Original Paper

SHORT COURSE PALLIATIVE RADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

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Abstract

This prospective cohort study was conducted at the Combined Military Hospital, Dhaka during January 2003 to December 2005. Thirty patients with locally advanced stage III and stage IV squamous cell carcinoma of head and neck were treated with a short course palliative radiotherapy (30 Gray in 10 fractions over 2 weeks). All (100%) patients with pain and 90% of patients with dysphagia, dyspnoea and disturbed sleep had greater than 50% relief in symptoms after radiotherapy. Dysphonia and cough were satisfactorily relieved in more than 60% of cases. Eight of 30 lesions in this study had complete response; 14 lesions had a partial response; 4 lesions had no response; 2 lesions progressed under treatment. Response could not be assessed in two patients. Acute and late reactions were acceptable. After palliative radiotherapy 8(27%) patients were eligible for dose escalation and received further radiotherapy upto radical dose equivalent. It was concluded that short course palliative radiotherapy regimen evaluated is an effective treatment modality for sustained symptoms relief with good response rates and acceptable toxicity in locally advanced head-neck cancer.

Key words: Palliation, radiotherapy, short course, head and neck cancer.

Introduction

Head and neck cancer encompass a diverse group of tumour that frequently is aggressive in their biological behaviour. Risk factor for head and neck cancer include tobacco and alcohol use, viral infection and environmental exposure. The incidence of head and neck tumours correlates most closely with the use of tobacco. The staging of primary mucosal tumours of that area varies with the anatomic location. However staging system for metastases and stage groupings are nearly uniform for all mucosal sites. Prognosis correlates strongly with stage of diagnosis. For patient with locally advanced disease at time of diagnosis (i.e, stage III and IV disease), survival drops markedly. In general, head and neck tumour may be treated using a single modality for early-stage disease (stage I or II) but may require multimodality therapies for advanced disease (stage III and IV)[1].

Squamous cell carcinoma of head and neck (SCCHN) comprises over 25% of the overall cancer burden in some of the developing countries. A large majority of them present in advanced incurable stage which carries a poor prognosis with patients dying of uncontrolled loco-regional disease[1]. Short course (hypo-fractionated) radiotherapy (high dose per fraction, leading to short duration) is an approach that could be pursued in this subset of patients given the need to balance quick and effective palliation on one side and limit treatment-related toxicity on the other. Despite a plethora of high-quality evidence on the benefits of short course palliative radiotherapy in patients with advanced solid tumors, there is shortage of such data in advanced SCCHN. There is a paucity of guidelines in the existing literature regarding the optimal palliative regimen for these patients with inadequate information on time, dose, and fractionation[2]. Practices have ranged from using a short course of large daily fractions for achieving palliation to delivering conventionally fractionated radical doses of 60-70 Gy in the hope of prolonging the duration of palliation[3-7]. It is debatable whether a course of prolonged radiotherapy identical to curative schedules with high toxicity is logical or not[3,5].

The present study was carried out to evaluate the outcome of short course Palliative radiotherapy (PRT) in patients with locally advanced SCCHN.

Materials and Methods

This prospective cohort study was conducted at the Combined Military Hospital, Dhaka during January 2003 to December 2005.The study population consisted of 30 locally advanced stage III and stage IV SCCHN.

Eligibility criteria: The eligibility criteria were biopsy-

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proven squamous ell carcinoma of head neck, stage IVB disease, i.e., surgically not resectable due to disease extent (e.g., infratemporal fossa extension, carotid invasion, prevertebral fascia invasion, etc. or fixed/fungating neck nodal masses), stage IVA or III disease with poor performance status (Karnofsky performance status ranged from 50 to 70), no previous history of surgery, radiotherapy or chemotherapy, no recurrent disease, non-nasopharyngeal, paranasal sinuses (PNS), salivary gland and thyroid gland primaries and no previous history of cancer.

