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Original Study

Effect of Fractionated Dose of Radiotherapy on Oral Mucosa in Head and Neck Cancer Patients: A Cytological Assessment

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Abstract

Background

Cancer therapy couples with it a plethora of complications of short and long term effects which can be so distressing that patient may tolerate only lower less–effective doses of therapy, may postpone treatments or will discontinue treatment entirely. Fractionated dose of radiotherapy coupled with therapy induce local or systemic infections due to high cellular turnover rates of the oral mucosa, diverse and complex microflora and trauma to oral tissues. Several mucosal abnormalities often results in epithelial and glandular destruction and inflammation, which can be so devastating that it may cause atypical changes on the area exposed to radiation. Thus, the aim of this study was to investigate the feasibility of using cytological evaluation to detect oral epithelial atypia among Head and Neck cancer patients receiving fractionated dose of radiotherapy.

Methods

Study was conducted on 125 head and neck cancer patients receiving radiotherapy. Subjects were divided into 5 study groups on the basis of fractionated dose of radiotherapy from 10th–50th fractions respectively. Mucosal changes were evaluated by exfoliative cytology and atypical changes and inflammatory cell infiltration were assessed.

Results

Without prior knowledge of the subjects’ group, oral epithelial atypia was detected with increase fractionated dose of radiation. Dense inflammatory infiltrate were identified in nearly all study groups irrespective of dose of radiotherapy.

Conclusion

Cytological atypia and inflammatory infiltrates were detected after exposure to radiotherapy.

Keywords

Atypia, cytology, oral mucosa, radiotherapy, inflammatory infiltrate.

Introduction

Head and neck cancer treatment mainly comprises of a combination of radiotherapy and surgery with an adjuvant concomitant chemotherapy recently. About two–thirds of patients with head and neck cancer present with local or regionally advanced disease and are usually treated with both surgery and radiotherapy or with multimodality treatment (incorporating radiotherapy and chemotherapy). These cancer therapies can thus lead to procession of complications which are complex, dynamic pathobiological processes that lower the quality of life and predispose patients to serious clinical disorders. The oral cavity and oropharynx are common sites for radiation–induced adverse effects. In 90–100% of patients whose irradiation fields include the oral cavity,

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some degree of oral complication will develop as a result. Oral complications of radiotherapy in the head and neck region occurs due to the deleterious effects of radiation, which affect not only the oral mucosa itself but also the adjacent salivary glands, bone, dentition, and masticatory musculature and apparatus. Most common adverse effects of radiotherapy includes mucositis, local or systemic infection, salivary gland dysfunction, taste alteration and pain, which later lead to secondary complications such as nutritional disorder, xerostomia or haemorrhage.

In Head and Neck cancer patient’s radiation dose needed for treatment depends upon the location and extent of tumor, and whether or not radiotherapy will be used on its own or in combination with other treatment options. A dose of 2 Gy per fraction five times per week delivered to most head and neck cancer patients up to a total dose of 64–70 Gy. Deleterious effects of radiotherapy on oral mucosa is related to the daily and total cumulative dose of radiation, the volume of irradiated tissue, and use of concurrent radiation–sensitising and mucositis–inducing chemotherapeutic drugs.

The exfoliative cytology is conventionally used for screening and diagnosis of oral mucosal lesions, it may also be applied and preferred over clinical assessment to monitor therapy related changes. Many reports have described various cytoplasmic and nuclear changes after radiation therapy. These changes include cellular enlargement, vacuolization, cytoplasmic granulation, nuclear enlargement, pyknosis, karyorrhexis, karyolysis, multinucleation, micronucleation, nuclear budding, and binucleation.

Effect of radiotherapy on oral mucosa depends on many factors such as dose fractions, concentrations and duration. So far none to very few studies have shown mucosa changes due to fractionated dose of radiotherapy treatment. Thus aim of the present study was to investigate the feasibility of using cytological evaluation to detect oral epithelial atypia amongst head and neck cancer patients receiving fractionated dose of radiotherapy.

Materials and Methods

In this study, the effects of fractionated doses of radiotherapy were assessed on oral mucosa by cytology, on 125 patients with the age range of 16–70 years who were undergoing radiotherapy at Jawaharlal Nehru Cancer Hospital and Research Centre, Bhopal (MP). The study group comprised of 125 head and neck cancer patients, 25 each were divided in a Group A–E receiving fractioned dose of radiotherapy from 10th –50th fractions of doses each respectively, distribution of study groups is given in Table 1. Oral cancer patients, with bad oral hygiene, tobacco users and alcohol dependence are excluded from the study.

Sample Collection

Patients in each group were subjected to clinical assessment with prior consent from concerned authority followed by taking cytological smear. Cytological smears of exfoliative cells were collected from buccal mucosa (covering both cheeks) by brush and the obtained materials were directly smeared on clean glass slides and immediately fixed in 95% ethyl alcohol, while they were wet, and sent to the cytopathology laboratory for further processing.

