Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

Original research article

Locally unresectable ongoing head and neck cancer's, reirradiation with concurrent chemotherapy

[1]Dr. Vikash Babu G., [2]Dr. Mounika N., [3]Dr. Vijay Kumar M.

[1]Assistant Professor, Department of Radiation Oncology, Kamineni Academy of Medical Sciences and Research Centre, L.B. Nagar, Hyderabad, Telangana, India

[2]Senior Resident, Department of Radiation Oncology, Kamineni Academy of Medical Sciences and Research Centre, L.B. Nagar, Hyderabad, Telangana, India

[3]Professor & HOD, Department of Radiation Oncology, Kamineni Academy of Medical Sciences and Research Centre, L.B. Nagar, Hyderabad, Telangana, India

Corresponding Author:
Dr. Vijay Kumar M

Abstract

Background and objective: To evaluate the rates of immediate locoregional response and acute toxicities associated with the reirradiation and oral capecitabine treatment of locoregionally recurring, unresectable squamous cell carcinomas of the head and neck.

Method: Forty patients met the study's inclusion criteria and were randomly assigned to receive re-irradiation for previously treated inoperable and/or irresectable tumours using conventional fractionation (2GY per fraction, 5 days a week, up to a total cumulative dose of 120GY, including the prior RT dose) and Capecitabine (500 mg once daily) during treatment.

Result: The average time between the first and second radiation treatment sessions was 20 months. Our experiment showed an overall 90% response rate, with 20 patients showing a complete response, 16 showing a partial response, and 4 showing stable disease. Fifteen patients experienced grade 2 toxicity, and thirteen individuals experienced grade 3 toxicity in the pharynx. A median cumulative lifetime dosage of 116 GY was found.

Conclusion: In this prospective single institutional trial, reirradiation and chemotherapy are being combined for the first time to treat recurrent SCCHN. We conclude that chemotherapy-assisted reirradiation up to a total dose of 60GY is feasible and efficient in carefully selected patients with manageable initial toxicities.

Keywords: Head and neck cancer, chemotherapy, SCCHN, radiotherapy, T. Capecitabine

Introduction

Cancer is an intricate genetic disease that develops from a number of different mutations. As a result of these genomic alterations, proto-oncogenes are turned on and tumour suppressor genes are silenced. Squamous cell carcinoma of the head and neck (HNSCC) has been connected to a number of different genes and genetic processes. Some estimates place the percentage of cancers where genetics have a major role at 10%. Relatives of patients with head and neck cancer have an increased risk of acquiring cancer themselves [1, 2, 3] and research has shown that oral cancer tends to cluster in certain ethnic groups. Multiple studies have found that the risk of developing oropharyngeal cancer increases thrice for people with a first-degree relative who has had HNSCC. India is a rapidly developing country, and as a result, the medical and scientific communities there have made tremendous strides in recent years. Non-infectious diseases are currently the leading cause of death and illness worldwide. When compared to other types of illness, infectious diseases are decreasing in prevalence. Cancer is becoming increasingly common among Indian adults. Head and neck cancers tend to strike both the elderly and the young. 3 Some cancers are more likely to develop in certain environments or at specific latitudes. Population density varies widely and significantly [3, 4, 5].

The occurrence is still high in the developed countries. Head and neck cancer remains more common than in industrialised countries. The most common types of head and neck cancers in India are those of the oral cavity and pharynx. Oral and pharyngeal cancers are the fourth most common cancer in women and the third most common cancer in men in developing countries. The increased number of cases of head and neck cancer can be directly attributed to the increased use of tobacco products [5, 6, 7]. Increases in cancer diagnoses lead to an increase in fatalities. Oropharyngeal and buccal mucosa cancers are more common in tobacco users. Morbidity from chewing tobacco and betel nuts reduces one's standard of living. Use of tobacco products and alcohol can affect the development of cancers of the head and neck.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

Pipe and cigar smokers are more likely to contract oral and lip cancers because of the high concentration of tobacco smoke in their mouths. In conclusion, the two lakh cases of head and neck cancer diagnosed in India each year can be attributed to low socioeconomic status, oral tobacco use in various forms, the use of lime with betel nuts and betel leaf, smoking, and alcohol intake [8, 9, 10].