Pretreatment evaluation and symptoms: These patients were previously staged and a decision was made in the Multidisciplinary Joint Clinic for treatment with palliative radiotherapy as a single modality. Patient and family were explained by the team regarding the advanced and incurable stage of disease and the likely short duration benefit of palliative irradiation was discussed and written informed consents were taken. Baseline symptoms were assessed using a questionnaire incorporating a 11 point numerical scale[8] for scoring pain, dysphagia, dysphonia, cough, insomnia and dyspnoea. Symptoms were scored on a scale of 0-10 and graded as mild (score 1-3), moderate (4-6) and severe (>6). Analgesics were prescribed in accordance with the WHO pain ladder[9]. Antitussive and sedatives were prescribed for relief of cough and insomnia.

Treatment plan: External beam radiotherapy was delivered to a dose of 30 Gy in 10 fractions over 2 weeks, each fraction of 2 Gy per day. The field size was kept conservative in order to encompass gross primary and nodal disease with 1-1.5 cm margins. Prophylactic nodal irradiation was not undertaken. The plan was to limit the volume of normal tissue in order to prevent excessive morbidity. All patients were treated on 6 MV linear accelerator machine with appropriate immobilization using bilateral oppose open or anterolateral wedged fields, once daily for five days a week.

Follow-up and recordings: Primary end point of the study was symptom relief in the fourth week after the end of radiotherapy and secondary endpoints were objective response and toxicity. All patients were reviewed at least once weekly or more frequently during radiotherapy for assessing toxicity. At each review, patients were specifically asked regarding the percentage of symptom relief as compared to baseline. Final symptom relief for the purpose of this study was assessed at the completion of radiotherapy. Tumor response at first follow-up (at 6 weeks) after the completion of treatment was documented for reporting.

A provision was made in this study that patient achieving more than 50% symptom relief and partial response at primary/nodal sites (objective regression by 50%) and in a good physical condition (able to maintain daily activities and oral intake) at 01 month after PRT course, would be advised further radiotherapy for a curative intent. The further radiotherapy was delivered by similar radiation portals, at 2 Gy per fraction, to achieve a total radiobiologically equivalent dose of 66 Gy and the spinal cord was shielded at 44 Gy equivalents. This was calculated by the time-dose-fraction (TDF) method taking into account the dose-fraction schedule of PRT and the subsequent gap in days[10].

Primary and nodal tumor response was noted as partial response (PR), complete response (CR), stable disease (SD), progressive disease (PD) or not evaluative (NE) according to the standard WHO criteria. Radiation reactions were also evaluated as per standard world health organization (WHO) criteria[11].

Results

The study group had 22 male and 8 female patients with a mean age of 55 years and mean Karnofsky performance status (KPS) of 60. The primary tumors were mostly (37%) located in the larynx (table-I) and least in alveolus. Seventy percent patient reported with Stage IV disease (table-II).

Table-I: Distribution of cases by site (n = 30).

Site	Number of cases	Percentage
Larynx	11	37
Hypopharynx	08	27
Oropharynx	07	23
Tongue	03	10
Alveolus	01	03
Total	30	100

Table-II: Distribution of cases by stage (n = 30).

Site	Number of cases	Percentage
Stage III	09	30
Stage IV	21	70
Total	30	100

Histopathologically all causes were squamous cell carcinoma. Pain was present in 80%, while dysphagia, insomnia, cough, dysphonia and dyspnoea were reported by 70%, 66%, 46%, 43% and 30% patients respectively. Five patients required nasogastric intubation for absolute dysphagia. Pain and other symptoms were graded as mild, moderate and severe (table-III).

Table-III: Symptoms before radiotherapy (n=30).

Symptoms	Mild	Moderate	Severe	Total
Pain	09	11	04	24
Dysphagia	02	12	07	21
Insomnia	02	08	10	20
Cough	05	05	04	14
Dysphonia	03	07	03	13
Dyspnoea	-	04	05	09

All 24 patients had greater than 50% pain relief (table-IV). No patient required narcotic analgesics. All 9 patients with dyspnoea had >75% relief. 19/21, 9/14 and 8/13 patients had >50% relief of dysphagia, cough and dysphonia respectively. As a result of symptom relief, 18/20 patients could sleep better. Eight of 30 lesions in this study had complete response; 14 lesions had a partial response; 4 lesions had no response; 2 lesions progressed under treatment. Response could not be assessed in two patients as they didn't attend for follow-up (table -V).

Table-IV: Relief of symptoms after palliative radiotherapy.

