REVIEW ARTICLE

RE-IRRADIATION IN HEAD AND NECK CANCERS: A WISE SELECTION FROM AVAILABLE DATA

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ABSTRACT

Recurrence of cancer within radiation field is the most dreaded news after curative radiation therapy in head and neck cancer patients. Surgical treatment of these sites is always challenging, which becomes worse after radiation. With the introduction of conformal modalities, the chances of re-irradiation of recurrent cancer are being explored for many years now. In spite of increased use of reirradiation there are not much published criteria or guidelines in these groups of patients. The objective of this literature review is to identify the most commonly used patient selection criteria, radiation doses, fields, impact of newer technology and outcomes in terms of local control and survival.

Keywords: Re-irradiation, Chemoradiation, Recurrent, Head and neck cancer

INTRODUCTION

Even today, more than 2/3rd of patients of head and neck cancers will present in advanced stage. Almost half of these patients will have recurrence after radical treatment.[1]. In Radiation Therapy Oncology Group (RTOG) experience, previously irradiated patient has 1% per year risk of second malignancy.[2] Currently, the treatment of choice in these patients is surgery. Various options such as salvage surgery, radiotherapy, chemotherapy, chemoradiation or palliative treatment are prescribed as per the stage, local extent and time since last radiotherapy. Addition of post-op radiation to salvage surgery remains controversial. Re-irradiation in previous radiation field for a recurrent tumor or second malignancy was earlier considered unsafe and toxic.[1] Chemotherapy alone in this setting gives median survival of only 5 to 9 months.[3] Therefore, if disease is unresectable, definite re-irradiation with or without chemotherapy is offered. Even though the chance of cure is low, it has to be weighed against the risk of toxicity because there are no other better treatment options available.

Prognostic factors for recurrent or secondary head and neck cancer

Patient's selection and individualization of treatment is very important in management of recurrent head and neck cancer. Theoretically recurrent tumors or second malignancy in same fields will have a poor prognosis. Selection of patients with better prognosis and giving them best possible treatment plan is essential. De Crevoisier et al, in the study on role of re-irradiation, found that the only two factors affecting the risk of death is surface and volume of second radiation field. Overall survival rate of patients irradiated with an area less than 125 cm^2 or a volume less than 650 cm^3 was higher than that of the patients treated with an area more than 125 cm^2 and a volume more than 650 cm^3 ($P = .08$ and $P = .03$, respectively).[4] This finding was also shown by Chen et al, in his study where in a multivariate model, the investigators found that the re-irradiation volume is the only factor independently associated with death. In subset of patients with tumors <27 cm^3, the 2-year local control rate was 80%.[5,6] Surgery followed by postoperative RT showed better 5yrs survival (49%) than definite RT (20%) with p value of 0.003 in a retrospective study by Hoeberts et al, but selection bias cannot be ruled out.[7]

Some studies showed that second primary tumor has better prognosis than recurrent disease. This can be explained by presence of resistant clonogen in recurrent case which has survived previous radiation and proliferated over the time.[1] A normogram to assess the prognosis of these patients was developed by Tanvetyanon T et al, where various prognostic factors like performance status, co-morbidity, tumour bulk, isolated neck recurrence were considered for prediction in the normogram. It predicts the probability of death within 24 months of re-irradiation.[8] Minimum of at least 6 months interval from previous radiotherapy is taken as inclusion criteria for re-irradiation by most of the authors.[4] In RTOG 9610, patients who had gap interval of more than 3 years between two sessions of radiation had 1 yr survival of 48% compared to 35% in patients with interval less than 3 years. Patients receiving re-irradiation within 6 months to 1 year after

previous radiation had survival of only 5.8 months which is comparable to chemotherapy only.[9] Pre-existing comorbidities and organ dysfunction are important prognostic factors for patients undergoing reirradiation. For those with comorbidities and organ dysfunction, reirradiation largely serves as a palliative therapy.