Local recurrence is responsible for the majority of treatment failures and 50-60% of patient deaths in patients with head and neck cancer. These tumour recurrences are also associated with poor symptom management and a drastically diminished quality of life. Given that the majority of recurrences happen during the first two years after primary treatment and that 80% of recurrences occur in previously high dose irradiated areas, it is obvious that treating these recurrences is a challenging therapeutic challenge. If these tumours are resectable, surgical removal is the best option, albeit survival chances vary widely depending on where the cancer originated. Surgery is often irradical with close or positive margins because to the location and size of the tumour. Radiation increases the risk of morbidity because it causes changes in tissue that impede tissue healing. Only 15-25% of patients will be able to undergo salvage surgery due to the severity of the disease, medical contraindications, or patient rejection, and radiation-induced changes that hamper healing. Palliative chemotherapy is only used for unresectable cases of head and neck cancer that have already been treated with radiotherapy. This approach has only offered minimal palliation, with median survival times ranging from 5 to 9 months [11, 12, 13].

With solely supportive care, the median survival time for patients is a dismal 3-5 months. Therefore, patients with previously radiotherapy-treated, unresectable squamous cell carcinoma of the head and neck (SCCHN) have few options for salvage therapy. It's important to remember that even in the face of a shrinking tumour, one's quality of life may improve. The median survival time with only chemotherapy is less than six months. Therefore, new therapeutic approaches are needed. The agent selected must improve the efficiency of reirradiation without creating undue health risks. Capecitabine is an orally administered medication that has shown outstanding efficacy when used in conjunction with radiotherapy. The enzyme thymidine phosphorylase is essential for the conversion of capecitabine into its active metabolite, and its expression is higher in tumours than in healthy tissue. As a result of radiation upregulating thymidine phosphorylase expression in tumours, capecitabine's local action is enhanced in irradiated cancer regions. For these reasons [13, 14], capecitabine makes for an excellent combination partner in the pursuit of a topographically limited sensitising impact inside the irradiation area.

Material and Method

Patients with previously treated locally recurrent unresectable squamous cell carcinomas of the head and neck were enrolled in this prospective single-arm research between June 2022 and May 2023 at Department of Radiation Oncology, Kamineni Academy of Medical Sciences and Research Centre, L.B. Nagar, Hyderabad, Telangana, India. We included 40 individuals who had squamous cell carcinomas diagnosed in our clinic and confirmed by histology. After receiving approval from our institution's ethics board to begin enrolling patients, we immediately set out to do so. All patients who participated in the trial gave their informed consent.

Inclusion criteria

Patients must meet the following criteria to be eligible for this study.

- Recurrent squamous cell carcinoma of the head and neck as confirmed by biopsies.
- Primary tumour sites: oral cavity, oropharynx, hypopharynx, larynx.
- No evidence of distant metastases.
- Age 18-60 years.
- ECOG performance Status 2.
- Ineligible for definitive surgical resection.
- Anticipated cumulative spinal cord dose will be limited to 50GY.
- Maximum prior RT 75.

Exclusion criteria

- Non-squamous histology.
- Nasal tumours, paranasal sinus tumours, nasopharyngeal tumours and salivary gland tumours.
- Patients who refuse chemotherapy at any stage during treatment.
- Undergone treatment for any other form of cancer.
- Have insufficient kidney, liver and bone marrow reserves.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

Result

Table 1: Age Distribution

Age Group	No. of Patients
30-40	9
40-50	15
50-60	13
60-70	3

The age groups 40-50 and 50-60 have the highest age distribution in our study. The main reasons for this age distribution include the frequency of exposure to tobacco and tobacco products, as well as other kinds of tobacco. In India, the incidence of head and neck malignancies is now on the rise among young individuals.

