

Radiotherapy and Concomitant Hyperthermia in the Treatment of Recurrences of Previously Irradiated Head and Neck Region Tumors

Marina Amorim^{1*}, Catarina Silva¹, Sara Simões¹, Maria Adelina Costa², Graça Fonseca², Cármen Calçada¹, Joana Vale², Fátima Rodrigues², Paulo Genésio², António Moreira Pinto³, André Ferreira³, Carla Sousa³ and Paulo Costa^{1,2}

¹Radiation Therapy Department, Hospital de Braga (Rua Sete Fontes, São Victor 4710-243, Braga, Portugal).

²Radiation Therapy Department, Júlio Teixeira S.A, CUF Institute (Rua Fonte das Sete Bicas, nº170, Senhora da Hora 4460-188, Porto, Portugal).

³Medical Oncology Department, CUF Hospital (Circunvalação 14341, 4100-180 Porto, Portugal).

*Correspondence:

Marina Amorim, Radiation Therapy Department – Hospital de Braga (Rua Sete Fontes, São Victor 4710-243, Braga, Portugal, Tel: +351253027140.

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ABSTRACT

Background: Recurrences of head and neck tumors (HNT) are associated with a poor prognosis. Many of these patients have previously undergone radical radiation therapy with dose limitations for critical organs. In this context, re-irradiation may carry an increased risk of complications. The combination of radiotherapy with hyperthermia (RT/HT) has gained importance in these patients due to its complementary tumoricidal effect, allowing for lower radiation doses and a consequent reduction in toxicity. This study aims to describe the experience of our department in treating recurrent HNT with RT/HT and to evaluate its therapeutic impact on early response and quality of life.

Material and Methods: A retrospective study of 12 patients with recurrent HNT treated with RT/HT between March 2019 and July 2021. All patients received the same scheme, consisting of radiotherapy twice a week with a 3-day interval, at a dose of 32 Gy in 8 fractions, and 1 hour of hyperthermia once a week, 30 minutes after the radiotherapy session. Hyperthermia was administered using the CelsiusTCS42 system, a non-invasive capacitive hyperthermia device that emits a radiofrequency of 13.56 MHz, allowing for focal and selective tumor temperature increase.

Results: The median age was 61 years (range 48-89). The most frequent location was the maxillary sinus (4 cases), followed by the larynx (2 cases). In all cases, there was a complete response in terms of pain/bleeding control. Control of infection/necrosis was achieved in 75%, and a complete response was observed in 50% of the patients. The treatment was generally well-tolerated, with no reports of grade ≥ 3 toxicity.

Conclusion: In our study the combination of RT/HT has demonstrated to be a feasible and safe strategy in addressing the recurrence of previously irradiated HNT. In addition to the observed physical impact, there was also a noticeable psychological impact, given the location of the disease in exposed areas related to basic activities of daily living. Further studies will be needed to assess late response, duration of remission and the combination with systemic therapy.

Keywords

Recurrence, Head and Neck Neoplasms, Radiotherapy, Hyperthermia.

Introduction

Head and neck tumors (HNT) not only represent a potentially fatal diagnosis but often result in significant disfigurement and disruption of essential functions, including eating, swallowing,

breathing, and speaking [1]. Recurrences of head and neck tumors are associated with a poor prognosis, with palliative treatment being the only option in most cases [2]. Many of these patients have previously undergone radical radiation therapy, and at the time of re-irradiation, the dose tolerance of critical organs (spinal cord and brainstem) poses a limitation to treatment. While the combination of RT with cisplatin or cetuximab offers improved survival rates, the heightened toxicity and patients' comorbidities highlight the necessity for a radiosensitizer with lower toxicity [3]. For recurrent HNT, the preferred treatment options are surgery or (re)irradiation, which are determined based on the tumor's location and prior irradiation history. However, only 20% of patients are suitable candidates for this approach, and the local tumor control rate after retreatment ranges from 26% to 52% [4,5]. Consequently, the 2-year overall survival for patients undergoing re-irradiation and chemotherapy stands at 10-20% [6]. Since many patients succumb to local recurrence or residual disease, there is a pressing need for improved loco-regional treatments. Hyperthermia has been recognized for its potential to enhance the therapeutic effectiveness against radiation-resistant tumors and several randomized trials have demonstrated benefits in tumor control and survival when hyperthermia is combined with radiation therapy [7-10]. The combination of radiotherapy with hyperthermia (RT/HT) has shown an important role in recurrent disease that has been previously irradiated, given its complementary tumoricidal effect. Hyperthermia at 39-45°C is considered one of the most effective radio sensitizers through inhibition of DNA damage repair, enhancement of 'S' phase cells as well as hypoxic cell sensitization, particularly of nutritionally deficient cells at low pH levels [11-13]. This article aims to describe our department's experience in treating recurrences of head and neck region tumors using the combination of RT/HT.

