Invited Lecture

New Developments in Radiotherapy for Head and Neck Cancer

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Introduction

In 2001 the American Cancer Society estimates that there were 40,100 new cases of squamous cell head & neck cancers and 11,800 deaths due to this disease in the United States alone. While there is considerable variation according to tumor site and stage, in aggregate local/regional failure causes approximately 50% of deaths, distant metastases account for about 20% of deaths, and second malignancies account for approximately 5% of deaths. The remaining 25% of deaths are due to "other causes" largely related to the basic life style of the typical head and neck cancer patient. Hence, any effective form of treatment must focus on the local control problem. Either surgery or radiation therapy are effective forms of treatment for early stage tumors while for moderately advanced tumors, the combination of surgery and adjuvant radiotherapy is more effective than either modality alone[1]. In this paper we will be concerned with the treatment of advanced, inoperable tumors where radiation therapy is the mainstay of potentially-curative treatment regimens. It is accepted that local control rates using standard fraction, once-a-day radiotherapy are suboptimal for advanced tumors and there has been considerable clinical work performed in trying to improve outcomes[1]. There are three areas that I will discuss : 1) altered fractionation radiotherapy, 2) concomitant chemotherapy and radiotherapy, and 3) intensity modulated radiotherapy (IMRT). Altered fraction radiotherapy and concomitant chemotherapy and radiotherapy can be thought of as trying to exploit biological differences in the responses of the tumor and the surrounding normal tissues to the treatment regimen while IMRT can be thought of in terms of moving selectively up the dose response curve for the tumor while staying at the same (or perhaps a lower) level on the normal tissue complication curve.

Altered Fractionation Radiotherapy

There are currently two basic approaches which are being investigated in an attempt to find a more optimal radiation treatment fractionation schema :

Hyperfractionation which refers to using smaller fraction sizes, multiple daily treatments, a higher total dose of radiation, and a total treatment time that is about the same duration as for conventional radiotherapy. The basic idea with this approach is to take advantage of the difference in the shapes of the cell survival curves between tumors and late responding tissues in order to deliver a higher dose of radiation without increasing the late effects of treatment. A typical example for head and neck cancer would be to give 1.2Gy/Fx bid to a total dose of 81.6Gy[2-4]. The interval between fractions must be approximately 4.5−6 hours to allow for adequate repair of damage to normal tissues[5].

Accelerated fractionation which refers to using a fraction about the same size (or perhaps slightly smaller) as used in conventional fractionation, multiple daily treatments, a shorter overall treatment time, and a total dose that is about the same (or perhaps slightly less) than given in the conventional radiation schema. The basic idea with this approach is to overcome the effects of tumor repopulation by shortening the overall time and hence improving tumor control for the same radiation dose without increasing the overall late effects. Following Ang[6] we will classify the various accelerated fractionation schemas in three categories : Type A -- a short, intensive course, Type B -- a split course, and Type C -- a concomitant boost. The CHART Regimen[7] which consists of giving 1.5Gy/Fx were given 3 times a day on 12 consecutive days to a total dose of 54Gy is a prototype regimen in Category A. The approach of CC Wang [1.6Gy/Fx bid to a total dose of 67.2Gy with a two week break after 38.4Gy][4][8][9] is a prototype regimen in Category B. The concomitant boost

approach of Ang et al[1.8Gy/Fx qd to 54Gy with an additional daily treatment of 1.5Gy/Fx to the final target volume being delivered during the final 12 days of therapy][4)6)10)] is a prototype regimen in Category C.

