



# Induction Chemotherapy in Locally Advanced Squamous Cell Cancer of the Head and Neck: Evolution of the Sequential Treatment Approach

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Cisplatin plus 5-fluorouracil (5-FU) (PF regimen) induction chemotherapy (IC) has been studied over the last two decades and has proven to be a durable and effective therapy for patients with locally advanced squamous cell cancer of the head and neck (SCCHN). Although randomized trials and meta-analyses have demonstrated that PF-based IC improves survival, reduces systemic metastases, and permits organ preservation, the effect on overall survival has been less robust than the results seen with cisplatin-based chemoradiotherapy (CRT) regimens. Differences in trial design, scheduling, and surgical interventions account for some of the variation in results. As studies have evolved, it has become evident that there are advantages to both approaches. This perception has led to the concept of sequential therapy (ST), the combination of IC, CRT, and surgery. ST programs are being studied intently in many centers. Phase II and III trials of ST regimens have reported unprecedented survival results in patients with locally advanced disease. In addition, the hypothesis that PF plus a taxane may result in an improved survival, compared to PF alone, for patients with locally advanced SCCHN on ST treatments is being tested in phase III trials. Although ST has not been compared head to head with CRT, early results support the use of this treatment paradigm in patients with poor prognosis SCCHN and should lead to definitive phase III trials in the near future. ST may represent the cutting edge of therapy for patients with curable, locally advanced SCCHN

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Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients. Worldwide more than 500,000 new cases are projected annually. SCCHN is a potentially curable malignancy when diagnosed at an early stage.<sup>1</sup> Unfortunately, patients often present with advanced locoregional disease, defined as either stage III (T3N0M0 or T1-3N1M0) or stage IV (T4N0-1M0 or T1-4N2-3M0).<sup>2</sup> The prognosis has remained poor in this group of patients. Following standard therapy with surgery, radiotherapy, or both, only approximately 45% of patients will be alive and disease-free after 2 years. Between 50% and 60% will develop locoregional recurrences within 2

years and 20% to 30% will develop distant metastases. Thus, with treatment by surgery and radiotherapy or radiotherapy alone, failure to control T3, T4, and/or N2-N3 (ie, stages III and IV) tumor occurs via two biologically distinct pathways, local recurrence and metastatic spread. In addition, definitive surgery for intermediate- or advanced-stage disease within the larynx, hypopharynx, and oropharynx leads to profound functional morbidity.

To address the morbidity of treatment and the failure of primary surgery and radiotherapy to achieve cure in the vast majority of patients with locally advanced SCCHN, chemotherapy has been added to treatment. Based on multiple randomized studies, chemotherapy has been shown to lead to four advantageous outcomes: (1) chemotherapy can substitute for primary site surgery, permitting primary organ preservation<sup>3-5</sup>; (2) chemotherapy improves locoregional control<sup>3-5</sup>; (3) chemotherapy can reduce distant failure<sup>3-5</sup>; and (4) chemotherapy can improve survival.<sup>6-11</sup> The optimal delivery of combined modality therapy has remained controversial both with regard to the scheduling and the content of

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therapy.<sup>12</sup> Three major approaches have been investigated: (1) primary induction chemotherapy (IC), before definitive surgery and/or radiotherapy; (2) concomitant treatment with chemotherapy and radiotherapy—known as chemoradiotherapy (CRT); and (3) more recently, sequential chemotherapy consisting of IC and CRT.<sup>13</sup>

## Induction Chemotherapy

Primary chemotherapy in SCCHN has been studied in an induction schedule for more than two decades. Its popularity has been motivated by reports of outstanding response rates in patients with advanced SCCHN. The notion that IC could enhance cure rates is rationally based on observations that cisplatin-based chemotherapy can shrink tumors in patients with markedly advanced SCCHN and result in a significant fraction of pathologically negative resections. Seminal observations by teams led by Charlotte Jacobs at Stanford University and Muhyi Al-Sarraf at Wayne State University demonstrated the feasibility of replacing surgery with IC and introduced the modern era of clinical investigation and treatment of SCCHN.<sup>14,15</sup> The rationale underlying the use of an induction treatment plan is based on the expectation that drug delivery is better in untreated, well-vascularized tumors, and that micrometastatic disease could be eradicated by high-dose therapy.<sup>16,17</sup> Further, the treatment-naïve patient is far more tolerant of the side effects of chemotherapy than the irradiated patient.