Material and Methods

We performed a retrospective study involving 12 patients with recurrent HNT who received treatment with RT/HT between March 2017 and July 2019. Patients eligible for hyperthermia treatment were adults of 18 years and older, with a Karnofsky Performance Score of ≥ 70 and histologically proven HNT. Exclusion criteria were systemic temperatures $>39^\circ\text{C}$, oxygen saturation $<90\%$, metal implants in the head and neck region, claustrophobia, and the presence of a pacemaker. Hyperthermia was administered using a non-invasive, local capacitive hyperthermia medical device (Celsius TCS – Tumor Cell Solution - 42+ GmbH D-51107), which through 2 active electrodes, emits a radiofrequency of 13.56 MHz, allowing for the selective focal elevation of tumor temperature (Figure 1). For radiotherapy, a computerized tomography (CT) scan was made while applying a patient-specific thermoplastic mask. All the patients underwent intensity-modulated radiation therapy (IMRT) twice a week (32 Gy in total, delivered at 4 Gy per day over a total of 8 fractions, with a 3-day interval between fractions) (Figure 2). Additionally, each patient received 1 hour of hyperthermia treatment per week, administered 30 minutes after the completion of the radiotherapy session, achieving 39-42°C in the target area, up to the patients' tolerance. Patients were weekly examined for the development of skin or subcutaneous burns

within 24 h after treatment. Toxicity was assessed according to the generic Common Terminology Criteria for Adverse Events (CTCAE) protocol, version 5.0.

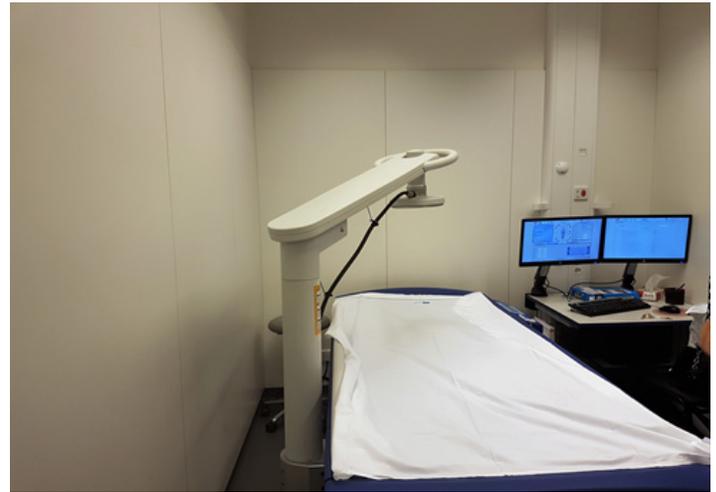


Figure 1: Celsius TCS 42 system.

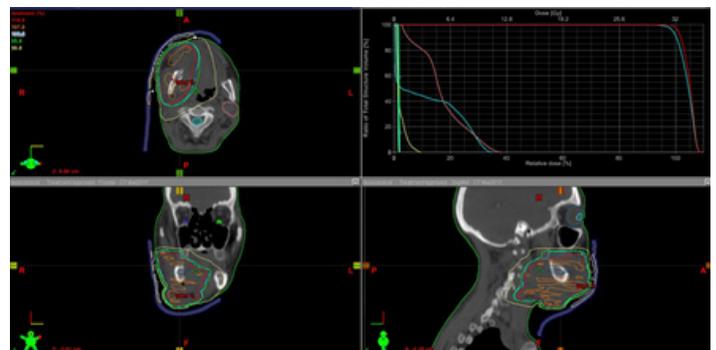


Figure 2: Example of a radiotherapy treatment planning.

Results

The study included a cohort of 12 patients with recurrent HNT with a median age of 61 years (range 48 to 89); 66% were male and 33% were female. The distribution of patients based on the tumor location was as follows: 4 in the maxillary sinus, 2 in the larynx, 2 in the skin, 1 in the hypopharynx, 1 in the oropharynx, 1 in the nasal cavity, and 1 in the parotid gland. None of the patients were undergoing other treatments during RT/HT, including chemotherapy or immunotherapy. Two patients did not complete hyperthermia treatment due to intolerance. After a median follow up of 16 months (range 2-24), 100% of the cohort, experienced improvement in pain and/or hemorrhage control. Additionally, 75% of patients achieved infection and necrosis control, and 50% of patients exhibited a complete clinical response in terms of tumor lesions. Figure 3 illustrates two examples of complete clinical responses 1 month after treatment. The most common acute treatment-related toxicity described was mucositis in 5 patients. There were no reports of treatment-related toxicities graded ≥ 3 in any of the patients.



