

RE-IRRADIATION IN HEAD & NECK CANCERS UPDATES, DILEMMAS AND FUTURE CHALLENGES

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Abstract

Although previously considered unnecessary and associated with a high toxicity rate, re-irradiation of head and neck cancers is currently an increasingly frequently used therapeutic option, both for curative and palliative purposes. However, there have been reports in the literature indicating 10-20% survival at 5 years for patients re-irradiated with the full dose. Without a consensus, the evidence argues for a re-irradiation dose of over 58Gy as being correlated with superior survival. Survival rates at 2 years were significantly higher (35%) compared to only 8% in favor of patients re-irradiated with a dose >58Gy. Carotid blow-out and osteoradionecrosis (ORN) of the mandible are currently more serious toxicities than potentially fatal myelitis, whose reporting rate was reduced, perhaps also because the subject benefits from extensive studies and clear dosimetric recommendations. Recent data suggest a possibility to limit the risk of carotid blowout and ORN by limiting cumulative doses to the carotid and mandible to <120Gy. Immunotherapy seems a feasible option for combination with re-irradiation. We have not yet identified data on combinations with new oncology therapies including vaccines, bispecific antibodies and antibody drug conjugates (ADC).

Keywords: re-irradiation, head and neck cancers, HNSCC, toxicity, carotid blowout, jaw ORN, immunotherapy

INTRODUCTION

The increasing use of intensity-modulated radiotherapy techniques, even proton therapy or carbon ion therapy, has made possible a superior protection of radiosensitive anatomical structures in the vicinity of the target volume, structures called organs at risk (OARs). Re-irradiation, considered useless or even detrimental in the past, being associated with severe toxicities, is now becoming a therapeutic option in both locally recurrent and distant metastases. In head and neck cancers, radiotherapy is considered one of the pillars of non-surgical treatment, with a well-established role both in the adjuvant setting and in definitive or palliative treatment. However, high-dose curative re-irradiation is reserved for carefully selected cases, so that the benefit-risk ratio is tilted in favor of the benefit. The combination of re-irradiation with chemotherapy, biological therapy or immunotherapy is currently being exploited in clinical trials,

but new combinations with antibody drug conjugates (ADCs), vaccines, bispecific antibodies are strategies that may bring favorable results in the future [1-7].

Even though the widespread enthusiasm regarding the use of re-irradiation is growing, Andratschke and collaborators mention in the article “Re-irradiation-still navigating uncharted waters?” several ideas that underlie and will underlie re-irradiation in the present and future. First, the absence of high-quality evidence and standardization of the method is reported. Another reality mentioned by the authors is the scarcity of preclinical data and the absence of data on the repair of healthy tissue. Image-guided brachytherapy and stereotactic ablative radiotherapy (SABR) will be among the strategies with the potential to be exploited. Patient selection, ensuring a workflow and an optimal balance between toxicity and tumor control remain of major importance [8].

With 24-50% recurrence rates after initial treatment, head and neck cancers are becoming prime candidates for new therapeutic options. A group from the University of Chicago published a report in 2006 including long-term outcomes for 115 patients treated with chemotherapy and re-irradiation for recurrent squamous cell carcinomas, as well as for secondary primary malignancies (SPM). The median cumulative dose was 131Gy, and the median re-irradiation dose was 65Gy, with a 3-year survival rate of 22%. Re-irradiation dose, surgical treatment before re-irradiation, chemotherapy with Cisplatin, Paclitaxel, or Gemcitabine, and re-irradiation doses > 58Gy were prognostic factors. The differences were major in the median overall survival (OS) rates at 3 years for radiation doses >58Gy (30% vs 6%). Six cases of carotid blowout and 13 cases of ORN of jaw were also reported, all grade 4 and 5 toxicities. Six cases of carotid blowout and 13 cases of ORN of jaw were also reported, all grade 4 and 5 toxicities. One case each of myelopathy and severe peripheral neuropathy were also reported. The conclusion of this study is that full-dose re-irradiation with concomitant chemotherapy is a viable treatment option and offers OS benefit for both recurrent and SPM cases. Similar results reported by De Crevoisier and colleagues at "Gustave Roussy" Institute, present a median cumulative dose around 120Gy. The 5-year overall OS rate was reported to be 9%, with volume irradiated and dose being the only variables associated with the risk of toxic death [9-12].

Re-irradiation in SPM. SPM (second primary malignancy) frequently reported in head and neck cancers, with an increasing incidence as survival improves and therapeutic options diversity. The prognosis in this category of cancers is also better than in the case of recurrences, with 5-year survival rates of 29% reported by Vaamonde et al. The increased incidence of

SPM in head and neck cancers treated with radiotherapy may be explained by the carcinogenic effect of irradiation, with field cancerization being reported especially in oral cavity malignancy. Like loco-regional recurrence, SPM affects both survival and prognosis. Salvage surgery is the main therapeutic method and is associated with a median OS of 40% at 2 years [13-15].

