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Phase II clinical trial assessing the addition of hyperthermia to salvage concurrent chemoradiotherapy for unresectable recurrent head and neck cancer in previously irradiated patients

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Abstract

Background This single-arm phase II trial aimed to assess the effectiveness and safety of incorporating hyperthermia into salvage concurrent chemoradiotherapy (CCRT) for previously irradiated unresectable recurrent head and neck cancer.

Methods We enrolled patients with non-metastatic recurrent head and neck cancer who had previously undergone radiotherapy (RT) and were unfit for salvage surgery. Eligible patients received hyperthermia during salvage CCRT. RT consisted of an upfront boost with 10 Gy in 2 fractions to gross tumor volume, followed by 40 Gy in 20 fractions to clinical target volume, for a total of 50 Gy in 22 fractions. Weekly hyperthermia for 6 sessions started after RT initiation; each session lasted for 40 min, beginning within 2 h after RT and maintaining a maximum temperature of 42 ± 0.5 °C. Concurrent chemotherapy included weekly cisplatin 20 mg/m^2 and docetaxel 10–12 mg/m^2 for 6 weeks. Primary endpoint was overall response rate (ORR). Overall survival (OS), progression-free survival (PFS) and toxicities were evaluated.

Results Among 35 eligible patients, ORR was 82.9%, with complete response in 54.3%, partial response in 28.6%, stable disease in 11.4%, and progressive disease in 5.7%. After a median follow-up of 2.7 years, median OS was 32.8 months (95% confidence interval [CI], 16.7–48.9), and 2-year OS was 57.1% (95% CI, 40.6–73.6). Median PFS was 14.9 months (95% CI, 5.7–24.1), and 2-year PFS was 34.3% (95% CI, 18.6–50.0). Acute mucositis was grade 0–1 in 68.6%, grade 2 in 25.7%, and grade 3 in 5.7%. Acute dermatitis was grade 0–1 in 85.7% and grade 2 in 14.3%. No definite burn injury occurred. Grade 3–4 leucopenia, anemia, thrombocytopenia accounted for 14.3%, 14.3%, and 8.6%, respectively. Osteonecrosis was noted in 12 patients. No grade 5 toxicity was observed.

Conclusions Adding hyperthermia to salvage CCRT greatly enhances tumor response and survival rates compared to historical re-irradiation outcomes for previously irradiated unresectable recurrent head and neck cancer, with manageable toxicities.

Trial registration ClinicalTrials.gov (Identifier: NCT02567383), Registered October 1 ,201 5 -https://www.clinicaltrials.gov/study/NCT02567383

Keywords Recurrent head and neck cancer, Hyperthermia, Concurrent chemoradiotherapy

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Background

Despite aggressive efforts to combat head and neck cancer, a significant number of patients experience locoregional recurrence or develop metastatic disease. The prognosis for recurrent head and neck cancer is generally poor, with a median overall survival ranging from 6 to 12 months [1–5]. Only a select group of patients with locoregional recurrence is eligible for surgical salvage [6–8]. For patients with unresectable recurrent disease or those unsuitable for surgery, salvage nonsurgical treatments including radiotherapy (RT), chemotherapy, cetuximab or immunotherapy are recommended. However, the tumor response rate was only 10 to 36% in salvage chemotherapy with or without cetuximab [4], less than 20% in immunotherapy alone [3], and 52% for chemotherapy combined with high doses re-irradiation [1]. Notably, prior full-dose radiotherapy (RT) restricts the potential for re-irradiation due to normal organ tolerance limits. In this context, there is a compelling need for innovative and effective treatment approaches to improve the outcomes of this challenging patient population.

Hyperthermia sensitizes cells to radiation or chemotherapy at temperatures below 43 °C [9–11]. Early studies in the 1990s demonstrated the synergistic effects of hyperthermia when combined with radiation or chemotherapy, and positive phase III trials have supported hyperthermia's efficacy in various cancers, including head and neck cancer [12–20]. It has demonstrated the potential to enhance local control and achieve durable responses. A Japanese study showed that hyperthermia plus chemoradiotherapy (CCRT) with docetaxel and cisplatin provided good pathological response and locoregional control rates in primary advanced oral cancer patients with N3 metastatic lymph nodes [21]. Hyperthermia combined with CCRT may have its role in the management of recurrent head and neck cancer, which has not been reported.