The Wayne State two-drug regimen combining 100 mg/m<sup>2</sup> cisplatin on day 1 and 1,000 mg/m<sup>2</sup>/d continuous infusion 5-fluorouracil (5-FU) over 5 days (PF regimen), has been the most effective regimen and has remained the gold standard in advanced SCCHN.<sup>18</sup> The clinical benefits of chemotherapy have been demonstrated when this regimen was incorporated into the treatment of patients with locally advanced disease in four randomized trials that resulted in organ preservation, reduced distant metastases, or significant improvements in survival in PF-treated patients compared to the control populations.<sup>3,5,8,10</sup> Reported response rates have averaged 60% to 80%, with complete responses in 20% to 30% of patients.<sup>3,5,8-10,19,20</sup>

Although it remains considerably controversial, IC can be considered a standard therapy in at least two clinical situations, organ preservation in resectable patients, and therapy of those patients with aggressive high-volume and/or unresectable tumors.<sup>3,5,8,10</sup>

## Resectable Patients and Organ Preservation

The interpretation of the results of induction trials is confounded by the potential variables that are encountered in setting the goals and the structure of clinical trials of IC as opposed to CRT studies. There is a substantial difference, for example, in the end points of studies for organ preservation, and those in patients who have unresectable disease. In organ preservation studies, equivalent survival is an accepted end point if laryngeal or tongue function is maintained, while survival is the appropriate end point in unresectable disease.

Importantly, the timing of therapy can be altered by the structure of scheduled treatments. For example, performing nodal surgery or primary site “salvage” surgery after IC but before radiotherapy might have a negative impact on survival. The definition of resectability is based on objective and nonobjective parameters, including the TNM (tumor, node, metastasis) stage of the tumor, anatomic considerations, expected postsurgery morbidity, the patient’s general health condition, concomitant illness, and the surgeon’s experience. The inclusion of patients with considerable comorbidity, delays in therapy, premature surgical salvage, and inappropriate chemotherapy choices are all potential factors that confound the results of induction trials. Primary tumor location is also an important factor when considering prognosis and organ preservation. Intermediate-stage and high-volume lesions of the larynx, base of tongue, and hypopharynx can benefit from an organ preservation strategy but have different natural histories, sensitivities to therapy, and prognoses.<sup>4,12</sup>

The first phase III organ preservation trial, the Veterans Affairs (VA) Larynx Trial, was published in 1991.<sup>5</sup> This study compared IC with PF followed by radiation to no chemotherapy and initial laryngectomy followed by radiation therapy. It showed that patients randomized to IC had similar survival compared to patient treated with total laryngectomy. Organ preservation was achieved in approximately two thirds of the patients and the rate of distant metastasis was decreased. A study of pyriform sinus cancer performed by the European Organization for Research and Treatment of Cancer (EORTC) also demonstrated an equivalent survival between the chemotherapy and surgical arms, with organ preservation achieved in one third of the patients.<sup>3</sup> Both studies included primarily patients with intermediate-stage disease. These landmark studies have clearly established that intermediate-stage patients treated for organ preservation with a nonsurgical approach were not penalized in terms of survival.

Several studies attempted to replicate these data and were unsuccessful, most notably a Groupe d’Etude des Tumeurs de la Tête et du Cou (GETTEC) trial that studied laryngeal cancer.<sup>21</sup> This trial included very few patients, 69 in total, and had significant early morbidity, which suggested poor patient selection and treatment monitoring. This study highlights problems encountered with many trials in SCCHN: the inclusion of patients who are inappropriate for aggressive treatments by virtue of underlying morbidities or psychosocial disability. Patients being treated with an intensive therapeutic regimen that includes chemotherapy and radiotherapy must be able to tolerate the treatment and, if organ preservation is an issue, they must be capable of rehabilitating from the therapy. Combined modality therapy can lead to devastating short- and long-term morbidity, which must be addressed. Late toxicity and mortality are not well appreciated in many clinical trials.<sup>11,22</sup>

More recently, IC for organ preservation has been compared to CRT and daily single-fraction radiotherapy in the Intergroup 91-11 trial.<sup>4</sup> For the intermediate-stage patients entered on this trial, CRT with bolus cisplatin led to greater laryngectomy-free survival than radiotherapy alone, without a significant loss of survival. IC was intermediate and not

significantly better compared to radiotherapy or worse than CRT. Thus, in this intermediate population, CRT appears to be a more efficient and potentially effective therapy than radiotherapy alone.