Retrospectively analyzing data from 42 cases diagnosed with SPM and re-irradiated using the IMRT technique, Merino et al. reported a median OS of 28.9 months and a median 2-year OS rate of 54.6%. ECOG 0 or 1 performance status was an inclusion criteria in the study, and radiotherapy dose >60Gy was a prognostic factor. The rate of grade ≥3 toxicities was 10% [16].

Even though there are some guidelines for selecting patients for re-irradiation, retreatment with radiotherapy of previously irradiated tissues remains a challenge. A multicenter study that included 7 centers and 412 patients aimed to identify prognostic subgroups. Only patients who were initially irradiated with a dose ≥40Gy and who also received ≥40Gy at re-irradiation using the IMRT technique were included. Statistical analysis included Gray competing risk method and Cox proportional hazards regression. The rate of grade 3 and grade 4 toxicities was 4.4% and 1.2%, respectively. Recursive partitioning analysis (RPA) identified 3 prognostic groups with different OS. The first group included patients > 2 years after the first irradiation with resected tumors, class II included cases with un-resected tumors or patients ≤ 2 years who are not dependent on a tracheostomy or feeding tube. The remaining patients were included in class III. The 2-year OS rate was identified as 61.9%, 40% and 16.8% for classes I, II and III respectively. The authors of this classification propose the selection of patients based on this classification for treatment and inclusion in clinical trials, mentioning that group III patients are not

candidates for chemotherapy and re-irradiation. Using the RPA classification, the study proposed by Lee and colleagues identifies 2-year OS rates of 87.5% for patients included in class I, 51.8% for patients included in class II, and 0% for cases included in prognostic class III [17, 18].

A carbon ion re-irradiation study proposed by Yang et al., which included 15 patients, mentions re-irradiation doses between 57.5Gy and 69Gy with a daily fraction dose of 2.5-3Gy. The group included both soft tissue sarcoma, squamous cell carcinoma and esthetic neuroblastoma. At 1 year after completion of treatment, rates of OS, local progression free survival (LPSF), distant metastasis free survival (DMFS) and progression free survival (PFS) of 69.3%, 53.0%, 92.9%, and 48.2%, respectively, were reported. The rate of severe adverse events (AEs) was reduced, with only one case having grade 4 hemorrhages which, although treated with embolization, subsequently caused the patient's death [19].

Organs at Risk (OARs) – Priorities in Re-radiation. In nasopharyngeal cancer, re-radiation has historically been associated with high rates of late toxicities including trismus, dysphagia, neuropathy, temporal lobe necrosis, and endocrine dysfunctions. IMRT has demonstrated feasibility and the ability to limit adverse effects, delivering a potentially curative dose of ≥ 60 Gy. The addition of radiosurgery or intra-cavitary brachytherapy to external beam radiotherapy has also been associated with a favorable toxicity profile. Patients re-irradiated with 45Gy delivered by IMRT followed by a brachytherapy boost of up to 20Gy had an 8% rate of grade ≥ 3 AEs, compared to a 73% rate of severe AEs associated with IMRT alone. A study of 151 patients re-irradiated with a median dose of 70.4Gy (range 62.1Gy to 77.6Gy) identified high rates of high-grade toxicities, 12.6% for cranial nerve palsy,

13.2% and 19.9% for hearing impairment and imaging-detected cerebral radionecrosis, respectively. In the case of combined re-irradiation with radiosurgery, doses of 11-35Gy are used. A dose of 45Gy and median target volume of 16.9 cc was associated with local, regional and local control of 8%, 66%, and 83%, respectively [20-21].

Embring et al identified a cumulative dose of 119Gy as the cut-off value for the carotid artery, with a dose above this value being associated with an increased risk of carotid blowout. The data are consistent with published values, confirming the dosimetric constraint of 120Gy required to limit this severe and potentially fatal toxicity. The same radiation dose cut-off value is also associated with the risk of jaw ORN. High re-irradiation dose, high dose at the first course of radiotherapy, cumulative dose received by a specific organ (e.g. carotid artery, jaw), concurrent chemo-re-irradiation, short time interval between courses of radiotherapy, prior surgery and large re-irradiation volume have been identified as predictive factors for severe late toxicities. However, it should be noted that there is still no consensus on all toxicities. A single case of laryngeal necrosis was reported by Bots et al., analyzing data from 137 re-irradiated patients [22-25].

