## An Overview of Organ Preservation Approaches in Cancer Management Radiation Oncologist's Perspective

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The new millennium has seen the successful integration of radiation oncology in the multidisciplinary treatment along with surgery and chemotherapy with considerable improvement in cure rate especially for patients with locally extensive disease. These efforts have resulted in greater emphasis on preserving or restoring function after the treatment with all primary and adjuvant therapeutic modalities. It has been realized that it is not sufficient to offer therapy to patients based exclusively on antitumor efficacy but impact of treatment on the patient's subsequent recovery and functional rehabilitation must also be considered. However first and foremost, treatment should be directed at maximizing oncologic control and cure. **Functional preservation may be of paramount importance, however, when loco regional control and survival rates are similar between modalities**.

The definition of organ preservation merits consideration. It is defined as sparing any organ from removal and subsequent loss of function. However, not all organs are equal; some are considered more critical to physiologic functioning than others. The key question is how to define a critical organ? In the treatment of breast and prostate cancer, the role of organ preservation is well established. The psychological importance of these organs is undisputed, but it can be argued that they are not critical to physiological function and quality of life. Thus it needs to be emphasized to preserve speech, bladder and bowel function which have a greater impact on all spheres of physiological and psychological function. Organ preservation is a concept requiring a multidisciplinary approach of surgery, chemotherapy and radiotherapy with the goal of attaining the highest probability of cure with the least morbidity.

The success of organ sparing treatment continues to evolve and has become standard of care in selected tumors. The landmark milestone in this context was the Veteran Affairs Laryngeal Cancer Study Group (VALCSG) which included 332 patients stage III-IV squamous cell carcinoma of larynx. In the neoadjuvant arm, larynx preservation was achieved in 107(64%) patients while functional larynx was observed in 65(39%). This was followed by Head and Neck Intergroup Trial RTOG91-11 which

compared RT alone to induction chemotherapy and concurrent chemo radiotherapy. The larynx preservation was statistically significant in concurrent arm (70% vs 75% vs 88% p<0.001). These preserved larynx were associated with increased side effects of radiation which raised a concern that the concept of organ preservation will attain popularity with reduction in their intensity only.

The dream was realized with the advances in radiation physics and computer technology which made it possible to aim radiation more precisely than in the past. 3Dimensional radiotherapy (3DCRT) utilized predetermined array of treatment fields but sometimes, optimal dose distributions were not achieved, particularly when the targeted structure had highly irregular shapes, with a combination of convex and concave contours (like prostate gland). With the advent of intensity modulated radiotherapy (IMRT) era, the changing paradigm shifted from wide field radiation to conformal radiation and thus led to better sparing of critical organs. IMRT achieves unprecedented conformity of the radiation dose, by applying two complex concepts of inverse treatment planning and modulation of the radiation beam. It includes improvement in immobilization devices, treatment techniques (3D-CRT, IMRT, Image Guided Radiotherapy, Stereotactic Radiotherapy / Stereotactic Radiotherapy), Sophisticated planning algorithms(Pencil beam, convolution),Advanced dose calculation (Monte Carlo photon transport), Superior treatment verification (Digitally reconstructed radiograph, Portal imaging) and Precise treatment delivery (Tumor Tracking, Adaptive RT).

To achieve this one has to depend on the accurate identification of target volumes and this is particularly important in head and neck and prostate cancers which have close proximity to multiple critical structures. Several guidelines have been published in last few years which developed a consensus for contouring of Gross tumor volume(GTV) and Clinical target volume(CTV) for various sites and thus a standardization of techniques. But it should not be forgotten that the **imaging plays an important aspect** in deciding whether to offer organ preservation to particular patient .Computed tomography (CT) has been the mainstay of anatomical treatment planning for many years, enabling some delineation of soft tissue as well as radiation attenuation estimation for dose prediction. Magnetic resonance imaging (MRI) enables superior soft-tissue visualization and MRI /CT fusion delineated nodal volume 50% larger than CT alone. Over the last few years the use of functional imaging, particularly with **positron emission tomography (PET) scan** has become popular in oncology. It has shown its importance for tumor staging, prediction of tumor response, selection and /or delineation of radiotherapy target volumes, assessment of tumor response and/or early recurrence or as a tool to evaluate modification in organ function after treatment. However, use of FDG-PET for target volume

delineation vary in terms of specificity and sensitivity and how much radiotherapy will gain from it and how this progress will be implemented in routine procedure is still unresolved.

