PERSPECTIVE SECTION

Treatment Intensification in the 'High-risk' Individual

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Abstract

The high-risk individual merits treatment intensification. However, there are concerns with CERT. More supportive care is necessary as toxicity is higher. Treatment related death is a reality. Hence before we set out to prescribe concurrent chemoradiation we would need to stratify them according to the risk factors, their performance status and bear in mind the costs involved in intensive support during treatment.

Apart from chemoradiation we need to explore emerging treatment strategies such as fractionated radiation therapy, and targeted therapies such as epidermal growth factor receptor blockade which might offer better if not similar results but with lesser toxicity.

Keywords: Head and neck squamous cell carcinoma, chemotherapy, radiotherapy.

THE PROBLEM!

For the past 3 decades locoregionally advanced head and neck cancers have been treated with combined surgery and radiotherapy.[1] Despite technical advances and better understanding of the disease biology, locoregional control rates have remained static. We can at best hope for 5 years survival of 40% and a distant metastasis rate of 25%.[2]

RISK ANALYSIS

Without doubt patients with locally advanced disease will fail locoregionally and those with locoregionally uncontrolled disease will have higher incidence of distant metastases.[3] But amongst these patients with indicators of 'High-risk' for failure[4] were those with more than two lymph nodes, extracapsular spread, oral cavity primary, close or positive mucosal margins, perineural spread, lymph nodes more than 3 cm, delay in adjuvant treatment and low performance status. This called for a rethink in the treatment strategies. Some additional treatment was required for this subset of high-risk individuals.

CHEMOTHERAPY

Since the late Eighties, chemotherapy has been used in various combinations in the management of head and neck cancers. The meta-analysis of chemotherapy in head and neck cancer (MACH-NC) group[5] evaluated the use of chemotherapy in 87 trials with over 16,000 patients. Their analysis suggested an 8% improvement in overall survival with the concomitant use of chemotherapy and radiation therapy. They also showed an overall 5% benefit at 5 years. The overall pooled Hazard Ratio (HR) was 0.88 ($p < 0.0001$). Amongst 50 concomitant trials the HR was 0.81 ($p < 0.0001$). Similar results were obtained in the trials with postoperative RT (HR = 0.80), conventional RT (0.83) and altered fractionated RT (0.73). No significant difference was seen between monochemotherapy (0.84) and polychemotherapy (0.77). The magnitude of the benefit was higher ($p < 0.01$) for platinum-based CT (0.75) than for other CT (0.86). Also seen was a decreasing effect of CT with age ($p = 0.01$). In certain trials (Intergroup #0034, RTOG #88-24) the pattern of failure was found to be modified by addition of CT and it translated as reduced rate of tumor recurrence and decreased distant metastasis in CT containing arms.

Role of chemotherapy? It might help in:

- Inhibiting repair of lethal and sublethal damage induced by radiotherapy
- Radiosensitizing hypoxic cells
- Reducing tumor burden leading to improved blood supply

- Synchronizing and redistributing tumor cells into more sensitive G2-M cell phase
- Inducing apoptosis

Utility of chemotherapy in a combined form with radiation over radiation alone in the adjuvant setting was the logical next step of evaluation. Two groups the RTOG in USA[6] and EORTC in Europe[7] undertook Phase III Randomized Controlled Trials addressing the issue of adjuvant concurrent chemoradiation (chemotherapy enhanced radiotherapy–CERT) in high-risk individuals. The trial designs were similar with one arm receiving the standard regime of postoperative radiotherapy (60–66 Gy, 2 Gy/Fr, 6 to 7 weeks) whilst in the experimental arm postoperative radiation was given along with cisplatinum every three weeks (100 mg/m^2 Day 1, 22, 43). Both the trials were well conducted with adequate number of patients giving their results enough statistical power. About 800 patients were randomized in the two trials and were well stratified to remove any bias.