Table 2: Sex Distribution

Sex	No. of Patients
Male	30
Female	10

Due to the documented cause of tobacco use in men compared to women, men are the dominate group. Head and neck cancers are also brought on by females chewing on areca nuts and leaves.

Table 3: Performance Status of ECOG

ECOG	No. of Patients
1.	17
2.	23

One crucial instrument in making the decision to reirradiate is the ECOG performance status. The performance status, together with age and other parameters, determines the patient's tolerance to chemotherapy and radiation.

Table 4: Site of Malignancies

Site	No of Patients
Oral Cavity	15
Oropharynx	11
Hypopharynx	9
Larynx	5

The oral cavity was the most often occurring place in our investigation. Oral cavity falls after the oropharynx, hypopharynx and larynx. The tongue is the most typical location of recurrence for malignancies of the oral cavity.

Table 5: Staging of Tumour

r Tumour	No. of Patients
rT0	00
rT1	00
rT2	16
rT3	20
rT4	04

The patient's presentation stage is a crucial prognostic factor for the success of the treatment. The majority of individuals in our study have T3 and T2 cancer stages upon presentation. Reirradiation is used to treat individuals who are all ineligible for surgical intervention. Compared to t3 and t4 lesions, t1 lesions can be operated on with clearing. Most single institution trials regard staging to be a significant prognostic factor. De gustave *et al.'s* large single institution trial came to the conclusion that staging is one of the key indicators of how reirradiation for head and neck malignancies will turn out.

Table 6: Nodal Staging

Nodal	No. of Patients
N0	18
N1	12
N2	10

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

In recurrent head and neck malignancies, local recurrence is the most frequent type of failure when compared to regional recurrence. Comparatively to individuals who present with either local or regional recurrence alone, regional recurrence plus local recurrence is a less frequent presentation.

Table 7: Previous Treatment

Previous Treatment	No. of Patients
Radiation Alone	8
Radiation à Surgery	6
Surgery à Radiation	6
Radiation + Chemotherapy	20

The majority of the patients in our study had radiation plus chemotherapy as initial care. The radiobiology of the cancer is crucial in determining how the surgical site's vascularity, perfusion, and tumour resistance will change. Additionally, it suggests that most diseases with an advanced stage have returned.

Table 8: Chemotherapy Received Earlier

Chemotherapy Received	No. of Patients
Weekly CDDP	9
3 Weekly CDDP	13
CDDP + 5FU	10
CDDP + Paclitaxel	8

No conclusive data exists to support the radiobiology of chemotherapy in recurrent settings. The perfusion of the medication, availability in the tumour area, decreased drug resistance, radiosensitive action, cumulative effect of cell death [tumouricidal dose], and less side effects are common requirements for chemotherapy in the context of reirradiation of head and neck cancer. Radiation combined with full-dose chemotherapy utilising cisplatin 5-Fu paclitaxel combinations will cause toxicity to normal tissues.

Table 9: Radiation Fractionation

Previous Fractionation	No of Patients
Conventional	23
Hyperfractionation	11
Accelerated	06

The previous treatment's various fractionation schedules are another crucial consideration because they may be related to the long-term toxicity. Hyper fractionation has a low bed dosage in the normal tissue areas when compared to ordinary fractionation. When compared to traditional and other fractionations, the late toxicity is modest.

Table 10: RT Dose Earlier

Prior RT Dose	No. of Patients
70-80 GY	09
60-70 GY	22
50-60 GY	07
40-50 GY	02

The bed dose for the present reirradiation was calculated by using decay factor and formula.
Present Bed Dose= Decay Factor X Total Dose [Previous] Decay Factor = (T/T+R) 0.11.