**IMRT being a 'less forgiving'** form of radiation therapy with regard to the effects of geometric uncertainties imposes more stringent requirements to account for both intrafraction and interfraction uncertainties. Treatment verification has been carried out using a variety of technologies including: megavoltage portal imaging, kilo voltage portal/fluoroscopy, cone beam CT, ultrasound and optical surface imaging. Four dimensional radiotherapy(4DRT) aims to track and compensate for target motion during radiation treatment, minimizing normal tissue injury, especially critical structures adjacent to the target, and/or maximizing radiation dose to the target. Stereo tactic body radiation therapy (SBRT) and Cyber knife, constructing very compact high-dose volumes in and about the tumor, takes advantage of the technologic advancements in image guidance and deliver ablative dose fractionation to the target capable of both disrupting tumor mitosis and cellular function. Carbon ion and proton radiation are further expected to offer benefits especially in tumors that are known to show low radio responsiveness against photon radiation and are located in normal tissue that is sensitive against photon radiotherapy again favoring the goal of organ preservation.

However the next decade will witness a paradigm shift in which morphological multi-modality imaging will be heavily integrated with molecular-functional imaging. Molecular probes for imaging in vivo gene expression (e.g. oncogenes such as myc or tumor suppressor genes such as p53 telomerase activity, over-expressed receptors (e.g. HER-2/neu), apoptosis, protease activity, hypoxia and angiogenesis have been evaluated.. Recently, a clinical evaluation of PET imaging with 18F-FMISO has been performed in patients with head and neck cancer to explore the feasibility of dose-painting hypoxic regions with IMRT. The dose to the hypoxic region could be escalated by approximately 20% to a prescription dose of 84 Gy, while keeping the organs at risk at the same tolerance levels and is expected to bring about both an improvement in local tumor control and in cause-specific survival with reduced morbidity profiles. It must be emphasized, however, that these are hypothetical proposals that require clinical studies for validation. These advances have led to functionally preserved bladder and anal canal, marked decrease in xerostomia and late dysphagia along with better, faster and lasting palliation by delivering higher doses and significant decrease in toxicity of all sites. IMRT at one end of spectrum has its positives but with this technological innovation comes at spiraling rise in equipment, trained manpower, increased man-hours and quality assurance which directly or indirectly has to be passed on the patient.

**Brachytherapy** is one of the oldest and most established techniques which allow the radiation oncologist to achieve doses that are markedly higher than almost any other radiation modality with the potential added benefit of a favorable dose rate and highest conformality. When combined with various types of external beam irradiation, the prospect exists for marked dose enhancement and optimized therapeutic ratio. A major difference with brachytherapy compared to other modalities is the marked technical skill and operative experience of the radiation oncologists doing these procedures. Unlike other modalities that have a greater reliance on computer control and planning, the route to success for brachytherapy is in the judgment, skill, and technique of the physicians performing the procedures. Equally important is the role of the medical physicist, partnering with the radiation oncologist, in planning and implementing the procedures. The role of brachytherapy in oncology management has continued to evolve over the years. The indications have changed, and new applications of adaptive brachytherapy have been discovered. The first available clinical results using MRI approach shows increased local control in both limited and advanced diseases with 95-100% patients showing less than 5% severe late morbidity. For these reasons, brachytherapy has continued to be a major aspect of radiation oncology and a major strategy for oncologist's desire to perfect conformal therapy. Brachytherapy also provides an effective technique for the retreatment of patients with recurrent, persistent, or second primary head and neck malignant tumors in a previously irradiated region.

The classic teaching of radiobiology regarding altered fractionation always allured the mind of radiation oncologist to explore this domain but in view of increased late side effects, it could never be utilized to its full extent. But with the progress seen in the manipulation of cytotoxic agents in conjunction with radiotherapy there are now new avenues to explore as classical dose and fraction size limits may no longer apply. **Altered fractionation deserves a second look in light of the explosive growth and development of radiation therapy.** The traditional dose limits that are based on the tolerated dose to surrounding normal tissues may no longer be limiting since normal tissues are now avoided to a large extent. The use of IMRT with its inherent dose in homogeneity results in fractionation differences even with once-daily delivery. The distribution of mucositis may change, but intensity of mucositis during IMRT is similar to or even greater than conventional RT because of the common use of accelerated fractionation in IMRT (e.g., 66 Gy in 30 fractions or 70 Gy in 33 fractions).