Inclusion Criteria

EORTC 22931 *Feb 1994–Oct 2000*	*RTOG 95-01* *Sept 1995–April 2000*
• SCC of oral cavity, oropharynx, larynx, hypopharynx • Surgical margins microscopic involved • Extracapsular extension in positive LN	
• Stage III/IV except Larynx T3N0 • Level IV/V +ve LN in oropharynx/oral cavity • Vascular embolism • Perineural infiltration	• Two or more +ve LN

Study Endpoints

EORTC 22931	*RTOG 95-01*
• **Primary:** Disease free survival • **Secondary:** Overall survival, Locoregional control Distant metastasis Second primary Treatment toxicity	• **Primary:** Locoregional control • **Secondary:** Overall survival, Disease free survival Treatment toxicity

Patient Characteristics

	EORTC 22931	*RTOG 95-01*
Randomized	334	416
Age	All < 70 years	7% > 70 years
Site	Hypopharynx 20%	Hypopharynx 7 to 12%
Positive margins	28%	18%
Histology	19% PDSCC	33% PDSCC

Treatment Compliance

	EORTC 22931	*RTOG 95-01*
Compliance–CT	49% completed 3 cycles of CT	61% completed 3 cycles of CT
Compliance–RT	4% recvd < 60 Gy 25% Rx interruptions	80% recvd planned dose
Delay	32% in CTRT and 25% in RT had delay > 6 weeks before adjuvant therapy began	< 1% had delay

Adverse Effects

	EORTC 5 years estimates	*RTOG 2 years estimates*
Grade 3+ acute toxicity	41% *vs* 21% (p = 0.001)	77% *vs* 34% (p < 0.001)
Late toxicity	38% *vs* 41% (p = 0.25)	21% *vs* 17% (p = 0.29)
Death	–	2% in CTRT

Treatment Outcome

Outcome endpoints	*EORTC 5 years estimates*	*RTOG 2 years estimates*
Disease free survival	47% *vs* 36% (p = 0.04)	54% *vs* 45% (p = 0.04)
Overall survival	53% *vs* 40% (p = 0.02)	64% *vs* 57% (p = 0.19%)
LR failure	17% *vs* 31% (p = 0.007)	19% *vs* 30% (p = 0.01)
Impact on distant mets	21% *vs* 25% (p = 0.61)	20% *vs* 23% (p = 0.46)
Second primary	12% *vs* 13% (p = 0.83)	NA

The three objectives were:

- Reduction in locoregional failure: Locoregional control was better by 11 to 14% and disease free survival improved by 9 to 11%.
- Overall survival improved by 13% though not significant
- Distant metastasis rate was not reduced and second primary rate was similar.

Thus here is a Level I evidence proving benefit of adding chemotherapy to postoperative radiation for high-risk individuals. Though a strong evidence, there is some hesitation with its implementation as a standard of care. This is because of severe acute side effects in almost 80% of patients. Chemotherapy was not completed by one third of patients we are not sure if chemotherapy was solely responsible for the added benefit in these patients. Also in the earlier studies utilizing chemotherapy in the neoadjuvant

and concomitant settings the distant metastasis rate was reduced and one of the premises of giving it was to accrue this benefit. However, this has not translated in practice and both the trials have not shown any reduction in distant metastatic rate.

A recent metaanalysis[8] evaluated four trials with post-operative chemoradiotherapy in advanced head and neck cancers. The ones by RTOG[6] and EORTC[7] and those by Bacchaud JM et al[9] Smid L et al.[10] This metaanalysis supports the use of CERT with a pooled relative risk (RR = 0.59) which translates into a 41% reduction in loco-regional recurrence. It also showed a 12.5% improvement in locoregional control. As far as overall survival is concerned the four trials showed (RR = 0.80%) a 20% reduction in risk of death and a 12.5% improvement in overall survival. Toxicity is another issue when adding chemotherapy to radiation therapy. This review showed a definite increase in acute toxic events of Grade 3/4 in all trials almost to the tune of 77%. Late toxicities were not found to be significantly different though they have not been documented properly. The authors concluded that though chemoradiation in the adjuvant setting is beneficial there are several concerns. The most important are long-term results. Longer follow-up needs to be studied to look for overall survival advantages. Toxicity often limits completion of scheduled treatment and in almost one third of patients do not go on to complete full course of chemotherapy. Treatment related death and late toxicity may be a concern. Thus we have to understand that while we want to enhance results in advanced cancers we have to temper our enthusiasm by weighing the pros and cons vis-à-vis toxicity and benefit. We have to factor the element of higher supportive care for these patients and its attendant increase in cost.

What is Truly 'High-Risk'?

Do all the so called 'high-risk' factors merit this toxic treatment? Bernier J et al[11] analyzed the pooled data of patients from the RTOG and EORTC trials. They found Extracapsular extension (ECE) and/or microscopically involved surgical margins were the only risk factors for which the impact of CERT was significant in both trials. There was also a trend[12-14] in favor of CERT in the group of patients who had stage III-IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. Patients who had two or more histopathologically involved lymph nodes without ECE as their only risk factor did not seem to benefit from the addition of chemotherapy in this analysis.

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