## Unresectable Patients

In more advanced and unresectable cancer, the role of IC appears to be more secure.<sup>8,10</sup> Randomized trials have shown that IC can improve survival and local disease control, and it can prevent the occurrence of metastasis in patients with locally advanced resectable or unresectable disease.<sup>8,10</sup> Data supporting an effect on survival by IC derives from several recent randomized trials and from meta-analyses. The most recent meta-analysis specifically supported the use of platinum/5-FU (cisplatin or carboplatin combined with 5-FU after the Wayne State schedule) IC to improve survival. The impact of IC on survival was evaluated by Pignon et al<sup>9</sup> who combined data from 5,269 patients entered in 31 randomized clinical trials. Overall, the results showed a nonsignificant 2% survival benefit for patients receiving IC of varied regimens. However, a detailed analysis of 2,487 patients entered in 15 trials using platinum/5-FU chemotherapy demonstrated a significant benefit, with a 16% improved relative survival and a 5% absolute improvement in survival at 5 years compared to controls ( $P < .05$ ).<sup>23</sup> This was only observed in patients treated with platinum/5-FU-based chemotherapy. Several trials substituted carboplatin for cisplatin in the PF regimen because of its simpler toxicity profile and ease of administration. Cisplatin has been shown to be superior to carboplatin in randomized trials of platinum/5-FU regimens.<sup>24-26</sup> Thus, interpretation of some borderline negative induction trials, such as the trial reported by Depondt et al,<sup>7</sup> where carboplatin was substituted for cisplatin, should be performed with caution. This trial demonstrated an improvement in overall survival in advanced-stage IC-treated patients despite using carboplatin-based therapy.

The proper sequencing of IC with other modalities also has not been well explored. In a study by Paccagnella et al,<sup>10</sup> in resectable disease, when surgery was performed immediately in post-IC patients, there was no improvement compared to a surgery plus radiotherapy arm. The unresectable patients on this trial who went directly from IC to radiotherapy showed a significant improvement in survival compared to radiotherapy alone. Importantly, patients in the unresectable group underwent postradiation neck dissections if their primary site was pathologically negative. The failure to see improved survival in the resectable patients may have been the result of the delay to radiotherapy, inadequate surgery, and/or inadequate pretherapy surgical mapping. The subsequent GETTEC trial reported by Domenge et al took advantage of the same treatment plan.<sup>8</sup> This trial demonstrated a significant improvement in survival in both resectable and unresectable patients receiving PF chemotherapy. The different outcomes in the resectable arms between the Paccagnella and the Domenge studies may have reflected factors such as improved tumor mapping, surgical technique, and/or more efficient timing of radiotherapy.

Postchemotherapy biopsy for prognostic determination is underused in IC regimens. Al-Kourainy et al in 1987 found that patients who had a complete clinical response combined with a complete pathologic response at the time of surgery had superior survival compared to those who still had residual disease.<sup>27</sup> Similar data were obtained with regard to local control in the VA Larynx Trial reported by Spaulding et al.<sup>28</sup> Therefore, pathologic response is probably an accurate assessment of therapeutic efficacy and a predictive factor for primary site control after IC, although the predictive value may vary by site. IC has been used to predict who might be a candidate for organ preservation in newer ongoing studies.<sup>29</sup> Biopsy and response to IC might also be useful in setting the intensity of subsequent therapy.