Risk factors and contraindications against re-irradiations

Although patient's performance status, age, tumor bulk and many other disease and treatment related factors has to be kept in mind. But he most important factor which influence response to re-irradiation is interval since previous radiation. Longer duration from previous radiation has less chance of developing severe toxicity and higher chances of response to re-irradiation.[5] Severe toxicity to previous radiation is a major contraindication to re-irradiation. Thorough evaluation to assess for pre-existing sequelae of previous radiation should be done before considering the patients for re-irradiation. Occurrence of osteoradionecrosis (ORN) as such is a contraindication for re-irradiation. Presence of cartilage necrosis and edema of arytenoids, which places patient in high risk of aspiration and airway closure, should be ruled out.[5] Radiation myelitis is another limiting toxicity, which is a contraindication for radiation of any organ in the vicinity of spinal cord. Using conventional fractionation, the estimated risk of myelopathy is <1% and <10% at 54 Gy and 61 Gy, respectively.[10] Carotid blowout is a rare but fatal complication due to re-irradiation. In patients treated in a continuous course with 1.8–2-Gy daily fractions or 1.2-Gy twice daily fractions, rate of carotid blowout was 1.3%.[11] Chen et al has also reported that patients with more than 3 years from previous RT, KPS (Karnofsky Performance Score) 90-100%, tumor volume < 30 cm^3 and previous RT dose less than 50 Gy were associated with lower risk of Toxicity compared to patients with less than 1 years from previous RT, KPS < 70, tumor volume > 60 cm^3 and previous RT dose > 60 Gy of radiation.[5] Similarly Jae Y. Lee et al has shown in his study that shorter intervals to re-irradiation (<20 months) and larger re-irradiated PTVs (>100 cm3) were independent predictors of developing severe long-term toxicity in multivariable analysis. Probability of being free of severe toxicity was 94% in patients having smaller PTVs and longer disease free survival.[12]

Treatment considerations

Current management of recurrent head and neck cancer is dependent on its resectability. Surgery remains the first choice of treatment in resectable non metastatic lesions.[5] Complete resection gives long term survival of 25% to 45% in these patients. However even after complete resection with negative margins, these patients have very high local failure rates of upto 59 %.[13] There was a trend for decreased LRC among those with close/positive margins, and significantly worse prognosis in those with ECE and bone invasion despite adjuvant reirradiation, suggesting treatment intensification may be warranted for select patients with high-risk pathologic features. De Crevoisier et al reported 4-year survival of 43% and 5-year disease free survival of 26% in patients who had positive margins and/or lymph node involvement with extracapsular extension.[4] Considering these results, the Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) and the Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) conducted a phase III phase randomized trial to address this issue. Previously irradiated patients, were randomized to observation or re-irradiation (60 Gy over 11 weeks; 2 Gy/day) with chemotherapy (concomitant 5FU + hydroxyurea) after macroscopic surgical resection. Both local control and disease-free survival were improved in patients receiving postoperative re-irradiation and chemotherapy. However, there was no difference in overall survival.[14] Vinita Takiar et al has shown that LRC (Locoregional control) benefit with concurrent chemotherapy seems even more pronounced when added to adjuvant reirradiation compared with adjuvant reirradiation alone with corresponding 5-year LRC rates of 56.7% versus 31.4% (P=0.001). Survival and toxicity were not affected by the use of adjuvant concurrent chemotherapy, nor did the type of chemotherapy influence clinical outcomes.[15]

Role of definitive re-irradiation was evaluated by two prospective randomized trials RTOG 9610 and RTOG 9911. In RTOG 9610, Spencer et al showed that definitive radiotherapy combined with concurrent chemotherapy with 5 FU and hydroxyurea is feasible with acceptable toxicity. Median survival and estimated 1 yr survival was higher in secondary cancer (19.8 months and 54.2% respectively) in comparison to recurrent cancer (7.7 months and 38.4% respectively).[9] In RTOG 9911, Paclitaxel and Cisplatin were given with split course radiation therapy. Median survival was 12.1 month and estimated survival at 1 yr and 2 yrs were 50.2% and 25.9% respectively. [16] Phase III randomized trial by Tortochaux et al did not show any improvement in overall survival in patient receiving re-irradiation with concurrent 5FU and hydroxyurea in comparision to single agent methotraxate alone in palliative intent cases.[17] However, many questions remain unanswered regarding the optimal delivery of Re-RT and the best Chemotherapy agents, as well as questions regarding selection criteria of patient in order to achieve maximum benefit from radiotherapy or combination chemoradiation.