The prognosis for patients with treatment-failure head and neck cancer is disheartening, and the strategy of using hyperthermia in combination with salvage CCRT deserves exploration. The primary objective of the phase II study was to assess the effectiveness and safety of incorporating hyperthermia into the salvage CCRT regimen for patients with previously irradiated unresectable recurrent head and neck cancer. This study aimed to address the complex clinical scenario presented by these patients and to evaluate the potential clinical utility of hyperthermia as an adjunct therapy.

Methods

Study design and patients

This single-arm phase II study aimed at evaluating the efficacy and safety of combining hyperthermia with CCRT for recurrent head and neck cancer. This study was approved by the institutional review board (No. 20150205D) and was registered in ClinicalTrials.gov (Identifier: NCT02567383). All patients provided informed consent before any study-specific procedures were initiated. We enrolled patients aged 20 to 85 years with non-metastatic recurrent head and neck cancer who had previously undergone RT and were not suitable candidates for salvage surgical excision. Previously irradiated patients were defined as those with recurrent disease in areas previously treated with a cumulative radiation dose of 40 Gy or higher, with prior RT completed at least 6 months before initiation of re-irradiation to allow for sufficient recovery of normal tissues. Only patients who received conventional regimens of 1.6 to 2.2 Gy per fraction were included. Eligible patients included those who had previously received treatments such as surgery, chemotherapy, RT, targeted therapy, or various combinations of these modalities. Measurable lesions were identified through imaging examinations or endoscopy, with the distribution of these lesions not exceeding a 20 cm range. Patients were required to demonstrate tolerability for concurrent chemotherapy with cisplatin and docetaxel. Lastly, the study enrolled patients for whom no other effective treatment option was available, as determined by the treating physicians.

Exclusion criteria included cases where re-irradiation with the protocol doses was not tolerable and when evaluating future tumor response using image examinations or endoscopy was not feasible. Participation in other clinical trials, inability to undergo regular clinical follow-up, the presence of large metallic implants or tattoos, or medical conditions that posed risks to hyperthermia treatment were also grounds for exclusion. Difficulty with communication and other contraindications to hyperthermia treatment were also considered exclusion criteria. For communication difficulties, patients were assessed during the initial consultation and screening process. Evaluation included their ability to comprehend and provide informed consent, follow treatment instructions, and communicate effectively during hyperthermia sessions. Factors such as advanced dementia, severe cognitive impairment, or language barriers without adequate interpretation support were considered exclusionary to ensure patient safety and treatment compliance.

Regarding contraindications to hyperthermia, we excluded patients with conditions that could increase the risk of adverse events or hinder effective hyperthermia delivery. Specific contraindications included: active infections, severe skin conditions, open wounds or pacemakers at or near the treatment site; implanted metallic devices or prostheses within the target area that could interfere with uniform heat distribution; inability to remain in a stable position for the duration of the hyperthermia session.

The treatments received for the original primary cancer varied among the enrolled 35 patients. A total of 4 patients (11.4%) underwent surgery followed by RT, while 16 patients (45.7%) received surgery followed by CCRT. Definitive RT alone was administered to 3 patients (8.6%), and 12 patients (34.3%) were treated with definitive CCRT. All of them previously received RT as at least part of their treatment for head and neck cancer. A subset of patients received concurrent chemotherapy during their initial RT, typically with cisplatin-based regimens, depending on cancer staging, tumor features and institutional protocols.

Treatment protocol

Patients meeting the eligibility criteria underwent hyperthermia as part of salvage CCRT at conservative dosage levels. The prescribed treatment protocol involved an upfront boost with 10 Gy of RT administered in 2 fractions to gross tumor volume (GTV) over the first 2 weeks, followed by an additional 40 Gy in 20 fractions to clinical target volume (CTV) over the subsequent 4 weeks, resulting in a total of 50 Gy delivered in 22 fractions. Hyperthermia sessions were integrated once per week, commencing from the initial week of RT and extending for a total of 6 sessions. Each hyperthermia session extended for 40 min, commencing within 2 h after RT initiation, and maintained a maximum temperature of 42 ± 0.5 °C. The concurrent chemotherapy encompassed weekly administrations of cisplatin at a dose of 20 mg/m^2 and docetaxel at a dose of 10–12 mg/m^2 over the course of 6 weeks.