## Improving PF Induction Chemotherapy

Alternative regimens to PF, adding a third drug, or altering PF scheduling have been studied but most new treatments have proven to be no better or were in fact less effective than PF in randomized trials. These regimens include cisplatin, 5-fluorouracil, and leucovorin (PFL) and interferon-PF.<sup>30-32</sup> Most recently, the taxanes have been shown to have considerable activity in recurrent disease and have been investigated in combination with carboplatin or PF in the induction setting.<sup>33-36</sup> A non-PF regimen, TIC (paclitaxel, ifosfamide, and carboplatin), has shown considerable activity in phase II studies.<sup>37</sup> While carboplatin is an inferior agent to cisplatin in combination with 5-FU, it is unclear whether, when combined with a taxane or in TIC, it is less effective than cisplatin.<sup>24-26</sup> A single randomized trial in the recurrent setting with cisplatin plus paclitaxel (PTp) versus PF is pending, but no other studies are available.<sup>38</sup> In this study, by the Eastern Cooperative Oncology Group (ECOG), response rate was equivalent, toxicity with PTp was better, but PF had a better 1-year survival than PTp. High-dose induction carboplatin-paclitaxel (CTp) regimens have been studied in phase II with mixed results.<sup>39</sup> These regimens require cytokine support and observed response rates are relatively low.

Combinations of taxane plus PF have been studied extensively in phase II and selected studies with docetaxel in combination with PF are summarized in Table 1.<sup>33,40,41</sup> The majority of studies in curable, previously untreated patients have shown excellent results. The TAX708 study, a phase I/II, multicenter study of TPF (docetaxel 75 mg/m<sup>2</sup>, cisplatin 100 mg/m<sup>2</sup>, and 5-FU 1,000 mg/m<sup>2</sup>/d for 4 days) had easily controlled toxicity and excellent long-term survival. Forty-three patients were enrolled. The complete response rate was 40%, among which the pathologic complete response rate was 90%. The overall response rate was 93% and the overall survival rates at 12 months, 18 months, and 24 months were 98%, 90%, and 82%, respectively. Three- and 4-year survival rates are 78% and 64%, respectively. Long-term survival among all of the TPFL trials (TPF + leucovorin) and TAX708 has generally been excellent; however, some regimens, notably the high-dose TPFL treatments, have been relatively toxic. An analysis of long-term survival and site of failure in the TPF and TPFL regimens revealed that locoregional failure

**Table 1** Response Rates and Survival Outcomes in the Five TPF/TPFL and the Three PF Studies

Study	No. of Patients	CR	ORR (95% CI)	Median Survival	Overall Survival			
					12 mo	18 mo	24 mo	36 mo
TAX708 (TPF) <sup>36</sup>	43	40%	93% (81-99)	Not reached	98%	90%	82%	78%
TAX017HN (TPF) <sup>40</sup>	48	0%	71% (56-83)	18.5 mo	69%	54%	42%	Too early
TPFL-5 <sup>54</sup>	23	61%	100% (85-100)	Not reached	96%	83%	78%	78%
TPFL-4 <sup>55</sup>	30	63%	93% (78-99)	Not reached	90%	85%	80%	77%
Janinis (TPF) <sup>41</sup>	20	20%	90% (77-100)	Not reached	85%	85%	60%	Too early
opTPFL <sup>56</sup>	34	44%	94% (86-100)	Not reached	83%	NA	68%	62%

Abbreviations: TPF, docetaxel, carboplatin, 5-FU; TPFL, TPF, leucovorin; OPTPFL, outpatient TPFL; CR, complete response; ORR, overall response rate; CI, confidence interval; NA, not available.

predominated. Approximately 30% of patients had locoregional relapse after IC and hyperfractionated radiotherapy. Overall, survival among these trials was approximately 60% to 80% at 3 years. These data suggest that radiation therapy after IC can be improved, perhaps by incorporating CRT.