In the United States, early work using hyperfractionation to treat locally-advanced head and neck cancer took place at the University of Florida[11)]. Compared to historical controls, there was better local/regional control, a greater degree of acute mucositis, and equivalent late effects. The first large Phase III trials took place outside the United States. Datta et al[12)] reported on 176 patients treated in India who were randomized to either standard fractionation to 66Gy vs. 1.2 Gy bid to 79.2Gy. At 2 years local/regional control was 63% on the hyperfractionation arm vs. 33% on the standard arm ($p<0.001$). Pinto et al[13)] reported on 98 patients treated in Brazil who were randomized to either 66Gy via standard fractionation vs. 1.1Gy bid to 70.4Gy. These patients all had stages III and IV carcinomas of the oropharynx and so represented a reasonably homogeneous population. Local/regional control was 84% on the hyperfractionation arm vs. 64% on the standard arm ($p=0.02$). Horiot et al[14)] reported on an EORTC study involving 356 patients with oropharyngeal tumors who were randomized to either 70Gy standard fractionation vs. 1.15 bid to 80.5Gy. Local/regional control was 40% on the standard arm vs. 59% on the hyperfractionation arm ($p=0.02$). In all of these trials the acute mucositis was more severe on the hyperfractionation arm but the late effects were similar.

One of the most aggressive of the accelerated treatment regimens is the CHART (Continuous Hyperfractionated Accelerated RadioTherapy) approach. Doses of 1.5Gy/Fx are given 3 times a day on 12 consecutive days to a total dose of 54Gy. An early analysis of a Phase I/II study showed more severe early effects and 4 cases of radiation myelititis in patients whose spinal cords received 45−48Gy[7)]. This high incidence of myelitis cannot be satisfactorily explained on the basis of incomplete repair of nerve tissue between fractions. However, when the regimen was taken into a Phase III trial, the cord dose was limited to 40Gy. The randomized trial showed no difference in local/regional control or survival[15)]. There were no additional cases of myelitis with this lower dose.

In 1991 the Radiation Therapy Oncology Group (RTOG) began a randomized phase III trial testing 4 different radiation fractionation schemas for patients with inoperable squamous cell tumors of the head and neck[4)]. Standard fractionation at 2Gy per fraction to 70Gy was the control arm. Another arm was hyperfractionation radiotherapy at 1.2Gy/Fx bid to a total dose of 81.6Gy which was determined to be an acceptable dose on a prior dose-searching study[2)]. The remaining two arms were variants of an accelerated fractionation schema : Categories B and C. One of these arms was the split course regimen of C.C. Wang (described above) and the other was the concomitant boost regimen of K.K. Ang (also described above). The study closed in 1997 with 1073 patients being evaluable for analysis. A preliminary analysis[4)] yielded the outcome data summarized in the following table :

RTOG 9003:Outcome summary (2 year data)

	StdRT	HypFX	Accel/Split	ConBoost
Primary fail	43.7%	37.8%	43.0%	36.9%
Nodal fail	32.1%	26.6%	30.8%	33.3%
Dist Mets	17.8%	16.8%	18.0%	16.6%
Acute Tox	35%	54.5%	50.4%	58.8%
Late Tox	26.8%	28.0%	27.6%	37.2%

Analysis of the three altered fractionation regimens was done by comparing their outcomes with the standard fractionation arm. There was no improvement in local/regional control with the accelerated/split course but there was a statistically-significant benefit with the hyperfractionated ($p=0.045$) and concomitant boost ($p=0.05$) regimens. There was also a trend towards improved disease free survivals which did not reach statistical significance. As might be expected with local/regional failures accounting for only about 50% of the expected total deaths, all the arms were equivalent in terms of absolute survival. The incidence of grade 3 or greater (RTOG/EORTC scoring scheme) acute toxicity was worse on all three altered fractionation arms with the difference being statistically-significant. Only the concomitant boost regimen had significantly worse late effects compared to standard fractionation and this may be due simply to acute effects persisting beyond the 90 day cutoff point which defines the beginning of the "late effects" period.

Concomitant Chemotherapy and Radiotherapy

There are two basic intents to the addition of chemotherapy to the treatment regimen for head and neck cancer : 1) there is potentially a synergistic effect with radiotherapy by the chemotherapy altering the radiobiological parameters "α", "β", and the effective tumor doubling time "T_d" and

2) the chemotherapy might be effective at eradicating micrometastases and thus reducing the incidence of distant metastases.

