The Role of Concurrent Chemo-radiotherapy in Patients with Head and Neck Cancers: A Review

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Introduction

In the past, radiotherapy alone was the "traditional" and the standard single treatment for patients with unresectable and/or inoperable locally advanced head and neck cancers. Because of the poor results obtained with this approach in these patients, concurrent chemotherapy and radiation therapy has been investigated since the 1960s [1, 7]. The rationale for such treatment is to increase local control by overcoming radio-resistance and to eradicate systemic micro-metastasis. The most significant potential mechanisms of interaction between chemotherapy and radiation therapy are summarized in Table 1.

Initially, agents like methotrexate, hydroxyurea, 5-fluorouracil (5FU), or bleomycin were tested in combination with radiation therapy. Since each of these drugs produces mucositis and stomatitis, the local side effects of radiation therapy on the oral and oro-pharynx mucosa were increased, which resulted in poor patient compliance, more interruptions of radiotherapy, and no improvement in overall survival when compared to radiation therapy alone. Other important factor that resulted in not detecting survival advantage with the combined approach is the small number of patients randomized to each group that was unable to detect small but important differences of $\pm$ 10%.

Platinol compounds (cisplatin, carboplatin) alone do not induce mucositis and does not increase the local toxicity of mucositis of radiation therapy in patients with head and neck cancers. It is probably the best currently available radio-sensitizer, and it possesses all the mechanisms of interaction with radiation therapy that are summarized in Table 1. The clinical CR rate obtained with concurrent cisplatin and radiation therapy (single daily fraction) in patients with locally advanced head and neck cancers is in the range of 65% to 70% [2, 7]. The majority of the patients in these studies had stage IV disease. Cisplatin has been administered in various schedules: weekly, daily, days 1-5 every 4 weeks, and every 3 weeks. One randomized ECOG/RTOG trial with weekly administration of cisplatin at 20 mg/m^2 during radiation therapy vs. radiation therapy in locally advanced patients was negative [8]. The addition of another agent or agents in combination with cisplatin (i.e., 5FU or taxanes) concomitant with radiation therapy did not add to the clinical CR rate but increased in the local side effects, especially mucositis [3, 4, 9, 10, 11] [Table 2]. Thus, cisplatin alone appears to be the chemotherapeutic drug of choice for concurrent chemotherapy with radiation therapy in patients with head and neck cancers. At the present time, cisplatin alone given on a 3-week schedule is the most widely used in the United States.

Carboplatin, the second-generation platinum drug, possesses all of the radio-potentiation properties of cisplatin but has a different side effect profile. Carboplatin is used in a weekly schedule concurrent with radiation therapy in patients with head and neck cancers. The clinical CR rate reported in phase II studies with concomitant carboplatin and radiation therapy (single daily fraction) is in the range of 65% and 70%, which is similar to the clinical CR rate reported with cisplatin and radiation therapy [2,3,11] [Table 2]. For the last 15 years, our personal practice has been to use carboplatin rather than cisplatin in our concurrent chemotherapy and irradiation treatment, using a weekly dose of an AUC of 1.5 after induction chemotherapy or in the dose of AUC 2.0 without initial chemotherapy. In a comparison of radiation therapy alone or with either cisplatin or carboplatin in these patients, two randomized trials reported the superiority of either combination arms to the radiation therapy alone arm, with no statistical difference between the two combination arms [11, 12].

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Mitomycin C also possesses most of the radio-potentiation mechanisms of interaction with radiation therapy [Table 1]. Randomized trials comparing radiation therapy with or without mitomycin C showed improved local control but no differences in overall survival between the two groups [3]. More recently, gemcitabine and the taxanes have been tested for their radio-sensitizing effects. The clinical CR rate for the combination of taxanes alone or with other agents given concurrently with radiation therapy is approximately 65% [3, 6, 9, 10]. However, the local side effects, especially mucositis, are problematic.

1. Modification of the slope of the dose-response curve.
2. Decrease in accumulation or inhibition of repair of sub-lethal damage.
3. Inhibition of repair of potentially lethal damage.
4. Induction of tumor re-oxygenation.
5. Selective cyto-toxicity and/or radio-sensitization of hypoxic cells.
6. Increase in apoptosis.