## Chemoradiotherapy

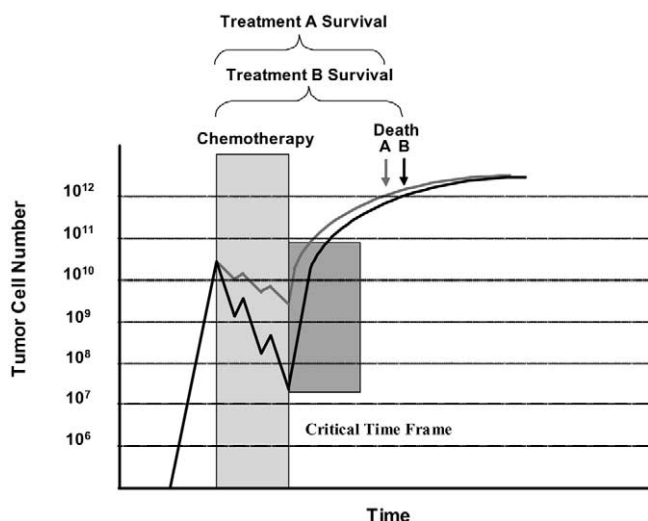
CRT makes biologic sense in locally advanced SCCHN because of the difficulty in controlling locoregional disease and the recognition that a variety of chemotherapeutic agents can enhance the effects of radiation. Enhancement occurs through direct cytotoxic mechanisms and by radiosensitization. Single-agent cisplatin, 5-FU, bleomycin, methotrexate, mitomycin C, and hydroxyurea have each been used with radiation therapy. The addition of some single agents to radiation improves response rates at the cost of additional local and systemic toxicity. Recognizing the pitfalls of meta-analysis, there is robust evidence for a survival advantage in patients receiving CRT, although there is also clear evidence of increased morbidity. The absolute survival advantage at 5 years associated with CRT is rather small, 8% at 5 years<sup>9</sup> ( $P < .001$ ), but this is larger than the 5% reported for PF-based IC.

Several randomized single-agent trials have been completed, and, as will be discussed below, some regimens have proven effective. An interesting single-agent regimen was developed by Harrison et al at Memorial Sloan-Kettering Cancer Center (MSKCC) and reported in 1991.<sup>42</sup> In this trial, cisplatin was given as a bolus every 3 weeks during the first 4 weeks of an accelerated concomitant boost (ACB) regimen. This trial formed the basis for the second arm of the recent phase III Radiation Therapy Oncology Group (RTOG) trial, comparing the Wayne State CRT regimen of daily single-fraction radiotherapy and bolus cisplatin every 3 weeks to this MSKCC regimen (ongoing RTOG-0129).

Multiple studies have evaluated cisplatin with or without 5-FU in combination with radiation, as both agents have been found to have radiation sensitizing effects *in vitro*. Taylor et al<sup>43</sup> gave cisplatin 60 mg/m<sup>2</sup> and 5-FU 800 mg/m<sup>2</sup> in 14-day cycles with conventional radiotherapy. They demonstrated an improved freedom from recurrence in patients treated with CRT compared to IC. There was, however, an

increase in mucositis requiring supportive care in the concurrent group. Other trials have given cisplatin at doses as high as 100 mg/m<sup>2</sup> every 3 weeks with tolerable toxicity. Gandia et al<sup>44</sup> treated head and neck cancer patients with cisplatin 80 mg/m<sup>2</sup> every 3 weeks for three cycles and 5-FU 300 mg/m<sup>2</sup>/d by continuous infusion for 7 weeks during radiotherapy to a total dose of 70 Gy given over 7 weeks with acceptable toxicity. Jeremic et al<sup>45</sup> compared standard radiotherapy with daily cisplatin or carboplatin and demonstrated improved survival with both platinum compared to radiation alone. Investigators at the University of Chicago have aggressively investigated the concurrent administration of hydroxyurea and 5-FU with cisplatin or paclitaxel and radiation therapy.<sup>46-48</sup>

Phase III trials have shown improvement in overall survival with CRT. A recently completed Intergroup study randomized patients with unresectable SCCHN to radiation alone, radiation plus bolus cisplatin, or split-course radiation with the first and third cycles of PF.<sup>11</sup> The 2- and 3-year actuarial survival rates were 23% for radiation alone, 35% for radiation and cisplatin ( $P = .016$ ), and 27% for split-course radiation plus PF ( $P = .13$ ). In the CRT arm, distant metastases were the most frequent cause of failure. A combination therapy regimen of carboplatin and 5-FU, delivered over 4 days, twice during a course of once-daily radiation therapy, resulted in significantly better overall survival in patients with resectable and unresectable oropharyngeal cancer. In this study, by Calais et al, survival was improved from 31% to 51% at 2 years with the addition of the chemotherapy to a standard radiotherapy program.<sup>6</sup> In contrast, Staar et al<sup>22</sup> compared chemoradiation with ACB radiation to ACB radiation alone. Overall survival was not improved, although the subset of oropharyngeal cases had a significant improvement in survival. Importantly, 30% of long-term survivors ( $\geq 2$  years) remain dependent on a feeding tube. There were significantly more patients (51% v 25%,  $P = .02$ ) with swallowing problems and continuous use of a feeding tube in the combined modality arm. This study was arguably negative and both arms engendered significant swallowing morbidity. The RTOG has embarked on study 0129 comparing their standard therapy, bolus cisplatin with single-fraction radio-