Xerostomia, trismus, dysphagia and skin toxicity were analyzed as toxicities associated with re-irradiation in a group of patients treated with a cumulative dose ≥ 100 Gy, having a dose ≥ 60 Gy in the first irradiation sequence and a dose ≥ 40 Gy in the re-irradiation sequence. For dose equivalence, the linear quadratic model was used, considering α/β ratio =3 for toxic effects in the case of late-responding normal tissues. Late toxicities were considered those AEs reported more than 90 days after the completion of re-irradiation. Only in the case of ORN of jaw, the Late Effects Normal Tissue/Subjective

Objective Management Analytic (LENT/SOMA) AE quantification score was used, for the other toxicities, the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) was the preferred scale, considering any toxicity of grade ≥ 3 as severe. In the study proposed by Embring et al., 26% and 51% of severe acute and late toxicities were reported, respectively. Of the study group, 7 patients died within the first 90 days of treatment and the most severe toxicities were reported 1.5-2 years after re-irradiation, with the median diagnosis time of severe AEs being 1.7 years. Tumor location, interval between radiotherapy sequences and target volume of re-irradiation were predictors of severe toxicity. The final evaluation concludes that the use of cumulative dose limitations < 120Gy could reduce the risk of carotid blowout and ORN of jaw [25, 26].

Re-irradiation in head and neck cancers – Future perspectives. Immunotherapy is currently the first-line treatment in recurrent and metastatic head and neck cancers refractory to platinum-based treatment, with the programmed death ligand PD-1 inhibitors Pembrolizumab and Nivolumab being approved following the favorable results of the KEYNOTE-048 and CheckMate 141 trials, respectively [27,28].

The combination of radiotherapy with immunotherapy remains an unsolved topic. The dual effect of immunotherapy, immunosuppressive and activator of antitumor immunity, but also the concept used in definitive head and neck cancers radiotherapy of elective nodal irradiation, possibly associated with the limitation of T-cells priming in lymph nodes, could be associated with a detriment in anticipated effect by adding immunotherapy to radiotherapy. The use of a single target volume, without involving elective volumes in re-irradiation of head and neck cancers, could activate the antitumor

immune response, being a booster for immunotherapy. These strategies are still under evaluation [29-31].

Ten patients with inoperable relapsed head and neck squamous cell carcinoma (HNSCC) previously treated with adjuvant radiotherapy and platinum-based chemotherapy were re-irradiated with 60Gy in 30 fractions plus Nivolumab. A median of 12 courses of Nivolumab were administered, with a median OS of 12 months, with a 12-month OS and LPFS rate of 50% and 30%, respectively. No radiation-related toxicities were observed, with only immunotherapy-related toxicities reported. Elevated CRP and low hemoglobin levels, as well as a neutrophil/lymphocyte ratio (NLR), were associated with poor LPFS. The authors conclude that combining immunotherapy with re-irradiation for HNSCC is feasible for carefully selected patients not eligible for surgery. Analyzing the initial experience with Nivolumab-based immunotherapy in 2 academic centers in Romania, the benefit of re-irradiation and immunotherapy was reported in cases of SPM treated with radiotherapy initially and re-irradiated after a long interval, even if the first course was conventional irradiation gamma photons from a cobalt-60 machine without image guidance [32, 33].

A multicenter phase II trial also demonstrated improved PFS by using immunotherapy 2 weeks before and subsequently concurrent with IMRT irradiation in a total dose of 66Gy in 33 fractions, immunotherapy being administered once every 2 weeks in a dose of 240mg, then once every 4 weeks in a dose of 480mg for a total duration of up to 52 weeks. The authors also noted a trend for worsening PFS for cases with increased blood level of PD1, KI67, and CD4 T cells [34].

CONCLUSIONS

In the context of new therapeutic options including re-irradiation in head and

neck cancers, there is the possibility of long-term survival in certain cases, limiting AEs by evaluating the cumulative dose to OARs being essential. While we already have conclusive data for the risk of myelitis, data regarding limiting the cumulative dose received by the carotids and mandible to <120Gy have been proposed more recently and could help in reducing the risk of carotid blowout and jaw ORN. SPM has a better prognosis than local recurrence and in this context an evaluation of the possibility of limiting the risk of other toxicities in re-irradiation setting including dysphagia/aspiration, temporal lobe necrosis, skin toxicity, and

xerostomia is necessary. An identification of dose-volume constraints in the case of re-irradiation could be obtained by analyzing a large volume of data. Re-irradiation concurrent with immunotherapy may be a less toxic option than the association with re-irradiation concurrent with platinum salts chemotherapy. The modulatory effect of radiotherapy on antitumor immunity could provide a synergistic benefit. Currently, we haven't identified data and studies regarding therapeutic associations of re-irradiation with new oncological therapies including vaccines, bi-specific antibodies (bsAbs) and antibody drug conjugates (ADC).

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