Table 1: Possible Mechanisms of Interaction between Concurrent Chemotherapy and Radiation Therapy

Gemcitabine plus radiation therapy in phase I-II studies produced a high CR rate in the primary tumor site but had a high incidence of grade 3-4 local toxicities, especially pharyngeal scarring and stenosis [3]. The combination of 5FU and hydroxyurea concomitant with radiation therapy is effective, but again, the local side effects are severe [3]. The addition of cisplatin or paclitaxel increased the effectiveness of the combination of 5FU and hydroxyurea, but the clinical CR rate was similar to that reported with radiation therapy plus cisplatin or carboplatin [Table 2].

Post-operative Concurrent Chemoradiotherapy

The "traditional" standard treatment for patients with resectable and operable locally advanced head and neck cancers is surgery followed by post-operative radiotherapy (RT). In spite of the complete resection for cure and obtaining negative margins and the addition of adjuvant post-operative RT the 5-year overall survival of these patients were about 30%. With the continued emerging evidence since early 1980s of concurrent chemo-radiotherapy is superior to RT only this led to our investigation of post-operative chemo-radiotherapy with cisplatin 100mg/m^2 day one with RT and every three weeks for a total of three cycles.

Postoperative concurrent chemotherapy-radiation therapy with cisplatin given every 3 weeks for three courses was investigated by the RTOG in a phase II study [2]. Patients with positive surgical margins and/or stage IV disease were treated with cisplatin 100 mg/m^2 on days 1, 22, and 43 during radiation therapy. These patients were compared to historically matched group with the same stage and site of cancers but with negative surgical margins. The local control rate was better in the patients treated with the combined chemotherapy-radiation therapy.

Bachaud et al. [13] in 1996 reported on the results of phase III prospective randomized trial comparing concurrent cisplatin 50mg given day one and then weekly during RT vs. RT only given post-operatively in locally advanced head and neck cancers. They reported statistically significant disease free survival and overall survival to the combined approach of post-operative chemo-radiotherapy in surgically operated patients.

Agents	No. of Series	No. of Patients	CR (%)	
			Range	Mean
Single: P	10	561	44-70	65
C	4	109	66-88	67
Pac	6	109	50-75	65
Double: PF	10	383	48-91	66
C Pac	4	163	57-78	71

Table 2: Results of phase II trials of concurrent chemo-radiotherapy with single and double agents

P= Cisplatin, C = Carboplatin, Pac = Paclitaxel. F = 5Fluorouracil

Two randomized trials have also addressed this question [14, 15]. One was conducted by the EORTC and the second from North America Inter-group [14, 15]. Both have included patients with high risks for local-regional recurrences and/or systemic metastasis. Although, the criteria used for the high risk selection did differ between these two important phase III prospective randomized studies. In both of these trials the dose of cisplatin was 100mg/m^2 IV given on day one with RT and every three weeks for a total of three cycles. Both were positive thus supporting the addition of chemotherapy concomitantly with radiation therapy in locally advanced cancers in the post-operative setup. The important results of these two studies were updated recently [16]. The EORTC randomized trial the local-regional failure rates were 17% vs. 31% (p= .007), disease free survival were 47% vs. 36% (p= .04) and the overall survival were 53% vs. 40% (p= .02) in favor of the concurrent chemo-radiotherapy post-operative approach.

Chemo-radiotherapy in Organ Preservation

The traditional standard treatment for patients with early local laryngeal cancers ($T_{1-3}N_0M_0$) was RT to preserve the speech for these patients. Those who failed such therapy may have surgery for their persistent and/or locally recurrent cancers. Usually total laryngectomy is performed in such cases.

Back in early 1980s we made the observation that patients responded to induction chemotherapy will respond to further RT treatment, and those who did not respond to such chemotherapy rarely will respond to subsequent RT [17, 18] [Table 3]. This led to multiple phase II trials of induction chemotherapy and responders had RT while none responders under went surgery followed by post-operative RT confirming our observation [2, 3]. This led to two major phase III prospective randomized trials for organ/speech preservations. In the US the Veteran Administration trial for patients with laryngeal cancers stages III and IV and the EORTC trial in Europe for patients with hypo-pharyngeal cancers in which more than 90% may need to have laryngectomy as part of their treatment [3, 19]. The design for both trials was similar but not exactly the same. Patients were randomized between surgery followed by post-operative radiotherapy vs. induction chemotherapy with cisplatin (P) and 5FU infusion (F) for two courses. Responders had a third course followed by RT. Non-responders to chemotherapy had the "standard" treatment of surgery followed by post-operative RT. In the EORTC study only those who had complete response to induction chemotherapy had RT. At five years the survival between the two groups was the same, but about 60% of those a live had preserved their larynx.

