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USE OF BIOLOGICAL PARAMETERS TO DE-ESCALATE CHEMORADIATION IN HPV ASSOCIATED SQUAMOUS CELL CARCINOMA OF DIFFERENT SUBSITES

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ABSTRACT

Human papillomavirus infection is now a well-established cause of many common cancers like cervical, other anogenital, and head and neck cancers. The mortality and morbidity rate associated with these cancers constitute a major burden especially for the underdeveloped and developing countries of the world, where they are more common. Traditionally, all these subsites are being treated with different chemoradiation protocols with variable results. Toxicities associated with the standard high dose chemoradiation protocols form a major obstacle in the completion of treatment for these patients and often affects the outcome negatively. Personal experience and published reports and reviews suggests that HPV associated squamous cell cancers are a distinct biological sub group of cancer which can be treated safely with reduced intensity of chemoradiation. The establishment of a similar de-intensified chemoradiation protocol for all HPV associated squamous cell carcinoma will certainly improve the quality of life of such patients.

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INTRODUCTION

Human papillomavirus infection is now a well-established cause of cervical, anogenital (anus, vulva, vagina and penis) and head and neck cancers (esp. oropharyngeal). (1) Radiation alone or in combination with chemotherapy is an effective modality of treatment for these cancers. Though early stages of these cancers can be treated with either surgery or radiation, chemoradiation is the standard treatment for locally advanced stages. Head and neck, and cervical cancers are very common in the underdeveloped and developing countries of the world, where they also usually present in a locally advanced stage for treatment making chemoradiation the primary modality of treatment. (2)

Now, the point to ponder is that these anatomical subsites have a common histology (predominantly squamous cell carcinoma), common etiology (HPV infection), common pathogenesis and are thereby biologically similar cancers. Inspite of all these similarities, the fact remains that they are being treated with different chemoradiation protocols with variable results.

DISCUSSION

The standard protocol for oropharyngeal cancer is to give about 70Gy of radiation in 35 fractions @ 2Gy per fraction over 7 weeks with concurrent weekly or 3 weekly Cisplatin. The standard protocol for cervical cancer is to give 45-50Gy in 25 to 28 fractions at the rate of 1.8-2Gy per fraction over 5 to 5.5 weeks with concurrent weekly cisplatin at a dose of 40mg/m^2 followed by HDR brachytherapy to a dose of 6-7Gy per fraction for 3 to 4 fractions. The protocol for anal canal cancer is to give 59.4Gy in 33 fractions @ 1.8Gy per fraction over 6.5 weeks with concurrent Mitomycin (10mg/m^2 on day 1 and 29) and either 5-FU (1000mg/m^2 i.v on day 1-4 and 29-33) or Capecitabine (825mg/m^2 PO BID on each day of radiation, throughout the duration of radiation).

Further, certain toxicities like mucositis during head and neck radiotherapy, and proctitis or cystitis during pelvic radiotherapy can be seen in almost 100% of the patients receiving curative intent treatment in varying intensities. Important factors defining the grade of these toxicities include the volume of tissue exposed, treatment dose and technique, and individual patient predisposition. (3) These undesirable and painful acute toxicities of curative radiation therapy pose a significant challenge in the delivery of the planned radical dose of radiation leading to delayed or even incomplete treatment at times, which may compromise with the final outcome of these patients.

Therefore, any ways to decrease these side effects will definitely lead to decreased morbidity, increased treatment compliance and probably improved outcome at least in terms of quality of life. Less

toxicities will also ameliorate the fear associated with chemoradiotherapy and hopefully some people who do not take treatment because of these toxicities will undergo treatment.

Till date, the advent of conformal radiotherapy has been the most effective and proven way of reducing toxicities and thereby improving up on the results. (4) However, this requires linear accelerators, simulation CT Scans, treatment planning systems along with trained expertise which is not freely available in many of the underdeveloped and developing countries of the world. Reducing the dose of radiation and thereby the toxicities without compromising on the tumour control rate is another promising and affordable way to improve the outcome.

Personal experiences and published case reports bears testimony to the fact that there are some patients who have shown a complete prolonged disease control, even after being treated with a reduced dose of radiation for reasons varying from high grades of toxicities to inability of the patient to stay near radiation facility due to financial and family problems. Many recent studies have also shown that HPV associated squamous cell carcinomas of oropharynx, cervix and anal canal regions are more radiosensitive than similar cancers not associated with HPV and may be treated successfully with reduced radiation and chemotherapy doses. (5-7)

CONCLUSION

As our current clinical guidelines for the treatment of squamous cell carcinomas do not account for the status of HPV, the question remains whether patients with HPV-positive SCC at different subsites may achieve similar results with reduced treatments as with the standard treatment. Another question is whether we can use a same de-intensified chemoradiation protocol for all HPV associated squamous cell carcinoma. The above new insights may contribute to the development of dose prediction parameters, including HPV status and other biological markers which are specific to individual patients in the future. We need to push our research forward in this direction as it will be a big help for the poor cancer patients, who cannot afford the expensive new conformal radiotherapy techniques and the supportive treatment required to manage the toxicities of conventional and high dose radiation.

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