Early trials tested the sequential use of chemotherapy and radiotherapy. To date there has been no consistent, overall improvement in local/regional control or survival. However, there have been several large, randomized studies that have shown a reduction in the incidence of distant metastases even though the basic intent of these studies was different. The Intergroup Study 0034 investigated the effect of adding sequential chemotherapy after surgery and prior to radiotherapy for patients with operable tumors[16]. The Head and Neck Contracts study compared three arms -- one with "standard therapy" consisting of surgery and postoperative radiotherapy, one with induction chemotherapy prior to "standard therapy", and one arm with induction chemotherapy followed by "standard therapy" followed by maintenance chemotherapy[17][18]. A Southwest Oncology Group (SWOG) study[19] investigated the use of induction chemotherapy prior to surgery, and the Veterans Administration (VA) laryngeal study[20] investigated using the response to induction chemotherapy as a predictor of radioresponsiveness. The Pardua, Italy study compared the effect of four cycles of neoadjuvant chemotherapy plus radiation to radiation alone for patients with inoperable tumors[21]. The common finding in all these studies was a reduction in the overall incidence of distant metastases for the patients on the chemotherapy arm (in the case of the Head and Neck contracts study it was only for the group on the maintenance chemotherapy arm).

Effect of induction chemotherapy on DIS

		p-value	
IG0034 (442)	15% vs. 23%	0.03	
H & N Contract (443)	13% vs. 22%	0.05	24%
SWOG (158)	10% vs. 22%	0.07	
VAH Larynx (332)	11% vs. 17%	0.001	
Padua, Italy (237)	14% vs. 38%	0.002	

A recent meta-analysis performed by the MACH-NC Collaborative Group showed no survival benefit to adjuvant or neoadjuvant chemotherapy in an analysis of 3670 patients who had been entered onto 39 different trials[22]. Hence, in other than in an organ preservation approach as is often used for advanced laryngeal cancer, interest has shifted to the use of concomitant chemotherapy. Because of space limitations I will confine my discussion to a few of the larger, multi-institutional trials.

An early success of the concomitant chemotherapy/radiotherapy approach was Intergroup study (IG0099) for locally-advanced nasopharyngeal cancer[23]. Nasopharyngeal cancer is unique among head and neck cancers in many respects and is felt to be one of the more chemoresponsive subtypes. Distant metastases are also a common failure mode for nasopharyngeal tumors and so the ability of chemotherapy to reduce the incidence of distant metastases was also thought to be a potential advantage. In the experimental arm patients were given concomitant chemotherapy consisting of cis-platinum at 100mg/m^2 every three weeks along with radiotherapy followed by 4 cycles of consolidation chemotherapy with cis-platinum and 5-fluorouracil (5FU). In the control arm patients were treated with standard fractionated radiotherapy. This study was stopped early when an interim analysis showed a statistically significant advantage to the experimental arm. At the time of closure median progression free survival was 52 months on the experimental arm vs. 13 months ($p<0.0001$) on the control arm and respective absolute survivals were "median not yet reached" vs. 30 months ($p=0.0007$).

The Radiation Therapy Oncology Group (RTOG) has recently completed a three-armed study (RTOG 91-11) for patients with Stages III & IV laryngeal cancer but excluding patients with T4 primaries[24]. The control arm was the same as the VA organ preservation arm, one experimental arm was standard fractionation radiation alone, and the other experimental arm utilized concomitant chemotherapy and radiotherapy. Preliminary results of this study are summarized below.

RTOG 99-11: Larynx preseavation protocol

Open 8/92-5/00	
Accrued 547 patients - 497 analyzable	
Preliminary analysis (2 year endpoint) - ASCO 2001	
Equivalent survival on 3 arms - 76%	
Survival with larynx (2 years)	
VA protocol - 58%	
Chemo/rads - 66%	N.S.
Rads - 52%	
5 year larynx preservation rate	
VA protocol - 71%	
Chemo/rads - 85%	
Rads - 64%	

While there was equivalent survival on all three arms, there was an distinct advantage in terms of larynx preservation on the concomitant chemotherapy/radiotherapy arm. A detailed analysis of this study which includes toxicity data has not as

yet been published.