Response to CT	No	CR to RT	%
None	18	1	6
Partial	42	22	52

Table 3: Response to RT after Subsequent Response to Induction Chemotherapy

CT = Chemotherapy, CR = Complete response, RT = Radiotherapy

With accumulated observation, phase II trials, and many phase III prospectively randomized studies showed that concurrent chemoradiotherapy were superior to RT only in patients with locally advanced head and neck cancers [2, 7]. Following these results, the US Inter-group Trial R91-11 conducted a study in patients with stage III-IV potentially resectable cancer of the larynx [20, 21]. Patients were randomized to three arms: (1) chemotherapy followed by radiation therapy as in the laryngeal preservation studies, (2) concurrent chemo-radiotherapy, and (3) standard once-daily radiation therapy alone. The trial selected only concomitant chemotherapy-radiation therapy as the experimental arm, and once-daily radiation therapy was used in the third arm rather than twice-daily (hyper-fractionated) irradiation, which may produce higher local control rates (organ preservation) than once-daily fraction radiation therapy. Patients with T4 cancers were not included in this trial. Patients with N2 or N3 neck disease underwent neck dissection at the end of their treatment, regardless of their response to the initial treatment. In the concurrent chemo-radiotherapy arm cisplatin 100mg/m^2 were given on day one with RT and every three weeks for a total dose of three cycles. No differences were reported in overall survival among the three groups, but patients who under-

went concurrent chemotherapy-radiation therapy had significantly higher organ preservation rates. The laryngectomy-free survival improved with concurrent treatment vs. radiation therapy alone (P=.018). Also, time to laryngectomy for concurrent treatment vs. induction (P=.0094) and for concurrent treatment vs. radiation therapy alone (P=.00035) was superior. The loco-regional control were 56% to RT only, 56% to induction chemotherapy followed by RT, and 78% to the concurrent cisplatin and RT (p<.01)[21]. Thus now the standard treatment for organ/speech preservation is the concurrent chemo-radiotherapy.

Concurrent Chemo-radiotherapy in Locally Advanced Cancers

The "traditional" treatment for patients with inoperable/unresectable locally advanced head and neck cancers has been RT. The 5-year overall survival of these patients usually is less than 20%. The majority of these patients recurs and died within eighteen months from the start of the treatment. When induction chemotherapy was introduced in the late 1970s these patients were included in these trials. When concurrent chemo-radiotherapy was introduced in the early 1980 with use of cisplatin, these patients were included in these trials.

Since concomitant chemotherapy-radiation therapy appears to be effective in phase II trials than RT alone. Later on at least seven prospective phase III trials comparing concurrent chemo-therapy-radiation therapy vs. radiation therapy alone have been reported [Table 4] [22, 28]. All were positive in favor of the combined-therapy arm. The majority of these randomized trials used hyper-fractionated radiation therapy as the standard arm and in combination with chemotherapy, despite previous reports of no improvement in overall survival when daily irradiation was compared with twice-a-day radiation therapy [3]. Also, the majority of these randomized studies used the combination of cisplatin-5FU with radiation therapy as the experimental arm, despite the previously reported phase II trials indicating a CR rate of approximately 65% to 70% using cisplatin-5FU concurrently with radiation therapy. This result was no different than administering cisplatin or carboplatin alone concurrently with radiation therapy. In the Intergroup study (SWOG and ECOG [27, 29]) for locally advanced and un-resectable head and neck cancers, patients were randomized into three arms: (1) single-agent cisplatin every 3 weeks during radiation therapy, (2) cisplatin-5FU with radiation therapy, or (3) radiation therapy alone. Standard daily fraction radiation therapy was

Authors	Treatment	Survival %	Year	*p* V alue
Merlano [22]	RT	10	5	< .05
	RT, PF	24		
Brizel [23]	RT bid	34	3	.07
	RT, PF	55		
Wend [24]	RT bid	24	3	< .05
	RT bid, PF	49		
Calais [25]	RT bid	31	3	< .05
	RT bid, CF	51		
Jeremic [26]	RT bid	25	5	.0075
	RT bid P daily	46		
Adelstein [27]	RT	20	3	.016
	RT, P	37		
	RT, PF + S	29		
Staar [28]	RT bid	39	2	.09
	RT bid, CF	44		

Table 4: Phase III Randomized Trials Comparing Concomitant Chemotherapy-Radiation Therapy vs. Radiation Therapy Alone in Squamous Cell Head and Neck Cancers

Bid = twice a day, RT = radiotherapy, S = surgery, C = carboplatin, F = ₀fluorouracil, P = cisplatin

given to all patient groups. The 3-year survival rates were 37%, 27%, and 23%, respectively [29]. The difference was only statistically significant (P=.014) between cisplatin plus radiation therapy and radiation therapy alone.