Symptoms	< 50% relief	50 - 75% relief	> 75% relief
Pain (n = 24)	-	09	15
Dysphagia (n = 21)	02	12	07
Insomnia (n = 20)	02	08	10
Cough (n = 14)	05	05	04
Dysphonia (n = 13)	05	06	02
Dyspnoea (n = 9)	-	-	09

Table-V: Objective response after palliative radiotherapy (n = 30).

Response	Number of patients	Percentage
Complete response	08	26
Partial response	14	47
Stable disease	04	13
Progressive disease	02	07
Response not evaluative	02	07
Total	30	100

Table-VI: Radiation reactions (n = 30).

Response	Number of cases	Percentage
Mucositis Grade - 1	19	63
Mucositis Grade - 2	11	37
Total	30	100

Table-VII: Extent of Radiotherapy (n = 30).

Radiotherapy	Number of cases	Percentage
Palliative radiotherapy only	22	73
Palliative radiotherapy followed by dose escalation	08	27
Total	30	100

At the end of PRT 19 patients had grade 1 and 11 patients had grade 2 mucositis. No patient had grade 3 mucositis (table-VI). After PRT a total of 8(27%) patients were eligible for dose escalation and received further radiotherapy up to radical dose equivalent (table-VII). Long term follow up was difficult since many patients were from distant areas. The follow up period ranged from 2 to 9 months with a median duration of 3 months. Of the 21 patients who returned for follow up, relief of pain and other symptoms persisted for at least 3 months. During this period 2 patient died, 4 patients developed new complaints; two had cough and the other two had dyspnoea. Two patients came back with progression of disease 6 months after completion of radiation.

Discussion

In the developing world, approximately 75% of patients with head and neck malignancies present with locally advanced disease[12]. Management of loco-regionally advanced SCCHN with curative intent has evolved considerably over time with active research, volumes of literature, large randomized control trials and meta-analyses supporting evidence-based guidelines. However, there has been very little interest in the palliative treatment of head and neck cancer in patients having incurable disease, poor performance status or significant co-morbidity limiting radical treatment. Attempts to cure such patients with aggressive multimodality treatment or intense radiotherapy regimens have not succeeded till date[13-15]. The 5-year survival even with aggressive multimodal approach is reported to be <20%, with a median survival under 12 months[14-16]. The need for significant supportive care due to highly acute morbidity associated with aggressive multimodality treatment coupled with poor compliance results in suboptimal outcome[17] and warrants caution in clinical practice. Loco-regionally advanced SCCHN represents a significant treatment challenge due to close proximity of tumor to several critical normal tissues, such as the spinal cord, salivary glands, mandible, nerves, major blood vessels and the organs of speech, swallowing, hearing and respiration. Common distressing symptoms include pain, dysphasia, dyspnoea, dysphonia, cough and disturbed sleep. There is sparse literature on palliative regimens for symptom control in advanced incurable SCCHN which precludes the generation of consensus guidelines and recommendations. It would thus seem prudent to explore the role of palliative radiotherapy for durable symptom relief with acceptable morbidity[18].

Untreated patients with advanced SCCHN succumbed to their disease in 3-6 months. In a large cohort of 808 untreated head and neck cancer patients (91% stage IV) followed-up longitudinally, the median survival was approximately 100 days only[5]. However, curative intent treatment with aggressive multimodality treatment has not shown clear benefit in patients with advanced incurable disease and palliative regimens seem justified[19-22].

There is a large body of high-quality evidence on the benefits of short course PRT in advanced solid tumors such as lung cancer, brain metastases, and bone metastases. However, such evidence is lacking for loco-regionally advanced incurable SCCHN. Until recently, short course PRT regimens had not been tested adequately in this patient population, with data being limited to retrospective series, case-control studies,

limited single-institution experiences, and small prospective trials with varying dose-fractionation schedules[23].