Table 11: Radiations Gap

Time Interval	No. of Patients
6 Months - 1 Year	05
1 Year- 2 Year	10
2 Year - 3 Year	12
>3 Year	13

One of the key factors affecting treatment tolerance and toxicities is the time between radiation treatments. When compared to other patients, those whose treatment intervals are longer than three years will tolerate another full dosage of radiation dose better. Some institutes still use radiation after six months. After six months, the majority of trials reirradiate cases, typically using conformal RT in addition to traditional method.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

Table 12: Feeding Tube

FT Requirements	No. of Patients
Before RT	12
During RT	13
After RT	15

The need for a feeding tube is an indirect indicator of dysphagia. Following reirradiation, it was discovered that patients who had a feeding tube were still able to swallow with a grade 2 or 3 dysphagia. The patient who needs a feeding tube before radiation may have late side effects from radiation therapy that has already been administered or odynophagia or dysphagia caused by tumour extension in a recurring situation.

Table 13: Mucositis Grade

Mucositis Grade	No. of Patients	Median Lifetime Dose
Grade 0	00	120GY
Grade 1	19	120GY
Grade 2	16	110-120GY
Grade 3	05	110GY
Grade 4	00	-

Grade 2 mucositis was present in the patients who got a mean lifetime dose of 120 GY. Only two individuals with 120 GY experienced grade 3 mucositis. The patients' tolerance is good with little toxicity, and the mean lifetime dose of 120 GY is tolerable.

Table 14: Dysphagia in Patients

Dysphagia	No of Patients	Median Life Time Dose
Grade 0	-	-
Grade 1	19	120 GY
Grade 2	17	120 GY
Grade 3	04	120 GY
Grade 4	-	-

Both the number of patients and the severity of dysphagia rose. The median lifetime dosage for patients with grade 2 toxicity is 120 GY. Therefore, when compared to prior single institution studies where toxicities remained on the higher side, our data reflects less toxicity.

Table 15: Doses Comparison

Response	<60GY	60GY
	No. of Patients	No. of Patients
Complete Response	3(11%)	17(23.4%)
Partial Response	4(15%)	12(17%)
Stable Disease	4(15%)	-
No Response	-	-
Overall Response	27.5%	72.5%

In our study, we also compared the therapy doses that patients received. When compared to patients who received less than 60GY, the patients who received 60GY and above responded well.

Discussion

Our studies have focused mostly on clinical efficacy and safety. Our research led us to conclude that reirradiation is an option for patients with advanced, recurring head and neck cancer. Acute toxicity was manageable, making future re-irradiation an option. We found that the rate of response was much higher than in previous meta-analyses and single-center trials. We also find out that chemotherapy is not a substitute for reirradiation. Researchers at the Gustave-Rossy Institute enrolled 169 people with terminal cases of head and neck cancer. The two-year response rate was 37% for complete responses and 21% overall. The typical length of survival was 10 months. Osteoradionecrosis affects 5-20% of patients, while mucosal necrosis affects 1-10%. Primary radiation was shown to have higher incidence and severity of toxicities when compared in this investigation. When compared to this study, our results (53%) were better in terms of both complete and partial replies (37%) [15, 16, 17].

In addition, this experiment had lower toxicity than the last one. Our study had a rate of 50% lower than that reported in the literature for grades 3 and 4 of acute mucositis. Prior to radiation therapy, xerostomia was present in the majority of patients. This is because the patient's earlier radiation treatment was performed using 2D methods, which were less sparing of the parotid function. Dry mouth, which is the

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

root cause of our patients' swallowing problems, has a negligible impact on the treatment's efficacy. We found no significant haematological consequences in our study. Studies have shown that CDDP with Hydroxyurea, CDDP plus Paclitaxel, and CDDP plus 5FU lead to higher incidences of grade 3 and grade 4 neutropenia. T. We found that capecitabine was safe and had fewer side effects than other chemotherapy drugs. Similar sensitising and focusing effects can be achieved with this medicine as with others. What's more, the vast majority of large-scale clinical trials show grade 5 toxicity. Our data does not show any grade 5 toxicity. Patients in studies at other institutions have been shown to experience complications such grade 5 mucositis, osteoradionecrosis, and carotid blow out [18, 19, 20].