Figure 3: Photographs of examples of complete clinical responses 1 month after RT/HT. A – Cutaneous recurrence of squamous cell carcinoma; B - Extensive recurrence of pharyngolaryngeal carcinoma.

Discussion

Recurrence of head and neck cancer after radiotherapy is observed in approximately 30–40% of patients [14,15]. Delivering an adequate radiation dose for the treatment of locally recurrent cancer after previous radiotherapy poses challenges due to the necessity of limiting the radiation dose to organs at risk. Re-irradiation cases often involve radioresistant tumors that are inherently challenging to manage locally, resulting in a generally unfavorable prognosis [16]. Chemotherapy is a commonly employed strategy to enhance the effectiveness of radiotherapy. Nevertheless, the use of chemotherapy can lead to amplified side effects related to radiotherapy and may entail potential systemic side effects, thereby limiting its application in patients with concurrent medical conditions [6]. Hyperthermia may offer an alternative to chemotherapy as a means of enhancing the impact of radiotherapy. In primary HNC cases, raising target temperatures to the range of 40–44°C has been shown to yield approximately a 20 percent increase in local control (LC) [5]. However, in the case of recurrent HNC, the role of adjunctive hyperthermia alongside radiotherapy has not been extensively investigated [3,17]. While a few isolated studies conducted on locally advanced HNT have shown promise, hyperthermia has not gained widespread acceptance within the field of oncology. This may be attributed to several factors, including a lack of adequately large randomized clinical trials, paucity of specialized hyperthermia equipment tailored for the head and neck region, limited thermometry techniques, and a scarcity of hyperthermia treatment planning software. In a systematic review and meta-analysis conducted by Datta et al. revealed an overall complete response with radiotherapy alone of 39.6% (92/232). With thermoradiotherapy, the overall complete response was 62.5% (137/219). The odds ratio was 2.92 (95% CI: 1.58–5.42) favoring the combined treatment of hyperthermia and radiation over radiation alone. Acute and late grade III/IV toxicities were reported to be similar in both groups [13]. Moreover, in a phase III trial conducted by Huilgol et al., hyperthermia-enhanced radiation

treatment yielded a higher complete response rate (42.4% in the radiotherapy alone group compared to 78.6% in the hyperthermia group) [18]. More recently, Kroesen et al. have developed the Hypercollar3D to enable improved application of hyperthermia for deeply located HNT as an adjuvant to reirradiation in recurrent or second primary HNT patients. They reported a complete response rate of 81.8% (9/11) at 12 weeks following definitive thermoradiotherapy. Two-year local control (LC) and overall survival (OS) were 36.4% (95% CI 17.4–55.7%) and 54.6% (95% CI 32.1–72.4%), respectively. Cumulative grade 3 or higher toxicity was 39.2% (95% CI 16.0–61.9%). Local control and local toxicity rates were comparable to those reported for recurrent or second primary HNC [19]. The results of our study have unveiled the success and high tolerability of RT/HT in the treatment of recurrences of previously irradiated HNT. In our cohort, 100% of the patients exhibited improved pain and/or hemorrhage control, while 75% achieved effective control over infection and necrosis. Impressively, 50% of the patients demonstrated a complete response to the treatment. Furthermore, it is noteworthy that there were no instances of treatment-related toxicities graded ≥ 3 among any of the patients in our study. Considering hyperthermia's ability to enhance treatment outcomes without increasing toxicity, further investigation of the combination of radiotherapy and hyperthermia for HNT is warranted [20].

Conclusion

The combination of RT/HT has proven to be a feasible and safe strategy in addressing the recurrence of previously irradiated head and neck cancer. This approach has yielded a favorable clinical response, ensuring effective local control. Moreover, it has led to a notable reduction or even complete disappearance of tumor lesions. The psychological impact of this treatment is significant, particularly due to the disease's location in exposed areas closely associated with essential activities of daily life. Further prospective randomized trials will be required to integrate hyperthermia as an essential component of the multimodality therapeutic approach, especially for locally/recurrent advanced HNTs.

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