The success story of radiotherapy will never be complete without the addition of chemotherapy. Negro, Vaitkevicius and Considine pioneered the concept of organ preservation as early as 1974 in anal canal which still remains the gold standard. With a combination of radiation therapy, 5-Fluorouracil (5-FU) and mitomycin C, it was seen that epidermoid anal cancers disappeared completely in the majority of patients, and radical surgery can be reserved for those with histologically proven residual cancer after radio-chemotherapy. The Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) of 87 trials showed that, whatever the sequencing of the 2 modalities, the addition of chemotherapy to radiotherapy yielded an improvement in survival, with an overall absolute benefit of 5% at 5 years. **However recent trials have shown that the reduced compliance due to poor tolerability inevitably impacts on treatment dose intensity leading to the delivery of suboptimal regimens.** Along this line, the development of chemo radiation in the framework of new organ and function preserving programs as a result of combining these with induction chemotherapy should be investigated in prospective phase III trials.

Recently, the combination of radiotherapy and epidermal growth factor receptor inhibition was proven to improve survival. This watershed showed proof of benefit of combining physically and biologically targeted modalities and reinforced the concept that improvements in local-regional control alone can in fact lead to significant improvements in overall survival. Challenges, however, still exist.

Since its inception, radiation oncology, more than any other cancer treatment discipline, has considered the late effects of therapy on normal tissues and organs. The Late Effects of Normal Tissue Conference (a collaboration of RTOG and EORTC) developed a scoring system -SOMA (subjective, objective, management, analytic) in 1995 to be used in all anatomic sites. However, Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) by National Cancer Institute which is been actively used, has been criticized for evaluating standard fractionation alone. However, most patients are now managed with multiple highly integrated modalities, often augmenting tissue injury and limiting our ability to describe any given effect to a particular modality. **The use of complex concurrent or hybrid (concurrent/sequential) schedules also undermines the usefulness of a simplistic temporally defined early-late construct.** Moreover, there is growing recognition that chemotherapy and surgery produce inherent long-term biologic and clinical effects as well. A long term data of toxicity profile will provide insights into potential targets and strategies for modulating response, which may in turn lead to effective interventions for altering the therapeutic ratio. The current challenge is to foster QOL research, primarily focused on phase III

trials, with clear hypotheses that can potentially lead to clinically meaningful interventions .These results will ultimately transpose QOL efforts directly into the clinical arena to not only add "years to life", but also "life to years."

With continued advances in strategies to detect cancer early and treat it effectively along with the aging of the population, the number of individuals living years beyond a cancer diagnosis can be expected to continue to increase. However, surveillance for recurrent disease in those patients who have shown a complete clinical response to primary chemo radiotherapy presents a continuous challenge. Long-term assessment is often confounded by the treatment effects of chemo- and radiation therapy, including edema, fibrosis, soft-tissue and bone or cartilage necrosis, dysphagia, chronic discomfort, and altered anatomy, not unlike the same issues facing evaluation after primary surgical therapy. These poorly documented data underscore the need for continued research in this ever-growing portion of the cancer survivorship spectrum. However, both locoregional disease failure and secondary index cancers (which occur in up to 40% of successfully treated patients) remain common. Re-treatment with conventional techniques to the head and- neck region can be problematic because of disease spatially approximating previously treated dose-limiting anatomy, such as spinal cord, brainstem, optic nerve, and mandible. IMRT allows conformal delivery of definitive doses with sparing of critical organs and thus a promise to improve both efficacy and morbidity in re-irradiated patients though with certain limitations.

Even the surgeons have accepted the concept and attempts have been made to do a less extensive, cosmetically acceptable, functional and organ preserving surgery without compromising the end results. **Da Vinci robot** helped to perform radical prostatectomies, cystectomies, partial nephrectomies, and adrenalectomies with more precision and miniaturization. Various prosthetic materials are now available for reconstruction of breast, jaw and other organs thus providing better outcome. **The other area where surgeon needs to sharpen their blades is to improve their skills towards palliative surgeries since this will be an important area to explore for failures of chemo radiation patients treated for organ preservation.** 

As radiation oncologist we need to understand that the pendulum has to remain in center away from surgical radicalism on the one hand and toxic concurrent chemo radiotherapy on the other. We must establish risk-based criteria for treatment selection and functional outcome—rather than celebrating a single modality of treatment over any other, whether surgery, radiotherapy, or chemotherapy.