Thus, concurrent chemotherapy-radiation therapy is the new standard therapy for patients with locally advanced disease who are not undergoing a planned surgical resection. The main question remains as to whether two fractions per day of radiation therapy or once-daily radiation with chemotherapy is the preferred schedule. Another question is whether a single agent or a combination of agents should be given concomitantly with radiation therapy. Radiation alone is inadequate therapy.

At least six meta-analyses have examined the addition of induction chemotherapy to local definitive therapy in patients with locally advanced cancer. The results differ depending on the type and the year of the studies included in these analyses. Study reports before the use of cisplatin-5FU in this population showed no benefit for induction chemotherapy. The meta-analyses that included studies after 1980s, especially those using cisplatin-5FU chemotherapy, showed superiority of chemotherapy followed by radiation therapy vs. radiation therapy alone [30]. All of the meta-analyses reported the superiority of concurrent chemotherapy-radiation therapy over radiation therapy alone; however, Pignon et al. [30] updated three meta-analyses from 63 randomized trials performed between 1965 and 1993 involving 10,741 patients. This meta-analysis confirmed the superiority of the overall use of chemotherapy, especially the concomitant use of chemotherapy-radiation therapy over radiation therapy only. The authors also reported the superiority of cisplatin-5FU administration as either induction or adjuvant therapy in these patients.

Recently, Browman et al. [31] reported a meta-analysis including 18 trials with 3,192 patients, in which concurrent chemotherapy-radiation therapy was compared to radiation therapy alone [Table 5]. Overall, the chemotherapy-radiation therapy arm was again superior to radiation therapy alone (P <.00001). Single fraction, two fractions irradiation a day, single agents, combination chemotherapy, and especially cisplatin-5FU provided statistically significant results. Only platinum-based chemotherapy plus radiation therapy was highly significant (P <.0001), while mitomycin C-based treatment was moderately significant (P=.032). Thus, we believe that single-agent cisplatin or carboplatin with radiation therapy should be the current standard treatment approach in patients with locally advanced cancers.

Concurrent Chemo-radiotherapy in Locally Advanced Nasopharyngeal Cancers

The standard treatment for locally advanced (stages III and IV) patients with nasopharyngeal cancers (NPC) before 1980 have been radiotherapy alone. The 5-year overall survival of patients with stage IV NPC with RT before 1980 has been less than 30% across the world. With the introduction of cisplatin as an active agent in patients with head and neck cancers, and as one of the best agent to give concurrently with RT, many phase II studies were initiated in NPC patients [Table 6]. Initially limited chemotherapy (induction only, concurrent only, or adjuvant only) were given with the RT in locally advanced NPC patients. This resulted in about 10-15% improvement in the 5-year survival of these patients when compared to a matched group treated with only total RT. Because of the small number of patients included in the phase III randomized trials most of these studies showed better local control and disease free survival with the limited combined approaches of combining chemotherapy (induction, concurrent, or adjuvant) with RT, but with no survival advantage. Also, many of these studies combined patients with all stages NPC and not only locally advanced (stages III and IV) patients into these randomized phase III trials.