There has been only one small randomized controlled trial of 64 patients with advanced inoperable SCCHN wherein patients were randomized to either conventional radiotherapy (60-70 Gy/30-35 fractions/6-7 weeks) or short-course hypofractionated radiotherapy (4Gy per fraction, 40-48 Gy/10-12 fraction/2-3 weeks, 4 fractions per week). The palliative benefits of radiation were comparable in both the arms and there was no reported difference in acute or late toxicity. In recent times, several novel radiotherapy regimens have been prospectively tested in the clinic with contemporary methodology and appropriate endpoints supporting the use of palliative radiotherapy[24]. The present study tried to quantify the benefit of a short course of radiotherapy for locally advanced SCCHN, delivering a reasonably high biological dose to achieve sustained local control and symptom relief while keeping the overall treatment time relatively short. We chose a short course hypo-fractionated regimen of 30 Gy in 10 fractions which is a commonly used and well tolerated regimen in PRT of other malignancies.

In this study, the two-week schedule provided greater than 50% symptom relief in 90% of patients who had pain, dysphasia, dyspnoea and disturbed sleep. Cough and dysphonia were relieved in more than sixty percent of cases. Overall response rate was 73%. Radiation toxicities were mild (grade 1- 2). After PRT 8(27%) patients were eligible for radical radiotherapy. Mohanti et al.[25] carried out a study on 505 patients with stage IV HNSCC, gave a uniform regimen of 20 Gy in 5 fractions, once daily over 1 week. They reported good symptom relief (P50%) in 57% for pain; 53% for dysphagia; 57% for hoarseness; 47% for otalgia; 76% for respiratory distress; and 59% for cough. At 1-month assessment, 189 (37%) achieved a partial response and had ambulatory physical state suited for further curative-dose radiotherapy. The main acute toxicity of palliative radiotherapy was patchy oro-pharyngeal mucositis and dermatitis. Median overall survival with palliative radiotherapy was 200 days. The 153 patients who went on to receive further curative-dose radiotherapy had significantly better overall survival (400 days). In the present study, symptoms control fairly correlates with this study. Radiation toxicities in the present study are less, which may be due to lower radiation dose per fraction. However, lower percentage of patients was eligible for radical radiotherapy in the present study, which may be due to inclusion of higher number of low performance status patients.

Recently, a multicenter Australian study[26] reported on 35 patients treated with a novel hypofractionated radiotherapy regimen (30 Gy in 5 fractions, 2 fractions per week, at least 3 days apart, with an additional boost of 6 Gy for limited volume disease). The overall objective response rate was 80%. The median time to progression and death 3.9 months and 6.1 months, respectively, with 7 (20%) patients surviving beyond a year. Overall quality of life improvement and symptom control were reported in 13 (63%) and 14 (67%) of the 21 assessable patients. Grade 3 mucositis and dysphagia were seen in 26% and 11% patients, respectively. The overall objective response and quality of life improvement and symptom control in the present study are comparable with this study. However, radiation toxicities in the present study are less, which may be due to avoiding additional boost of radiation. Due to the palliative nature of treatment, late tissue morbidity is not a significant issue in such patients treated with short course radiotherapy regimens. Significant chronic xerostomia and subcutaneous fibrosis on analyzable patients were acceptable and were not dose-dependant as patients receiving escalated doses did not have any worse late effect as compared to patients receiving 30 Gy.

The issue of stringent follow-up in advanced incurable disease treated with palliative intent is an important one and the problems of communication, logistics, resources, and geography in a developing country need to be recognized[27]. Thus post-therapy, a large majority of patients were offered only the best supportive care which they were encouraged to take at their native place.

Conclusion

A short course palliative radiotherapy can effectively restrain growths, relieve symptoms, reduce the need of continued supportive care and overall improves quality of patients' life in locally advanced head and neck cancers and helps in selecting patients for dose escalation. Short course palliative radiotherapy may be offered for patients with locally advanced head and neck cancer, who are unsuitable for other anticancer measures as well as long duration conventional palliative radiotherapy. Further large scale multicenter studies in this field are urgently demanded.

References

1. Ridge JA, Glisson BS, Lango MN, Feigenberg S. Head and neck tunors. In : Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ, editors. Cancer management : A multidisciplinary approach. 12th ed. New York: UBM Medica LLC; 2009.p.1-6.
2. Senn HJ, Glaus A. Supportive Care in Cancer - 15 years thereafter. Support Care Cancer 2002; 10:8-12.
3. Carvalho AL, Salvajoli JV, Kowalski LP. A comparison of radiotherapy or radiochemotherapy with symptomatic treatment alone in patients with advanced head and neck carcinomas. Eur Arch Otorhinolaryngol 2000; 257:164-167.
4. Corry J, Peter LJ,Costa ID, et al. The QUAD SHOT- A phase II study of palliative Radiotherapy for incurable head and neck cancer. Radiother Oncol 2005;77:137-42.