**Figure 1** A cell kinetic model for response and survival: the argument for timing in combined modality therapy. Rapid tumor regrowth would occur after induction chemotherapy if not treated immediately. Radiation provides a regional, encompassing treatment at the sites of original bulk disease. (Modified from Takimoto and Rowinsky.<sup>51</sup> Reprinted with permission from the American Society of Clinical Oncology.)

therapy from the Intergroup trials with bolus cisplatin with ACB radiation in a randomized phase III trial.

## Sequential Chemoradiotherapy

As described above, there is compelling evidence from randomized phase III trials and meta-analysis that IC and CRT each improve survival in patients with locally advanced SCCHN. There are advantages and disadvantages to each. IC provides high-dose systemic therapy, which treats distant disease and significantly reduces local and regional disease before the start of radiotherapy.<sup>12</sup> The latter effect has the potential to lead to a better functional outcome. With IC, toxicity is usually transient, but IC is associated with prolon-

gation of treatment and does not increase locoregional dose intensity. After treatment with IC, it is possible to assess prognosis and adjust the intensity of subsequent irradiation and surgery. CRT allows for increased locoregional dose intensity, arguably is ineffective systemic therapy, and is associated with considerable systemic and local toxicity. There is no method to assess prognosis and adjust intensity once CRT has started.

We, and others, have proposed and are studying methods of combining IC with CRT and surgery as sequential therapy (ST).<sup>12,13,39,47,49,50</sup> We have proposed an ST paradigm in which IC is followed by CRT; this is followed by surgery to complete the eradication of residual cancer in areas of bulk disease in the neck or for salvage of persistent primary site disease. We believe this paradigm may optimize therapy by attending to the known biology of SCCHN and the clinical observations of the last two decades of combined modality therapy in this disease. The immediate period after completion of IC may be a biologically critical time when tumor cells in the primary site and region are proliferating rapidly. This notion conforms to the theoretic tumor model recently published by Takimoto and Rowinsky.<sup>51</sup> As modified in Fig 1, this model may apply specifically to therapy of locally advanced SCCHN. This model, based on Gompertzian kinetics in which tumor growth rates are most rapid when tumor volume is decreased, predicts that the addition of a non-cross-resistant regional therapy with minimal delay, ie, CRT after IC, rather than a focused treatment, ie, surgery, at this critical time point should improve locoregional control. CRT at this point is superior to surgery by treating the entire region, rather than specific structures. Surgery can be applied after CRT to remove any residual nidus within the site of prior bulk disease.

Alternative ST plans have been investigated in phase II/III trials and have focused on different concepts of integration (Table 2). The University of Pennsylvania (Philadelphia, PA) sequential program<sup>39</sup> includes two cycles of very-high-dose carboplatin and paclitaxel (CTp) delivered with growth fac-

**Table 2** Sequential Chemoradiotherapy Trials<sup>13</sup>

	IC	CRT	Adjuvant Chemotherapy
TAX324, phase III	PF v TPF every 3 weeks × 3	Weekly carboplatin, SFX	None
University of Chicago, phase II, 1998 <sup>49</sup>	PFL + alpha interferon × 3	Split-course, concomitant 5-FU, hydroxyurea	None
University of Chicago, phase II, 2003 <sup>47</sup>	C/Tp weekly × 6	Paclitaxel, 5-FU, hydroxyurea, HF-XRT	None
University of Pennsylvania, phase II <sup>39</sup>	C/Tp every 3 weeks × 2	Paclitaxel weekly, SFX	C/Tp every 3 weeks × 2
MPCRN, phase II <sup>57</sup>	C/Tp every 3 weeks, 5-FU CI d 1-42	C/Tp weekly, SFX	None
ECOG 2399, Phase II <sup>52</sup>	C/Tp every 3 weeks × 2	Weekly paclitaxel, SFX	None
University of Michigan, phase II <sup>29</sup>	PF × 1	Cisplatin every 3 weeks, SFX	PF × 2 every 3 weeks
Madrid, phase III <sup>35</sup>	TpPF v PF	Cisplatin every 3 weeks, SFX	None