Typical example was reported in 2002 by Chan et al [32] in the preliminary report of their phase III study comparing RT to weekly cisplatin concurrent with the same RT which did not show survival advantage. In their subsequent follow-up report in 2005 there was a 5-year overall survival significance to the combined approach (70% vs. 58%, p=.049) [33]. They

Treatment	Risk Difference (%)	*p* Value
Overall results	1	< .00001
SF RT both arms	9 .2	.00041
HF RT same both arms	16 .6	.00008
Platinum-based CT	12 .1	< .0001
Mitomycin-C based CT	14	.032
5FU-based CT	10 .2	.11
Bleomycin-based CT	5	.36
Single agents only	10 .7	.0004
Combination CT regimens	11 .2	.0009
Combination cisplatin and 5FU	15 .3	< .0001

Table 5: Meta-analysis of Concurrent Chemo-radiotherapy vs. Radiotherapy alone in Patients with Advanced Head and Neck Cancers: Mortality

RT = Radiotherapy, CT = Chemotherapy, SF = Single fraction, HF = Hyper fractionation, p Values are two-tailed. Modified from Browman, et al. [31] *Head & Neck* 2001;23:579-589.

reported no significant improvement in overall survival for patients with primaries of T1 or T2, while, there were statistically significant overall survival improvement for patients with T3 and T4 disease.

In 2003 Lin et al. [34] reported on the results of randomized phase III trial comparing RT alone vs. concurrent chemo-radiotherapy using the combination of PF in patients with locally advanced NPC. They reported 5-year progression free survival of 53% vs. 72% (p= .0012), and 5-year overall survival of 54% vs. 72% (p= .0022) in favor of the concurrent approach.

In spite of these results, the standard treatment in 2007 for patients with locally advanced NPC is concurrent chemo-radiotherapy followed by adjuvant combination chemotherapy of cisplatin and 5FU 96 hour infusion as in North America Inter-group trial 0099 [35, 36]. For the last fifteen years we have been reversing the sequence of this total treatment in NPC by giving induction chemotherapy followed by concurrent chemo-radiotherapy. These have resulted in better tolerance for chemotherapy, with significant improvement in weight and nitrogen balance, and have the time to have teeth care before the start of concurrent chemo-radiotherapy. Also, the tolerance of the later was much better because of the improvement in weight in these patients. The five year survival to this change in sequence is about 90% in our hand, and as reported by others [Table 6].

Therapy	No. of Series	No. of Patients	5-Year OS (%)	
			Range	Mean
RT only	19	8,273	24-62	44
Limited CT with RT				
Induction CT	11	713	35-83	64
Concurrent CT	4	172	55-94	67
Adjuvant CT	5	181	54-80	70
Total Treatment				
CT+RT and adjuvant CT	3	162	70-80	77
Induction CT and CT+RT	3	92	83-94	86

Table 6: Survival in Non-randomized Phase II Studies of Treatment of Previously Untreated Nasopharyngeal Cancer

OS = Overall survival, RT = Radiotherapy, CT = Chemotherapy

Other important points to mention here is that three drugs regimen are superior to two drugs combination in patients with head and neck cancers in general, and in NPC in particular [6, 7]. This resulted in changing our induction chemotherapy to the combination of taxan, platinol and 5FU. Other important point to mention here is that concurrent carboplatin and RT is equivalent to concurrent cisplatin with RT with much less side effects of renal, nausea and vomiting, hearing loss and peripheral neuropathy. So we have changed our concurrent chemo-radiotherapy to carboplatin giving in weekly schedule. If the concurrent treatment is given after induction chemotherapy the dose of carboplatin is AUC 1.5 (AUC 2.0 without induction chemotherapy) day one and weekly during RT.

A meta-analysis comparing combined chemotherapy-radiation therapy vs. radiation therapy alone in locally advanced nasopharyngeal cancer included patients from six randomized studies (1,528 patients) [37]. The addition of chemotherapy to radiation therapy increased disease-free/progression-free survival by 37% at 2 years, 40% at 3 years, and 34% at 4 years after treatment. Likewise, the overall survival increased by 20%, 19%, and 21%, respectively, with chemotherapy plus radiation therapy. These results were further confirmed by another more recent meta-analysis in patients with locally advanced NPC [38].

Summary and Conclusions

Concurrent chemo-radiotherapy has become the standard treatment for patients with locally advanced head and neck cancers. In surgically operated patients post-operative concurrent chemo-radiotherapy is the standard of care. For organ/speech preservation and in patients who are not surgically operable the standard of care is concurrent chemo-radiotherapy. In patients with locally advanced NPC although concurrent chemo-radiotherapy was superior to RT only, the standard of care is concurrent chemo-radiotherapy followed by three courses of adjuvant combination chemotherapy. Single daily fraction irradiation is the standard of care when given concomitant with chemotherapy. Although, single agent cisplatin given on every three weeks schedule is the standard of care, this could be replaced safely and as effectively with weekly carboplatin given with RT with much less side effects and with similar efficacy.

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