In a separate meta-analysis involving 1908 patients entered onto 26 randomized trials, the MACH-NC Collaborative Group found an absolute survival benefit at 5 years of 8% with the use of concomitant chemotherapy ($p<0.0001$)[22].

There is evidence that concomitant chemotherapy can improve results even if non-standard radiotherapy regimens are used. A German study showed a benefit to concomitant chemotherapy and radiotherapy vs. radiotherapy alone for patients with locally-advanced head and neck cancer when a 1.6Gy bid split course was used[25]. The chemotherapy consisted of cisplatin and 5FU and the radiotherapy was administered in 3 courses corresponding with the chemotherapy administration. At three years there was improved local/regional control (36% vs 17%, $p<0.004$) and survival (48% vs 24%, $p<0.0003$) on the concomitant chemotherapy/radiotherapy arm. Interestingly, the rate of distant metastases was the same on both arms as was the incidence of significant late effects.

Intensity Modulated Radiotherapy(IMRT)

Noninvasive studies such as CT, MRI, and PET give the clinician unprecedented information about the location of gross tumor both in an absolute sense and in relation to critical adjacent normal structures. Modern radiotherapy centers exploit this information using sophisticated linear accelerators with computer-controlled, multi-leaf collimators. These facilitate custom blocking techniques which spare uninvolved normal tissues and allow for sequential changes in field geometry as a patient progresses through treatment. Noncoplanar field configurations, often using vertex presentations are standard techniques in the treatment of head and neck cancer located at the skull base or in the paranasal sinuses. Why are these advances important clinically? The advantages of improved tumor imaging is obvious as there should be fewer "marginal misses" than in the past. Another advantage relates to being able to give higher radiation doses to the tumor in a safe manner. Other things being equal, higher doses of radiation lead to higher tumor control probability. In the case of HNSCC, dose response curves generally exhibit a steep region wherein modest increases in radiation dose will give rise to significant improvement in outcome

IMRT is next step in the saga to improve dose localization. In this approach many different treatment fields are utilized with each field being divided into multiple segments with each segment delivering a prescribed amount of radiation[26]. Sophisticated computer programs are used to calculate the doses given by each of these field segments with the clinician being able to specify normal tissue dose constraints to be used in obtaining the "solution" for a particular patient. Head and neck cancer represents an ideal situation in which to apply this technique because with proper immobilization techniques, organ motion is not a major problem There often are critical normal structures in close proximity to the tumor and achieving a sharp dose gradient around the target while limiting the normal tissue dose offers the potential for significant therapeutic gain. Lee et al[27] have reported on the UCSF experience using this approach for nasopharyngeal cancer which yielded a 97% local/regional recurrence free survival in 67 patients with a median follow-up time of 31 months. There was less toxicity than would have been expected using concomitant chemotherapy and conventional radiotherapy.

IMRT should be considered as an "enabling technology" in that it allows the Radiation Oncologist to deliver higher doses of radiation to the patient either in the context of a "stand alone" conventional fractionation schema, in an altered fractionation schema, or in conjunction with concomitant chemotherapy. There are costs associated with this both in the context of resource utilization and also in terms of a higher background dose of radiation delivered to the patient due to radiation leakage through the treatment head of the linear accelerator which must be left on for a longer period of time. This can, in principle, increase the risk of second malignancies elsewhere in the body. A study specific for head and neck cancer was performed by Verellen and Vanhavere[28]. They compared the total body radiation dose for three patients using either standard parallel-opposed fields or IMRT delivered in a slice-by-slice approach. Six MV photon beams were used and the total body irradiation dose measured in a phantom. The average total body dose was 242 mSv using the conventional form of treatment compared to 1969 mSv using IMRT. Verellen and Vanhavere estimate that the risk of a radiation induced second malignancy was about 8 times greater using IMRT which is something that must be considered in the treatment of patients with early-stage, highly curable tumors[28].

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