Inclusion of lymph nodal region at risk in radiation field, still remain inconclusive. In most of the studies, radiation field included only gross tumour volume with margin for clinical target volume. The margin given to GTV depends on radiotherapy technique employed, either 3DCRT, IMRT or IGRT. Margin varied

from 5mm to 2 cm to obtain CTV.[4,9,18,19] In some studies CTV margin was reduced to as low as 1 mm when critical organ such as spinal cord and brain stem came in vicinity.[10,11] Dose prescribed in re-irradiation remains controversial. Higher re-irradiation dose are shown to give better response. In study by Salam et al, 3-year overall survival and locoregional control rate of patients who received re-radiation dose of > 58 Gy was 30% and 56%, as compared to 6% and 33% in patients who received doses of < 58 Gy.[20] Some experimental data showed that head and neck can tolerate cumulative dose of upto 130 Gy, and dose of spinal cord should be limited to 50 Gy.[6,21] At present recommended dose for re-irradiation in various studies are 60-70 Gy.[6] Newer treatment modality, such as IMRT (Intensity Modulated Radiation Therapy) or IGRT (Image Guided Radiation Therapy), improves precision, therefore improve therapeutic ratio. Lee et al reported that IMRT has offered possibilities for applying re-irradiation more safely with greater local control. They reported a 2-year disease free survival of 52% vs 20% in patients who underwent IMRT and patients who did not.[22] Image guided Radiotherapy improves tumour localization and reduces positioning errors.

Effects of advanced treatment modalities on head and neck re-irradiation

Technical advancement gives us independence to improve conformity and precision, although risk of omission should always be taken into consideration. SBRT (Stereotactic radiotherapy) provides higher conformal dose distribution with greater sparing of normal organs, therefore allowing delivery of higher radiation dose in shorter time. Stereotactic radiotherapy and radiosurgery are emerging as very good alternative to surgery in recurrent head and neck cancer. Roh et al reported an 80% response rate after 30 Gy (range 18–40 Gy) in 3–5 fractions administered using the Cyber-Knife system. A 2-year survival rate of 30.9% and a treatment death rate of 2.9% were reported.[23] In study by Unger et al, patients treated with Stereotactic radiosurgery, the 2-year OS and locoregional control (LRC) rates were 41% and 30%, respectively. Higher total dose, surgical resection, and nasopharynx site were significantly associated with improved locoregional control. Surgical resection and nonsquamous histology were associated with improved OS.[24] Rwigema et al did a review study on 85 patients who received SBRT with mean dose of 35 Gy. Those patient receiving dose < 35 Gy had lower local control as compare to those receiving > 35 Gy at 6 months (P=0.014). Local control and overall survival at 2 yrs was 48.5% and 16.1% respectively.[25] Similarly Proton beam therapy is a newer approach used in some centres with facilities available. Advantage of proton beam over photon beam is that it relatively spares normal tissue proximal to tumor, while rapid dose fall off spares normal tissue distal to tumor providing potential for dose escalation. In a multi-institute report by Romesser et al, 92 patients were re-irradiated with Proton beam radiotherapy (PBRT). The median dose was 60.6 CGy (Cobalt Grey Equivalent). Freedom from distant metastasis and overall survival at 1 year was 84% and 65.2% respectively, with acceptable acute and late toxicity.[26]

Guidelines and recommendations:

Although there are many articles to investigate the role of reirradiation in recurrent or second primary Head and Neck cancers, very few gives the overall insight to the actual use of the published data for selecting patients in clinical practice.[1] As per the available clinical data[1] and review of literature the following points need to be given a thorough consideration before selecting the patients for reirradiation.