Assessment of smears

The smears were stained using the Haematoxylin and eosin (H&E) staining method. Strict quality control

<table>
<thead>
<tr>
<th>Class of Cytology Smear</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Normal)</td>
<td>Indicates that only normal cells were observed</td>
</tr>
<tr>
<td>Class II (Atypical)</td>
<td>Indicates the presence of minor atypia but no evidence of malignant changes</td>
</tr>
<tr>
<td>Class III (Intermediate)</td>
<td>In between cytology that separates cancer from non-cancer diagnosis. The cells display wider atypia that may be suggestive of cancer, but they are not clear cut.</td>
</tr>
<tr>
<td>Class IV (Suggestive of cancer)</td>
<td>A few cells with malignant characteristics or many cells with borderline characteristics.</td>
</tr>
<tr>
<td>Class IV (Positive for cancer)</td>
<td>Cells that are obviously malignant.</td>
</tr>
</tbody>
</table>

Table 2: Different Class of cytological atypia.
measures were applied to increase the reliability and reproducibility. To serve as positive control 5 smears from histopathologically diagnosed oral cancer patients were taken. Smears were further examined under high (40X) power using a light microscope to assess the quality of staining. All included smears showed satisfactory staining quality and to avoid the assessment bias, cytological smears were labelled in such a way that the examiner was blinded to the groups of each subject.

Smears were graded from Class I–V on the basis of criteria given elsewhere. (13) (Table 2). Smears were divided into different classes on the basis of atypical features which mainly included: nuclear enlargement associated with increase nuclear cytoplasmic ratio, hyperchromatism, prominent nucleoli, irregular nuclear membranes and bi or multinucleation, scant cytoplasm, and variation in size and/or shape of the cells and nuclei. Along with assessing atypia, inflammatory cell infiltration were also assessed and categorised as minimal, moderate and dense respectively. Radiotherapy associated mucosal changes relating with fractionated doses were evaluated on the basis of atypia and were tabulated on excel sheet for analysis.

**Results**

**Oral Mucosal changes among different study groups**

In Study Group A; 12 (48%), 10 (40%) and 3 (12%) patients were found to have Class I, II and III cytological features respectively and none of the patients showed Class IV and V features. In Study Group B, 13 (52%), 6 (24%), 4 (16%), 2 (8%) were found to have Class I, II, III and IV cytological features respectively with no Class V features. In Study Group C; 10 (40%), 7 (28%), 3 (12%), 4 (16%) and 1 (4%) were found to have Class I, II, III, IV and V cytological features respectively. In Study Group D; 7 (28%), 3 (12%), 4 (16%), 6 (24%) and 5 (20%) were found to have Class I, II, III, IV and V cytological features respectively. In Study Group E; 2 (8%), 2 (8%), 4(16%), 12 (48%) and 5 (20%) were found to have Class I, II, III, IV and V cytological features respectively Fig: 1–3. Results obtained thus showed that cytological atypical features increase with increasing dose of radiation and fractions. Distribution of cytological changes with respect to therapy is given in Table 3.
Inflammatory cell infiltration among different study groups

With reference to the relation between therapy and inflammatory infiltrates, in Group A; 5(20%) and 20(80%) showed moderate and dense inflammatory cell infiltration. In Group B, 2(8%), 7(28%) and 16(64%) showed mild, moderate and dense inflammatory cell infiltration respectively. In Group C, 6(24%) and 19(76%) showed moderate and dense inflammatory cell infiltration respectively. In Group D, 1(4%), 3(12%) and 21(84%) patients showed mild, moderate and dense inflammatory cell infiltration respectively. In Group E, 1(4%) and 24(96%) patients showed moderate and dense inflammatory cell infiltration respectively. Thus on the basis of above findings in respect to inflammatory infiltration and therapy it can be concluded that irrespective of fractionation of doses, inflammatory cell infiltration is found to be dense among all study groups. Distribution of inflammatory cell infiltration with respect to therapy is given in Table 4.

Table 3: Distribution of cytological changes with respect to fractionated dose of Radiotherapy

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Class I (%)</th>
<th>Class II (%)</th>
<th>Class III (%)</th>
<th>Class IV (%)</th>
<th>Class V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>12 (48%)</td>
<td>10 (40%)</td>
<td>03 (12%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group B</td>
<td>13 (52%)</td>
<td>06 (24%)</td>
<td>04 (16%)</td>
<td>02 (08%)</td>
<td>-</td>
</tr>
<tr>
<td>Group C</td>
<td>10 (40%)</td>
<td>07 (28%)</td>
<td>03 (12%)</td>
<td>04 (16%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Group D</td>
<td>07 (28%)</td>
<td>03 (12%)</td>
<td>04 (16%)</td>
<td>06 (24%)</td>
<td>65 (30%)</td>
</tr>
<tr>
<td>Group E</td>
<td>02 (08%)</td>
<td>02 (08%)</td>
<td>04 (16%)</td>
<td>12 (48%)</td>
<td>65 (30%)</td>
</tr>
</tbody>
</table>

