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Acute radiation toxicity in head and neck and lung malignancies

Acute sequelae during radiation therapy can pose a challenge in the delivery of planned radiation doses and completion of intended treatment. Certain toxicities like mucositis during head and neck radiotherapy (RT) or pneumonitis during RT to the lung are seen in almost 100% of patients receiving curative intent RT though their severity may differ depending on several factors. The various predictors of acute toxicity are volume of tissue exposed to radiation, anatomic subsite exposed, treatment intensity, and individual patient predisposition.[1]

Mucosal injury remains an undesirable, painful, and expensive side effect of cytotoxic cancer therapy and is disheartening for patients and frustrating for caregivers.[2] A pilot study by Nonzee *et al*., claimed that the cost of management of oral mucositis among head and neck cancer patients added up to $17,000 per patient, with hospitalization being the significant driver of this escalated cost.[3] Almost 100% of patients treated with concurrent chemoradiotherapy (CT-RT) suffer clinically significant mucositis and more than 40% of these can be severe. The recommendations for the prevention of mucositis are use of midline blocks or conformal RT and use of benzydamine mouthwash during RT while prophylactic use of chlorhexidine and antimicrobial lozenges are not recommended during RT. Despite tremendous scope for research, very little has been done and the only agent approved for oral mucositis is palifermin, whose use is limited to patients undergoing high dose chemotherapy and total body irradiation ahead of autologous stem cell transplant.[1]

In the study by Chattopadhyay *et al*.,[4] in this issue of the journal, we commend the authors for attempting to address a very important issue in the optimal delivery of head and neck RT, that is, mucositis. To our knowledge, this is the first investigator-initiated prospective randomized trial to be reported among Indian patients. It is commendable also because it addresses a common hurdle encountered in one of the most common cancers in any oncology clinic in India. However, there are several problems with the present study, making its interpretation and application difficult. Primarily, the grading of mucositis was done by using the World Health Organization (WHO) grading alone, which is a highly subjective scoring system. The frequency of evaluation of mucositis was once weekly and hence the veracity of onset and duration of mucositis is questionable.

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In the pilot study by Huang *et al*., oral glutamine was tested against normal saline (used as a placebo) and the assessment was done daily.[5]

There is also no mention of nasogastric (NG) intubation and weight loss, which are useful surrogate indicators of severity of mucositis during RT. There is no mention of the pain associated with mucositis and the incidence of opioid use in the two arms, which again act as useful surrogates in assessing intensity.

A patient with WHO Grade 4 mucositis (cannot even swallow liquids) would find it difficult to swish-and-swallow 800-1,000 ml of water within a 2 h period, which was what the protocol desired. Pharmacokinetics of oral glutamine show that orally loaded glutamine peaks at 30-45 min after ingestion and declines steadily to normal range between 1.5 and 6 h, depending on the dose.[6] Even the recent systematic review by Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recommend the use of intravenous (IV) L-glutamine but only for patients planned for high-dose chemotherapy prior to hematopoietic stem cell transplant.[7]

In summary, trials attempting to mitigate the incidence of mucositis have shown promise, however there is a paucity of robust data in spite of a pilot study showing modest success more than a decade ago. The present trial has many questions to answer and does not provide us sufficient confidence in answering the question of the optimum use of oral glutamine in mitigating oral mucositis. The issue of mucositis management still remains an unresolved issue.

Radiation pneumonitis (RP) is the most common and dreaded complication in treating tumors of the lung, one that can have considerable impact on patient morbidity (quality of life and respiratory function) and rarely mortality. The incidence of clinically significant RP ranges between 13 and 37% of patients treated with radical RT for lung cancer.[8] The onset of RP is between 6 weeks and 6 months after RT conclusion. Pathologically, RP consists of an exudative interstitial and alveolar pneumonitis secondary to damage of alveolar epithelium and capillary endothelium by DNA and cell membrane damage by ionizing radiation.[9] A second pathophysiological process, a sporadic or "out-of-field" RP has been attributed to hypersensitivity with immune mediated bilateral lymphocytic alveolitis.[10]