A. Patient Related Factors:

Good Performance status is the most important factor required for patient to complete radiation with radical intent. Presence of any co-morbidity which can hamper treatment tolerance or response should be assessed before decision is taken for radiation.

Co morbidities which might lead to compromise on radiation dose or compliance and treatment interruption should be evaluated before radiation.

Sequelae to previous radiation are a contraindication to further radiation, such as patients with osteoradionecrosis, fistula, radiation myelitis, sever fibrosis or trismus should not be considered for radical reirradiation.

B. Treatment and Tumor Related factors:

Time since last radiation not only predicts radiation response but also give us idea about possible toxicity. Interval less than 6 months criteria since last radiation is exclusion in almost all re-irradiation studies. Time interval of more than 3 yrs is shown to give significant benefit when compared with less than 3 yrs. It takes minimum of 6 months for appearance of late reaction; therefore it is recommended to have at least 6 months interval since last radiation and preferably 1 year (considering the radioresistant tumor clone present after RT, 6 months might be very less time to actually consider radiotherapy again).

Radiation dose: Higher radiation dose increases tumor cell kill, therefore increasing probability of cure. Most of the studies done till now suggest that radiation dose should be kept atleast 58-60 Gy or more to achieve significant survival advantage.

Previous treatment with Conventional technique or conformal technique, Cobalt or Linear Accelerator, use of tissue compensator which might influence the

toxicity profile should be checked. In developing countries like India where due to resource limitations many patients are treated with cobalt machines and without tissue compensators the pre-existing toxicities and OAR (oragans at risk) doses may hamper the reirradiation dose. Although cumulative dose of 110-120Gy and spinal cord doses less than 50Gy should be considered as limit. Data regarding the other OAR like bone and soft tissue, vasculature is sparse.

Radiation Technique: Conformal radiation delivery techniques like IMRT, Stereotactic radiotherapy, Tomotherapy, Cyberknife, Gamma Knife, Proton Beam radiotherapy etc. etc. improves the radiation dose delivery by improving precision of radiation. These modalities allow increase in radiation dose and conformity to the tumor while sparing the normal surrounding tissue, hence gives opportunity to overcome relative radio resistance in previously radiated tissues.

Radiation field size area or volume is one of the most important prognostic factors. In some studies, it was the only relevant factor effecting radiation response. It is recommended to keep field size or contouring volumes to be as small as possible. CTV margins might be reduced to less than 5 mm with conformal techniques. Limited tumor volume increases cure rate and improve toxicity profile, therefore patient with negative neck node should not receive unnecessary elective neck node irradiation. Data suggests area less than 125 cm^2 or a volume less than 650 cm^3 and tumour volume <27 cm^3 are good predictors.

Although there is no cut off volume to select patients, we recommend that large volume involving multiple subsites should be avoided as they are unlikely to benefit from reirradiation but it's recommended to use case wise clinical judgment in these group of patients.

In patients who underwent surgery the post op RT should be considered for margin positive and extracpsular disease or PNI positive patients along with concurrent chemotherapy.

Use of concurrent chemotherapy should be considered in patients with good performance score.

Adequate supportive care before, during and after the course of treatment is very important factor in getting good compliance to the treatment.

CONCLUSION

Significant number of patients treated for advanced head and neck cancer presents with recurrence. Some survivors may also present with second primary tumors. In patients who presents with inoperable non metastatic recurrence or second primary, re-irradiation with or without chemotherapy remains the only option for cure. Even in patients who have surgically resectable disease, post op radiation seems to improve survival, especially in patients who have high risk feature in post operative histopathology. Toxicity due to cumulative dose is an important factor to be kept in mind. It becomes necessary to weigh the possible benefit of re-irradiation against toxicity or death oncologists in selecting the patients for re irradiation wisely. Reirradiation with or without chemotherapy should be administered in well selected patient, to improve loco regional control, progression free survival and overall survival at the same time maintaining a good quality of life.

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