The RT planning included generating a CTV with a 10 mm margin around the GTV to account for potential microscopic disease using computed tomography (CT) simulation. The planning target volume (PTV) was created with a 3–5 mm margin around the GTV or CTV. Risk organs were identified, and treatment plans were generated using intensity-modulated radiotherapy (IMRT) technique. The radiation therapy doses prescribed to the PTV were as mentioned earlier, with allowable variations of up to plus or minus 10% in adherence to the protocol. Any deviations from these prescribed doses were explicitly permitted under two conditions: (1) when physicians observed potential suboptimal tumor responses at 44 Gy in cumulative reirradiation doses, indicating the need for dose escalation to improve therapeutic outcomes; (2) when patients exhibited intolerability to treatment-related toxicities, requiring dose adjustments to maintain safety. For dose escalation decisions, suboptimal tumor response was assessed based on clinical examination, imaging findings (if available during the treatment course), and multidisciplinary discussions. All dose adjustments were documented in the patients' treatment plans and reviewed by the radiation oncology team to ensure consistency and adherence to protocol guidelines. The Pinnacle treatment planning system (Philips, ADAC, Milpitas, CA) was used for treatment planning. For IMRT re-irradiation, dose constraints for organs at risk were carefully considered to balance efficacy and safety. The cumulative dose to the spinal cord, brainstem, optic apparatus, cochlea, mandible bone, and carotid arteries should not exceed 54 Gy, 58 Gy, 58 Gy, 60 Gy, 114 Gy, and 120 Gy, respectively, with re-irradiation doses limited to < 6–10 Gy, < 10–15 Gy, < 8–10 Gy, < 15 Gy, < 54 Gy, and < 54 Gy, respectively. These constraints were adjusted based on the patient's prior treatment, the prior dose and interval, tumor location, and specific factors, under the guidance of a multidisciplinary team.

Hyperthermia was administered using radiofrequency (RF) capacitive devices, Thermotron RF-8 (Yamamoto VINITA Co., Osaka, Japan), which is a well-established treatment modality used in Japan since 1979 [22, 23]. The size of electrodes was determined based on the tumor's location, depth, and size [24]. Briefly, for large and deep-seated tumors, a pair of large electrodes was used; for superficial tumors, a small electrode was coupled to the lesions, opposing a larger electrode. By planning system provided by Thermotron RF-8, CT simulation was used for hyperthermia treatment planning to simulate an adequate regional temperature distribution to cover all target tumors including recurrent tumors and metastatic lymph nodes if any. Among all patients, thermometry probes were placed to monitor temperatures in tumor and normal tissues. For tumor sites, a sensor catheter with 4 thermometry points was placed to monitor intratumoral or intracavitary temperature whenever possible considering the tumor location and the patient's tolerability and agreement to invasive measurement. Thermometry probes were also placed on the surrounding normal tissues and skin within the hyperthermia area to monitor normal tissue and surface temperatures. The temperature was set not to exceed 43 °C. Heating power outputs were gradually increased up according to patient's tolerance. Patients were carefully instructed to mention any unpleasant sensation suggestive of hot spots, such as burning sensation, pressure or any pain. Patient-reported

symptoms during hyperthermia sessions, such as discomfort, burning sensations, or heat intolerance, were systematically documented by trained staff in real-time, both during and immediately after each session. When patients reported symptoms that exceeded a subjectively tolerable level, the heating power was temporarily reduced, and the treatment area was reassessed for hot spots or uneven heat distribution. In cases where symptoms persisted despite adjustments, sessions were paused or terminated based on clinical judgment. These data were documented in patient records but were not formally analyzed for this study, as the main study endpoints focused on treatment efficacy and safety rather than patient-reported outcomes. Nonetheless, this feedback mechanism played a crucial role in ensuring patient safety and optimizing the delivery of hyperthermia treatment.

Assessment

Patients underwent a range of evaluations, including history, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status and blood tests before and during the study. Image examinations (CT, magnetic resonance imaging, or positron emission tomography scan) and endoscopy were performed to demonstrate a non-metastatic recurrent head and neck cancer before study and to evaluate tumor response at week 12. Tumor response rates were assessed using Response Evaluation Criteria in Solid Tumors version 1.1, with a complete response (CR) indicating the complete disappearance of all lesions. A partial response (PR) was defined as at least a 30% reduction in the sum of diameters of target lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of diameters, with a minimum absolute increase of 5 mm. Stable disease (SD) was assigned when neither a sufficient shrinkage to qualify as a partial response nor an increase to qualify as progressive disease was observed. All adverse events, including treatment-related toxicities, were assessed according to the Common Toxicity Criteria for Adverse Events version 4.0. For toxicities of grade 3 or lower, dose reduction or delay was allowed based on physician's evaluation and the individual patient's tolerability. Hyperthermia combined with CCRT treatment was discontinued in the event of any grade 4 toxicities.

