Optimizing treatment in head & neck cancers - are molecular markers the answer?

The last decade has witnessed a paradigm shift in the management of head and neck cancers, characterized by more aggressive and intensive locoregional treatment. The addition of chemotherapy to the treatment algorithm in conjunction with radiotherapy has improved locoregional control rates. This has also resulted in a large number of patients being treated with an organ preservation approach thus avoiding mutilating and ablative surgery. Initial reports in the early 1990s showed that the addition of chemotherapy to radiotherapy resulted in similar control rates to the then standard of care of surgery followed by postoperative radiotherapy in the treatment of laryngeal and hypopharyngeal cancers. The important difference however was that nearly two-thirds of patients in the non-surgical arm were able to retain their larynx.

Subsequently, meta-analysis of randomized trials showed that the benefit of adding chemotherapy to radiotherapy was best seen when the two were used concurrently as against sequentially. More recently the benefit of concurrent chemo-radiotherapy has also been seen in the postoperative adjuvant setting. There is therefore enough level I evidence to suggest that concurrent chemo-radiotherapy is today the standard of care for the majority of patients with head and neck cancer.

However, these benefits of an improvement in locoregional control and organ preservation come at a cost. The concurrent use of chemo-radiotherapy is toxic with up to 70 per cent of patients experiencing grade III or IV toxicity. Moreover, a similar number of patients require intensive support by way of hospitalization and supplemental tube feeding to help them complete the prescribed treatment. This naturally translates into increasing treatment costs and a burden on existing health care facilities. This is a cause of major concern as the majority of head and neck cancer patients particularly in our country, present with advanced disease stages that qualify them for chemo-radiotherapy treatment protocols either upfront or as adjuvant therapy.

It is therefore important to balance the benefits of these intensive regimes against the anticipated side effects of toxicity and costs. This could best be achieved by identifying a subset of patients at the highest risk for tumour recurrence who could then be targeted with these intensive protocols while others could be treated with conventional regimes and spared from unnecessary toxicity and hospitalization. It would also be beneficial in improving the outcomes for patients treated on organ preservation protocols to be able to identify treatment responders upfront. As of today these subgroups of patients are identified based on clinical tumour node metastasis (TNM) and histological parameters.

The currently used TNM staging system has its limitations in that Stages III and IV locally advanced but operable cancers form a heterogeneous group comprising 14 different T and N stage combinations. A T3 glottic cancer with cord fixity and no nodes would behave much differently from a similar cancer with nodes or from a cancer with cartilage invasion.
Grade of differentiation, depth of infiltration, presence of lympho-vascular or perineural invasion, nodal involvement and extracapsular extension of disease are important histological parameters in identifying a poor prognostic subgroup but these are often unavailable to the treating clinician at the time of initial decision making. Moreover, treatment response varies among patients with these adverse factors as well. Other parameters are therefore required to identify the high risk group in order to optimize target therapy and thus maximize the therapeutic gain afforded by chemo-radiotherapy.

Molecular markers are increasingly being studied to compliment clinical and histological parameters to identify this high risk group of patients. Aberrant expression of growth factor receptors, cell proliferation markers as well as dysregulation of cell signaling molecules are commonly seen in solid squamous cell carcinomas and may serve as markers for poor prognosis. Markers for neck metastasis include proliferation markers such as PCNA and Ki67. However, these have been reported as significant predictors of metastases, in addition to clinical T stage and neck palpation. Cellular DNA content has also been an extensively studied parameter for both haematological and solid tumours. DNA diploid tumours are known to have a better prognosis with the best predictors of metastasis being depth of muscle invasion, double DNA aneuploidy, and histologic differentiation of the tumour. In the metastatic lymph node, aneuploidy with higher S phase fraction was found to be significantly related to early recurrence and poor prognosis. These findings are relevant as involvement of regional nodes is the single most important factor in influencing the prognosis of head and neck cancers.

As of today, there is no single marker that can predict treatment response or survival in patients treated with multimodality therapy. However, it is important to note that many such markers do show promise and there will be a time in the not so distant future when patient’s treatment will be individualized and based on the biology of the patient’s cancer. Gene expression profiling techniques combined with proteomics could help to define and select useful genetic and biomarkers of progression which could be used in combination with the TNM staging system and histological factors. These markers could well serve as potential therapeutic targets in drug development.

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