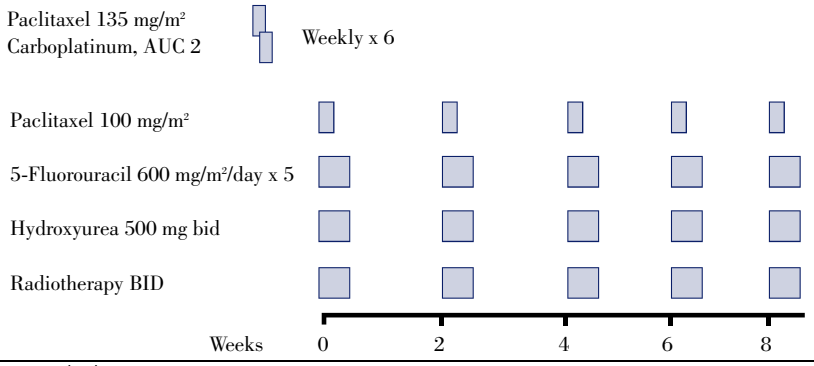
### *Sequential Chemotherapy*

Sequential chemotherapy is a new paradigm of curative of chemotherapy for locally advanced SCCHN. This combined modality treatment plan includes sequential induction chemotherapy, chemoradiotherapy, and surgery. A sequential treatment plan is distinct from both induction chemotherapy and chemoradiotherapy treatment plans.

The advantages and disadvantages of induction chemotherapy and chemoradiotherapy can be assessed systematically. Induction chemotherapy permits effective systemic exposure with full doses of therapy. Lower doses of chemotherapy are required by dose-limiting toxicity during chemoradiotherapy. This increases the risk of inducing partial resistance in distant tumor cell populations. Toxicity is also transient during induction chemotherapy, as opposed to the cumulative toxicity associated with aggressive chemoradiotherapy programs. After induction chemotherapy response can be assessed and further treatment based on this prognostic information. Finally, patients completing induction chemotherapy are in better condition for chemoradiotherapy because of improved nutrition, reduced tumor bulk, and better familiarity with the medical system and their disease. Systemic toxicity is increased during induction chemotherapy and induction chemotherapy does not improve local or regional dose intensity. Chemoradiotherapy can deliver increased local/regional dose intensity. Surgery, after chemoradiotherapy, to sites in the neck and as salvage can address sites of bulk disease and potential resistance to the combined chemotherapy and chemoradiotherapy. Given the advantages and disadvantages of induction chemotherapy and chemoradiotherapy, sequential chemotherapy might represent the most biologically effective use of both schedules.

Several trials have been reported that address sequential treatment plans as proposed here.[33,34] In the Chicago trial, patients were treated with a brief, intensive weekly course of chemotherapy with carboplatinum and paclitaxel, followed directly by intensive chemoradiotherapy (Figure 5).[34] Early results are encouraging. We have taken a somewhat different approach. We performed a phase I/II trial of weekly docetaxel given during daily radiotherapy. Patients who had a positive

**FIGURE 5. TREATMENT SCHEME FOR THE CHICAGO SEQUENTIAL TRIAL**




AUC=area under the curve.

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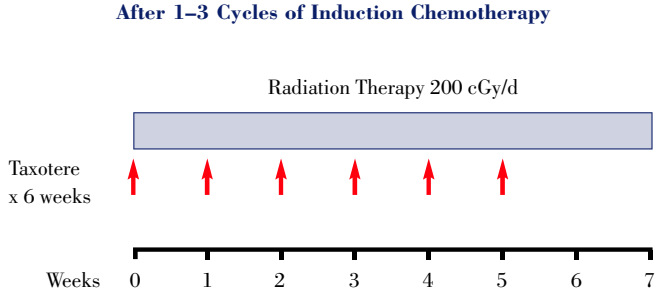
postinduction chemotherapy biopsy, a partial or nonresponse to induction chemotherapy, or an extremely poor prognosis were included (Figure 6). This trial has been completed and 16 patients have been treated at the MTD of docetaxel, 25 mg/m². Patients experienced considerable acute mucositis and there was a 40% incidence of delayed recovery of swallowing function. The 2-year event-free survival in this study is 65%, which is considerable for this population.

The Chicago trial did not adjust or select chemoradiotherapy intensity based on response to induction chemotherapy, and this is a significant difference between this treatment plan and the one we have performed. Patients with CRs or better responses to induction chemotherapy might be treated with a less intensive regimen. For example, the treatment plans used for the phase III North American Trial, TAX 324, comparing PF and TPF, are shown in Figure 4. TAX 324 is a sequential, combined-modality trial that includes chemoradiotherapy after induction chemotherapy with either PF or TPF for responders. This design differs from other induction trials by increasing local/regional dose intensity after a high-dose systemic treatment with a modified chemoradiotherapy approach. Weekly low-dose carboplatinum during chemoradiotherapy limits systemic toxicity while optimizing radiation sensitization.[35] With low weekly doses, neutropenia, thrombocytopenia, and nausea can be well controlled, while neurotoxicity, which might be expected with cisplatinum in this context, may be minimized.

Thus, sequential chemotherapy approaches may offer advantages over pure induction or chemoradiotherapy treatments by modulating the intensity of the different phases based on response, disease volume, and patient tolerance. The sequential therapy paradigm takes advantage of our current understanding of the biology of SCCHN. The value of such an approach will be determined in phase III comparisons with other approaches, and we should expect to see such trials during this decade.

**FIGURE 6. TREATMENT SCHEME FOR SEQUENTIAL TAXOTERE CHEMORADIOTHERAPY**

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