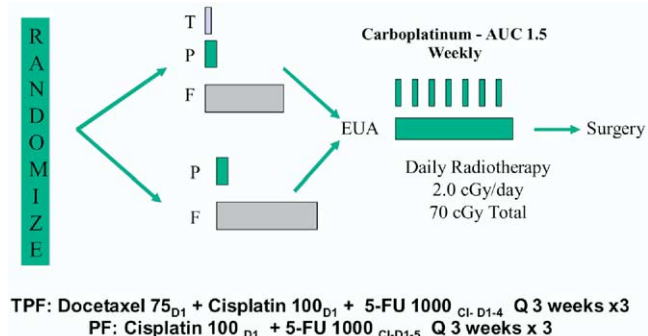
Abbreviations: C, carboplatin; SFX, single fractionated radiotherapy; Tp, paclitaxel; L, leucovorin; PF, carboplatin + 5-FU; HF-XRT, hyperfractionated radiotherapy; CI, continuous infusion.

tor support, followed by single-agent weekly CRT with paclitaxel. Surgery is reserved for nonresponders to chemotherapy and for patients with large neck nodes who have post-CRT neck dissections and adjuvant chemotherapy. With a 31-month follow-up, 3-year survival is 70%, but 62% of patients have no evidence of disease. The University of Chicago study<sup>47</sup> gave six weekly cycles of intensive CTp chemotherapy followed by THFX CRT. With a median follow-up of 28 months, the 3-year overall survival rate is 70%. The Minnie Pearl Cancer Research Network Trial performed a study of high-dose CTp for two cycles with a 6-week continuous infusion of 5-FU. This induction regimen was followed by CTp weekly with radiotherapy. Recent results of this trial are not available for review. Finally, Vanderbilt University Medical Center has recently completed a trial similar to the University of Pennsylvania trial.<sup>52</sup> Results are early but suggest a 66% 3-year survival with a median follow-up of 31 months.

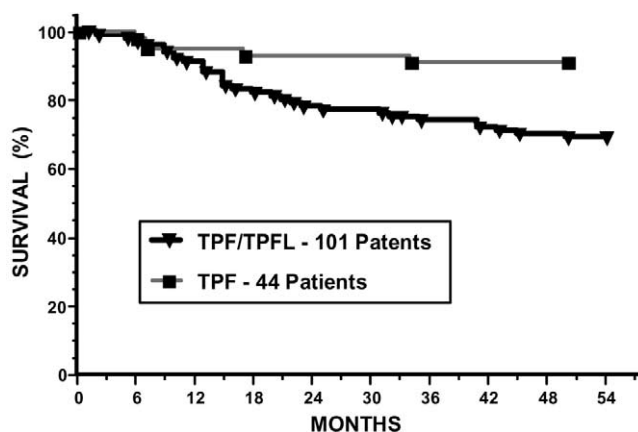
The University of Michigan (Ann Arbor, MI) has taken a different conceptual approach.<sup>29</sup> One cycle of PF IC is used to select patients for organ preservation or surgery. After one cycle, patients are assessed for response. Nonresponders undergo laryngectomy; responders receive CRT with bolus cisplatin. Two cycles of adjuvant PF are then given to complete responders. Survival and organ preservation rates are excellent. Survival at 3 years is 80%. This population consists primarily of resectable larynx cancer and is not directly comparable to the more advanced patients treated in the other sequential studies.

Phase II ST programs are reporting preliminary 3-year survival rates in the range of 60% to 80%. There is considerable controversy regarding the regimens to be used in the IC and CRT phases of treatment. The most studied and effective IC regimen is full-dose PF. Carboplatin is less effective than cisplatin when combined with 5-FU, and combinations of either cisplatin or carboplatin with paclitaxel or docetaxel have not been fully compared to PF. The combination of taxanes with PF has proven highly effective in phase II trials and is actively being assessed in phase III trials in comparison to PF.