In our study, we found no evidence of adverse events such carotid blowout, osteoradionecrosis, fibrosis of the constrictor muscle, or fibrosis of the cervical spine. In 2007, RTOG 9610 was released as a multi-institution trial. 17.6% of fourth graders and 7.6% of fifth graders in this study experienced acute poisoning after receiving a weekly regimen of 5FU and hydroxyurea in combination with 60GY of RT. In this study, a 2-centimeter margin was used to calculate the gross tumour volume. There is use of both a 2D and a conformal method. The amount of time that passes between radiation treatments is a major influence in how well the body responds to the treatment and how harmful it is. Patients whose treatment intervals are more than three years will have a better chance of surviving another full dose of radiation. Trial samples from our institution found that patients who received reirradiation after more than a year fared better than those who received reirradiation at 60 GY in terms of both survival and treatment tolerance. There is a correlation between the volume of the tumour and its impact on the patient's prognosis. This is due to the fact that both the intensity of the field and the exposure of healthy tissues to it are detrimental [21, 22, 23].

The dose of radiation must be increased if a greater response is desired. The cumulative tumoricidal dose and sensitising impact of chemotherapy must be maximised for each individual patient for the best possible response, with the fewest possible side effects. Field planning and toxicity are both heavily influenced by the total dose supplied to the spinal cord. The spinal cord may be regenerated, according to recent radiobiological findings. Radiation doses acquired in the past are partially stored in the spinal cord's memory. Some ideas suggest that as time goes on, people's memories deteriorate. Our study's upper dose limits were set in light of previous research indicating a 5–10% risk of radiation-induced myelopathy at 60 GY [22, 23].

Conclusion

In previously irradiated areas, loco-regional failure of HNSCC is somewhat complex. It poses a difficult problem after a full course of (chemo) radiation. For radiation oncologists, these diseases still have a chance of being cured in some circumstances with a favourable tumour biology. Salvage surgery continues to be the norm of treatment whenever possible. Approximately 20% of cases are still feasible. In cases of poor prognosis, immediate postoperative (chemo-) re-irradiation can be safely used after salvage surgery and significantly enhances loco-regional control. Adjuvant (chemo-) re-irradiation should be considered even though late radiation-induced complications are relatively common; for example, if there is a higher risk of locoregional recurrence due to positive surgical margins or lymph node metastases with extra nodal spread. Curatively intended (chemo-) radiation should be taken into consideration in carefully chosen cases of unresectable locoregional failure. We conclude that treating recurrent, unresectable head and neck cancers with full-dose radiation and T. capecitabine is doable. Comparing our study to other studies, the frequency and seriousness of toxicities are acceptable. However, compared to the toxicity of primary radiation, the toxicities caused by reirradiation are typically high. The potentially fatal consequences are uncommon. We can anticipate some long-term survivors with a full response with this strategy. Finally, when compared to chemotherapy alone, reirradiation has better response rates for disease-free survival, overall survival, and overall survival.

Funding support: Nil.

Conflict of interest: Nil.