* n(%) = Total no. of cases and prevalence in percentage

Table 4: Distribution of inflammatory cell infiltration with respect to fractionated dose Radiotherapy

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Mild n (%)</th>
<th>Moderate n (%)</th>
<th>Dense n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>-</td>
<td>05 (20%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Group B</td>
<td>02 (08%)</td>
<td>07 (28%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Group C</td>
<td>-</td>
<td>06 (24%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Group D</td>
<td>01 (04%)</td>
<td>03 (12%)</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>Group E</td>
<td>-</td>
<td>01 (04%)</td>
<td>24 (96%)</td>
</tr>
</tbody>
</table>

* n(%) = Total no. of cases and prevalence in percentage

Discussion

Treatment for head and neck cancers primarily involves 3 modalities: surgery, radiation, and chemotherapy, administered alone or in combination. Radiation therapy (RT) alone is the most common treatment for certain types of head and neck cancers, such as cancer of the nasopharynx, larynx, and oropharynx.Fractionation is the term used for radiation schedule and standard fractionation refers to radiation taken once/week. Schedules used to intensify treatment for more advanced tumours are known as accelerated fractionation or hyperfractionation. Most HNCC are treated with 2 Gy/fraction delivered five times/week, up to a total dose of 64–70 Gy. Effects of tumoricidal doses of radiation on healthy oral mucosa are divided into acute type, which occurs during treatment or shortly afterwards (2 – 3 weeks) and chronic types may occur months or even years after therapy.

Prevalence of oral complications from drug and radiation due to cancer therapy lies in the limited literature and potentially unreported. Cancer therapy adverse effects results from two mechanism: a direct effect of the drug or irradiation on the oral mucosa (direct stomatotoxicity) or an indirect result of myelosuppression from drug or radiation therapy (indirect stomatotoxicity). The direct inhibitory effects of radiotherapy on DNA replication and mucosal cellular proliferation result in a reduction in the renewal capacity of the basal epithelium and results in mucosal atrophy, collagen breakdown, ulceration, thrombocytopenia and leukopenia disturbing the haemostatic and immune–mechanisms of the patient. Whereas the indirect side effects in turn are due to collateral impact upon the oral cavity such as bone marrow suppression, loss of tissue immune cells, and loss of salivary protective elements.

Oral exfoliative cytology has now been widely accepted as a tool in the early diagnosis of atypia or malignancy. To assess the effects of cancer therapy, exfoliative cytology is used as a simple and cost effective method. This method might be ideal for screening the risk population. In this study, cytological atypia was quantified in smears obtained from patients exposed to fractionated dose of radiation therapy. So far few to none of the studies have been done using oral exfoliative cytology for the assessment of cytological atypia in smears obtained from patients exposed to fractionated dose of radiotherapy.

Present study showed increase class of cytological atypia with advancement of fractions of radiations. These findings propose that radiotherapy along with amount of fractions of radiation given, may be associated with oral cytological atypia. Previous studies reveal occurrence of
oral cytological changes in head and neck cancer patients receiving therapy, which is in accordance with our study. (11,12,19–21) Thus suggesting adverse effects of radiation on oral mucosa by several factors including: high cellular turnover rates of the oral mucosa, a diverse and complex microflora, and trauma to oral tissues during normal oral function.

Present study showed increase amount of dense inflammatory cell infiltration which is in accordance to a study made by Ahmed et al which showed increase amount of inflammation in response to cancer therapy. (21) These findings thus suggested that radiation induce inflammatory changes in buccal mucosa. This increase in chronic inflammatory infiltrates may be due to the fact that the patients were immuno-compromised, and were susceptible to different infections.

Mechanism underlying therapy–induced cytological atypia should be further evaluated by doing screening on more number of subjects and future studies should be done to underline the more appropriate pathogenesis through various molecular and karyotyping technique. Cytological changes induce by therapy can also be used to assess therapy response in such cancer patients, so a standard assessment tools and optimal method should be developed. Concurrent use of Radiotherapy and Chemotherapy these days considered to increase local control by overcoming radio–resistance and to eradicate systemic micro–metastasis may also increase the local side effects, especially mucositis, which further need to be evaluated cytologically. (22) Radiotherapy induced adverse effects may be minimized by introducing prior biological response modifiers, cytoprotective drugs, tissue-sparing radiation technique and surgical advances.

Conclusion

Radiotherapy can greatly damage the head and neck region as a result of cancer treatment. A complex and dynamic pathobiological process ensues that diminishes patient’s quality of life and often leads to serious clinical sequelae. Oral exfoliative cytology can be used to assess the mucosal effects of radiotherapy and can also be used to evaluate the therapy response as it is non–invasive technique and can be applied on a larger group of population. Within the limitations, present study shows the devastating effects of radiotherapy in different fractions thus aids in minimizing the consequences resulting from radiotherapy in head and neck cancer patients.

References