A multicenter, randomized, phase III trial, TAX324, comparing a sequential treatment plan of TPF (PF with docetaxel) versus PF induction therapy, followed by CRT with weekly carboplatin has been completed. This phase III trial has ac-



**Figure 2** The schema for TAX324: a randomized phase III trial comparing ST with TPF versus PF.

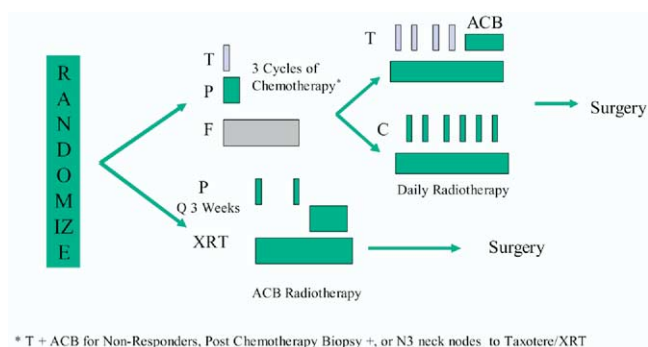


**Figure 3** Overall survival for the combined TPF and TPFL trials performed at Dana Farber Cancer Institute (DFCI) compared to the survival of patients treated on the TPF arm at the DFCI on TAX324. Patients on the TPF and TPFL trials were treated with three cycles of IC followed by hyperfractionated radiotherapy. Patients on the TAX324 trial were treated with TPF and CRT.

rued more than 530 patients (Fig 2). Early results from our center suggest a greater than 90% survival rate in the TPF arm at 2 years. In Fig 3, Dana Farber Cancer Institute patients treated on the TPF arm of TAX324 with ST are compared with historical, TPF leucovorin (L) patients treated with IC and hyperfractionated radiotherapy alone. Although not a scientifically valid comparison, for qualitative purposes the compelling differences suggest that the ST program may be highly effective.

A similar phase III trial comparing TpPF (with paclitaxel) versus PF with both arms followed by CRT with bolus cisplatin has recently been reported by the Madrid group.<sup>35</sup> Survival and organ preservation were better in the TpPF arm than in the PF arm, suggesting that the triple-drug combination was better. This, and the TAX324 trial, are possibly the first demonstrations that a three-drug regimen is superior to the two-drug PF regimen in SCCHN. Final analysis is pending on the Madrid trial, which recently completed accrual. The TpPF arm in this trial used a much reduced dose of 5-FU and factored surgery into the regimen between IC and CRT. Thus, the toxicity and response rate of TpPF may have been slightly diminished. In addition, based on the notion of tumor potential doubling time, we would predict that locoregional control would be better if CRT followed IC rather than surgery.<sup>51</sup> Furthermore, CRT intensity can be adjusted and may salvage poor or modest responders, while surgery can be directed at the larger bulkier and less responsive nodal disease in the postradiotherapy setting.<sup>53</sup>

The phase II and phase III results of ST plans have been outstanding. Two- and 3-year survival rates in advanced disease are unprecedented. This new paradigm of treatment has not been compared to a standard CRT regimen and phase III studies should be performed to definitively compare the paradigms of ST and CRT. We are planning a phase III trial comparing ST with TPF-CRT to cisplatin plus ACB (CRT-ACB) radiotherapy (Fig 4) as are others in the larger cooper-



**Figure 4** The schema for the Paradigm Trial: a randomized phase III trial comparing TPF-based ST versus CRT.

ative groups. We expect these studies to be initiated soon and to yield results that may change patterns of treatment.

## Conclusions

When we examine the evolution of IC over the last two decades, the development of a ST approach appears to articulate our advancing understanding of the biology of the disease and the experiences of past clinical trials. IC preceding CRT offers several potential benefits: (1) improved locoregional control, organ preservation, and function by dramatically reducing tumor volume prior to the start of CRT; (2) early identification of patients with resistant disease who might be better served by incorporation of surgery prior to CRT or more aggressive CRT approaches; (3) decreased rate of distant metastases; and (4) improved overall survival by increased locoregional control and decreased distant metastases. While ST makes sound biologic sense, it still remains experimental. It may well be that ST is a viable and reasonable alternative for patients with good performance status and locally advanced disease despite the lack of phase III trials establishing the relative efficacy of this paradigm. However, phase III trials remain the final determinant as to whether this is truly an improvement over IC or CRT.

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