References

1. Salama JK, Vokes EE. Concurrent chemotherapy and re-irradiation for locoregionally recurrent head and neck cancer. Semin Oncol. 2008;35:251-261.
2. Wong SJ, Machtay M, Li Y. Locally recurrent, previously irradiated head and neck cancer: concurrent re-irradiation and chemotherapy, or chemotherapy alone? J Clin Oncol. 2006;24:2653-2658.
3. Kao J, Garofalo MC, Milano MT, *et al*. Reirradiation of recurrent and second primary head and neck malignancies: a comprehensive review. Cancer Treat Rev. 2003;29:21-30.
4. Salama JK, Vokes EE, Chmura SJ, *et al*. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. Int. J Radiat. Oncol. Biol, Phys. 2006;64:382-391.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

5. Milano MT, Vokes EE, Salama JK, *et al*. Twice-daily reirradiation for recurrent and second primary head-and-neck cancer with gemcitabine, paclitaxel and 5-fluorouracil chemotherapy. Int. J Radiat. Oncol. Biol. Phys. 2005;61:1096-1106.
6. Biagioli MC, Harvey M, Roman E, *et al*. Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated, recurrent head and neck cancer. Int. J Radiat. Oncol. Biol. Phys. 2007;69:1067-1073.
7. Haraf DJ, Weichselbaum RR, Vokes EE. Re-irradiation with concomitant chemotherapy of unresectable recurrent head and neck cancer: a potentially curable disease. Ann Oncol. 1996;7:913-918.
8. Kasperts N, Slotman B, Leemans CR, Langendijk JA. A review on reirradiation for recurrent and second primary head and neck cancer. Oral Oncol. 2005;41:225-243.
9. Chopra S, Gupta T, Agarwal JP, *et al*. Re-irradiation in the management of isolated neck recurrences: current status and recommendations. Radiother Oncol. 2006;81:1-8.
10. Garofalo MC, Haraf DJ. Reirradiation: a potentially curative approach to locally or regionally recurrent head and neck cancer. Curr Opin Oncol. 2002;14:330-333.
11. Langendijk JA, Bourhis J. Reirradiation in squamous cell head and neck cancer: recent developments and future directions. Curr. Opin. Oncol. 2007;19:202-209.
12. Nagar YS, Singh S, Datta NR. Chemo-reirradiation in persistent/recurrent head and neck cancers. Jpn J Clin Oncol. 2004;34:61-68.
13. Berger B, Belka C, Weinmann M, *et al*. Reirradiation with alternating docetaxel-based chemotherapy for recurrent head and neck squamous cell carcinoma: update of a single-center prospective phase II protocol. Strahlenther Onkol. 2010;186:255-261.
14. Platteaux N, Dirix P, Vanstraelen B, Nuyts S. Outcome after re-irradiation of head and neck cancer patients. Strahlenther Onkol. 2011;187(1):23-31.
15. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope. 2000;110:1-18.
16. Parsons JT, Mendenhall WM, Stringer SP, *et al*. Salvage surgery following radiation failure in squamous cell carcinoma of the supraglottic larynx. Int J Radiat Oncol Biol Phys. 1995;32:605-609.
17. Hong WK, Bromer R. Chemotherapy in head and neck cancer. N Engl J Med. 1983;308:75-79.
18. Siu LL, Soulieres D, Chen EX, *et al*. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital phase II consortium and National Cancer Institute of Canada Clinical Trials Group Study. J Clin Oncol. 2007;25:2178-2183.
19. Shin DM, Khuri FR, Glisson BS, *et al*. Phase II study of paclitaxel, ifosfamide and carboplatin in patients with recurrent or metastatic head and neck squamous cell carcinoma. Cancer. 2001;91:1316-1323.
20. Burtness B, Goldwasser MA, Flood W, *et al*. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in meta-static/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol. 2005;23:8646-8654.
21. Smith RE, Thornton DE, Allen J. A phase II trial of paclitaxel in squamous cell carcinoma of the head and neck with correlative laboratory studies. Semin Oncol. 1995;22:41-46.
22. Dreyfuss AI, Clark JR, Norris CM, *et al*. Docetaxel: an active drug for squamous cell carcinoma of the head and neck. J Clin. Oncol. 1996;14:1672-1678.
23. Forastiere AA, Shank D, Neuberg D, *et al*. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer. 1998;82:2270-2274.