During the past two decades, the dose escalation was revisited many a time in earnest search of better cure of head and neck cancer (HNSCC) by the North American radiation oncology community and the European counterparts alike. The escalation limit was raised as high as 80 ɭ in the European trials surpassing the US trials of 75ɭ mark singly with altered fractionation radiation (AF) or in many trials with chemotherapy (CT) in combination.

In 1999 Calais et al premiered with a 24% gain in local regional control and unprecedented 20% gain in 3-year survival with concomitant carboplatin/5-flourouracil and 70ɭ radiation therapy (XRT) regimen. Since then most studies focused on concomitant CT and dose escalation (DE) XRT. Unfortunately in their final review in 2004, the 5-year survival gain declined to a mere 6% failing to sustain the original 20% level with a staggering 54% late complication rate which had not been analyzed in the 1999 review³.².⁰

High hopes for CT/DE XRT looked rather dim until the results from two meta-analyses came in; by Pignon et al with CT/XRT in 2000, later by Bourhis et al with DE, AF/XRT in 2006.

First, the 2- and 5-year absolute overall survival benefit from concomitant CT/XRT was 8% but with a caveat of “uncertain benefit size” attributed to an 11% heterogeneity factor with the data base. The overall survival from all type CT/XRT was only 4% underscoring negative benefit from neoadjuvant CT. Secondly, the 5-year absolute survival benefit from DE, AF/XRT was with a razor-thin margin of 3.4%¹.³

Main shortfalls with prevailing CT/XRT are invariably in the treatment toxicities.

We are at the crossroad either to radically depart from DE/XRT dose or to modify the CT scheme because the two in current intensified mode cannot co-exist meriting each other. We have come to learn “less is more”.

Marginal benefit from current treatment is often outweighed by invariable toxicities and life-compromising late morbidities such as loss of organ function, swallowing dysfunction, permanent G-tube and/or tracheostomy dependency, crico-pharyngeal stenosis and life-threatening aspiration pneumonia in addition to devitalizing damages to the bone and soft tissue.³.⁷. QOL following intensified CT/XRT is stigmatized by the needs of frequent medical attentions and over-extended provider’s caring time and facilities which add to the concerns of cancer care cost overrun.

Are we myopic to miss or callous to dismiss the downsides of the intensified CT/XRT? In late 1988, we serendipitously learned that potentially beneficial physical properties of low dose rate radiation might be additive in the definitive treatment of oral and oropharyngeal cancer (OC, OPC).

The interaction of different physical properties from low dose rate brachytherapy (LDR BT) and XRT lends itself favorably to increasing the therapeutic ratio result-
ing satisfactory tumor control and normal tissue preservation.

Palladium radionuclide has an average energy of 27 keV with 17 day half-life which meets our requirements as a low energy particulate energy emitter with short half-life and shorter average life conducive to rapid tumor regression and relative safety of the surrounding normal tissue.

Such potential benefits may be further enhanced by the increased RBE and decreased oxygen enhancement ratio (OER) inherent to LDR BT with little or no radiation exposure hazard.

For instance, 10–30mCi of palladium in 0.6–1mCi per source embedded in tumor volume at 1.0cm distancing and 1.0cm spacing gives rise to an ideal planning tumor volume (PTV) dose of 50Gy (+− 10%) which approximates dose required to “kill” 50% of cell population (D50) for most HNSCC. This has been clinically validated in our department since the 1990s.

This concept is alien to the tumor dose boosting brachytherapy historically in practice employed after the 4–5 week of XRT. Such brachytherapy is often limited by the applicability depending on anatomical location, size of tumor and arguably in the face of appropriate question of “can it be superseded by the precision XRT such as intensity modulated radiation therapy (IMRT)?”, theoretical advantage from continuous low dose rate radiation aside.

In order to ensure tumor control without XRT escalation, we enlist therapeutic neck dissection for cN+ neck. Surgical neck clearance is a prudent choice on the basis of several planned neck dissection studies after intensified CT/XRT showing viable residual tumor cells in 20–35% of the so-called clinical responders10–12. First and foremost, control of the neck must be given a priority before embarking on the primary tumor issue.

Palladium-103 brachytherapy to the primary and synchronous therapeutic neck dissection of the involved neck is followed by IMRT with median tumor dose (TD) of 56Gy commencing in one week to 10 days. In so doing, the primary tumor will have received a nominal aggregate of 90Gy, 40Gy of which is from LDR BT build-up dose in the average life time. During the initial 2 half-lives (34 days with palladium) it will have completed its gainful therapeutic role.

This treatment protocol was inaugurated at Yale in the late 1980s and 185 cases were accrued through 2008 allowing a minimum 2-year follow-up.

Seventy-five percent of the 185 cases received no chemotherapy. LDR BT, therapeutic neck dissection and less than radical dose XRT gave rise to a consistently high overall local regional control rate of 76%: 82% in tonsillar, 77% in base of tongue and 58% even in pharynx cancer respectively.

The overall local regional failure rate was 14% and distant failure rate was 6%. As shown in the Kaplan-Meier analyses for the entire cohort and breakdown by sub-sites in T-stages in the attached Figures 1, 2a–c, the results are as promising as expected.

The highlights of this protocol are summarized in the following:

1) 0% life-threatening treatment toxicities; no soft tis-

Fig. 1 Kaplan-Meier analyses for the entire cohort

![Graph showing Kaplan-Meier analyses for the entire cohort](image-url)
Fig. 2 Kaplan–Meier analyses breakdown by sub-sites in T-stage
sue or bone necrosis, no swallowing dysfunction, permanent G-tube dependency or crico pharyngeal stenosis or aspiration pneumonia resulted from this treatment.  
2) Timely control of the primary and neck metastasis initiates the “downstream effect” which positively impacts on overall survival by minimizing local regional failure and forestalling distant failure.  
3) The role of CT is indeterminate in this setting.

The oropharynx is an intricate multi–task organ indispensable to deglutition, phonation, alimentary and respiratory pathway. It is for this reason that the oropharynx deserves more measured and salubrious therapeutic option keeping functional integrity and QOL outcome as a priority consideration.

Excepting some T4, most T-stage oropharyngeal cancer (OPC) deserves serious consideration for optimized treatment eschewing DE/XRT or platinum compound including chemotherapy\(^{11,12} \). It is our view that T-stage is not a dominant factor in chemotherapy decision, reason being that LDR BT in combination with XRT is a therapeutically assurable option in the control of OPC in our hands.

In reality, the absolute 5-year survival advantage from CT/DE XRT is in the 6% range at the cost of 2–3 fold higher level of toxicities and morbidities. In addition, there is a mounting concern about the outlasting toxic effects from platinum based chemotherapy.

At the pinnacle of intensified chemotherapy and DE/XRT, the validated survival benefit is still elusive while treatment toxicities and morbidities are untenably high.

We urge to reflect on our current treatment strategy to better accommodate the needs of each type and every site of HNSCC, particularly in OPC.

References