5. Ghoshal S, Patel F, Mudgil N, Bansal M, Sharma S. Palliative radiotherapy in locally advanced head and neck cancer: A prospective trial. Indian J Palliat Care 2004;10:19-23.
6. Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000; 36:1032-1037.
7. Chen MA, Vaughan A, Narayan S, Vijayyakumar S. Palliative radiotion therapy for head and neck cancer: Towards an optimal fraction scheme. Head and Neck 2008; 30:1586-1591.
8. Price DD, Harkins SW. Psychosocial approaches to pain measurement and assessment. In: Turk D, Melzac R, editors. Handbook of Pain Assessment. New York: Guildford Press; 1992. p. 165-179.
9. World Health Organization. Cancer pain relief and palliative care, report of a WHO expert committee. WHO Tech Rep Ser 1990; 804: 1-73.
10. Hall EJ. Radiobiology for the radiologist. 3rd ed. Philadelphia : PA Lippincott; 1998. p 239-258.
11. World Health Organisation. WHO Handbook for reporting results of cancer treatment. Geneva Offset Publication 1979; 48: 1-42.
12. Mohanti BK, Sharma DN, Lad P, Bissau BM. Palliative therapy. In: Rath GK, Mohanti BK, editors. Textbook of Radiation Oncology principles and practice. 1st ed. New Delhi: Churchill Livingstone; 2000. p. 201-212.
13. Dobrowsky W, Naude J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Radiother Oncol 2000; 57:119-124.
14. Fu KK, Clery M, Ang KK, Byhardt RW, Maor MH, Beitler JJ. Randomized phase I/II trial of two variants of accelerated fractionated radiotherapy regimens for advanced head and neck cancer: results of RTOG 88-09. Int J Radiat Oncol Biol Phys 1995; 32:589-597
15. Grau C, Prakash Agarwal J, Jabeen K, et al. Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial. Radiother Oncol 2003; 67:17-26.
16. Vikram B. Cancers of the head and neck region in developing countries. Radiother Oncol 2003; 67:1-2.
17. Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarizing adverse events of cancer treatment by the Radiation Therapy Oncology Group. Lancet Oncol 2007; 8:613-624.
18. Agrawal JP, Nemade B, Murthy V,et al. Hypofractioned , Palliative radiotherapy in locally advanced head and neck cancer. Radiother Oncol 2008;89:51-56.
19. Basal A, Adam J, Panzarella T, et al. Radiotherapy for brain metastases: defining palliative response. Radiother Oncol 2001; 61:71-76.
20. Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Radiother Oncol 2002; 64:275-280.
21. Hayter CR, Huff-Winters C, Paszat L, Youssef YM, Shelley WE, Schulze K. A prospective trial of short-course radiotherapy plus chemotherapy for palliation of dysphagia from advanced esophageal cancer. Radiother Oncol 2000; 56:329-333.
22. Galiana R, Boladeras A, Mesia R, et al. Twice-a-day radiotherapy for head and neck cancer: the Catalan Institute of oncology experience. Radiother Oncol 2002; 64:19-27.
23. Talapatra K, Gupta T, Agarwal J, Lascars S, Shrivastava S, Dinshaw K. Palliative radiotherapy in head and neck cancers: evidence based review. Indian J Palliat Care 2006; 12:44-50.
24. Weissberg JB, Pillsbury H, Sasaki CT, Son YH, Fischer JJ. High fractional dose irradiation of advanced head and neck cancer. Implications for combined radiotherapy and surgery. Arch Otolaryngol 1983; 109:98-102.
25. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S. Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study. Radiother Oncol 2004;71:275-80.
26. Porceddu SV, Rosser B, Burmeister BH, et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment-hypo trial. Radiother Oncol 2007; 85:456-462.
27. Burns L, Chase D, Goodwin WJ. Treatment of patients with stage IV cancer: do the ends justify the means?. Otolaryngol Head Neck Surg 1987; 97:8-14.