The risk factors for RP can be broadly classified into clinical and dose and volume related. In the recent individual patient meta-analysis by Palma *et al*., among patients undergoing chemoradiotherapy for non-small cell lung cancer (NSCLC), factors predictive of the development of RP were V20 (odds ratio (OR) 1.03 per 1% increase in V20, $P = 0.008$), chemotherapy regimen (OR for carboplatin/paclitaxel 3.33, relative to cisplatin/etoposide; $P < 0.001$),

and with a trend toward significance for advanced age (OR per 10-year increase 1.24, 95% CI 0.97–1.59, $P = 0.09$). Fatal pneumonitis is uncommon (1.9%) and is associated with total daily dose greater than 2 Gy (7% if >2 Gy vs 1.5% if ≤2 Gy, $P = 0.01$), V20 (OR 1.09 per 1% increase, $P = 0.044$), and tumor location (1% for upper lobe, 0% for middle lobe, and 5% for lower lobe, $P = 0.007$).[11]

The management of RP begins with supportive care like supplemental oxygen with nebulization when necessary, antitussives and expectorants. The mainstay of management is oral steroids with methyl prednisolone 1 mg/kg/day continued for several days and slowly tapered off. Adjunctive antibiotics should be used when the risk or suspicion of secondary infection is suspected. Other immune suppressors like azathioprine or cyclosporine-A have been attempted in resistant or steroid intolerant cases.

The study by Agrawal *et al*.,[12] is a retrospective analysis which comes with a myriad of limitations. The sample size of 52 with at least three different treatment schedules (neoadjuvant chemotherapy followed by RT, lower doses of RT, and higher doses of RT) does not confer a status of uniformity among the subjects for comparative analyses. However, we commend the authors for bringing out the importance of RP in the Indian setting. Their effort in attempting to set a standard for Indian patients using the receiver operating characteristic (ROC) curve is commendable. This could contribute to the development of predictive dose parameters specific to Indian patients in the future.

In the absence of positron emission tomography-computed tomography (PET-CT) or invasive investigations to evaluate the mediastinal nodal status, it is possible that the entire abnormal mass may have been included in the planning target volume (PTV), but a PET-CT may have shown an atelectatic focus. A significant impact of PET-derived contours on treatment planning has been shown in 30–60% of the plans with respect to the CT-only target volume.[13] This could have increased the volume of PTV leading to higher ipsilateral lung volumes receiving at least 5 Gy.

The study has focused only on the dosimetric parameters and mentioned in passing one clinical parameter namely forced expiratory flow (FEV) 1, but has not analyzed its association with RP. To the authors' credit, tumor location has been analyzed and found clinically insignificant to the development of RP. Clinical parameters like age, gender, baseline performance status, smoking status, underlying lung disease, and tumor location have all been reported to be predictive factors for the development of RP.[14-16]

The only significant parameter from the multivariate analysis is V5-ipsi in the development of Grade 2 RP, however not for Grade 1 pneumonitis. A 'relative V5' has been described by Wang *et al*., to be significantly predictive of Grade 3 or more RP.[17] However, a dose of 0-5 Gy (and the volume of lung receiving it) appears too small for a dose to contribute to Grade 2 or 3 RP. The association could possibly be statistically significant but not clinically relevant. Multivariate analysis by Barriger *et al*., from a prospective study did not show V5 (or V10, V15, V20, V25, V30) to be a significant predictive factor in the development of severe acute RP.[18]

There was no significant difference between the volume of PTV and development of RP. Dang *et al*., have shown that the volume of PTV to volume of Lung ratio is a predictive factor for Grade 2 RP but not Grade 3 RP, more so in the population of <70 years.[19]

In conclusion, in the presence of conflicting data for each parameter and lack of robust evidence, we are none the wiser in predicting RP. Multiple meta-analyses are available on RP, but each has their own findings. There is a dearth of a large prospective, randomized controlled trail (RCT) validating these parameters. In the ideal setting, a multicentric attempt at prospectively studying the predictive factors for RP should be set-up to resolve the why, how much and when on RP.

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