Statistics

This study employed a Gehan two-stage design to evaluate the preliminary efficacy of the treatment. Initially, the expected response rate was set at 40% ($p_{\text{expected}}=0.4$). In the first stage, 6 patients ($n_1=6$) were enrolled to rapidly assess efficacy, with a 95.3% probability of observing at least one response if the treatment's true efficacy matched the expected value. Notably, 4 of the 6 patients in the first stage responded, yielding an observed response rate of 67% ($p_{\text{observed}}=0.67$).

The sample size for the second stage was determined based on the observed response rate of 67% in the first stage. Following Gehan's original recommendation, the upper bound of Wald-based confidence interval is often used for efficiency in exploratory trials. To provide a more robust evaluation of treatment efficacy, the upper bound of the 80% Wald-based confidence interval for p_{observed} was adopted and calculated as:

$$p_{upper} = p_{observed} + Z \times SE_{observed}$$

where $Z=1.2816$ (for 80% confidence level) and the standard error (SE) of the observed response rate: $SE_{observed} = \sqrt{p_{observed}(1-p_{observed})/n_1}$. Substituting these values, $p_{\text{upper}}=0.9161$. To achieve a precision of 5% ($SE_{\text{precision}}=0.05$), the total sample size was calculated using the formula:

$$SE_{precision} = \sqrt{\frac{p_{upper}(1-p_{upper})}{n}}$$

where $p_{\text{upper}}=0.9161$. This resulted in $n=31$. Accounting for an assumed 10% dropout rate, the final sample size was adjusted to $n_{\text{adjusted}}=35$ to ensure sufficient power and precision to evaluate the treatment efficacy. Since 6 patients were already enrolled in the first stage, an additional 29 patients were recruited in the second stage.

The primary endpoint was the overall response rate (ORR), defined as the percentage of CR and PR case numbers among all patients at week 12. Descriptive statistics were presented using percentages for categorical variables and medians with the ranges included in parentheses for continuous variables. Furthermore, we conducted analyses of overall survival (OS) and progression-free survival (PFS) and meticulously recorded any observed toxicities. Survival curves were generated and analyzed using the Kaplan–Meier method, with the Log-rank test employed to assess the statistical significance of differences between subgroups. Statistical significance was set at a p-value of <0.05 (two-tailed). All statistical analyses were carried out using the Statistical Package for Social Sciences software, version 20 (SPSS, Inc., Chicago, IL).

Results

In this study, a total of 35 eligible patients were enrolled, representing a diverse cohort with a median age of 61 years (ranging from 37 to 73 years). The majority of the patients in the cohort were male, accounting for 91.4% of the total, and all had an ECOG

Table 1 Patient and disease characteristics ($n=35$)

Age, years, median (range)	61 (37–73)
Gender (Male: Female)	32:3
ECOG performance status	
0–1	35 (100%)
2	0 (0%)
Original primary sites	
Oral cavity	21 (60%)
Oropharynx, Hypopharynx or Larynx	7 (20%)
Nasopharynx or paranasal sinus	7 (20%)
Pathology type	
Squamous cell carcinoma	28 (80%)
Undifferentiated carcinoma	7 (20%)
Treatment for original primary cancer	
Surgery followed by RT	4 (11.4%)
Surgery followed by CCRT	16 (45.7%)
Radiotherapy alone	3 (8.6%)
CCRT	12 (34.3%)
Previous RT details	
Dose, Gy, median (range)	66 (60–74)
Fraction number, median (range)	33 (29–40)
Target volume	
Primary site plus regional lymph nodes	33 (94.3%)
Primary site only	2 (5.7%)
Technique	
IMRT	34 (97.1%)
3D-CRT	1 (2.9%)
Interval from previous RT, months, median (range)	34.2 (6.1–242.3)
Recurrent sites for salvage	
Local	16 (45.7%)
Regional	8 (22.9%)
Local–regional	11 (31.4%)

Values are number (percentage) unless otherwise noted

ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy

performance status of less than 2 (Table 1). All participants had previously undergone RT for head and neck cancer. The median previous radiation dose was 66 Gy (range, 60–74 Gy) delivered in 33 fractions (range, 29–40). The median interval from previous RT was 34.2 months (range, 6.1–242.3 months). Among all 35 eligible patients, 33 (94.3%) previously received RT to the local–regional area (primary site plus regional lymph nodes) for their initial head and neck cancer, while 2 (5.7%) were treated only to the primary site. Regarding the technique used in the initial RT, 34 patients (97.1%) were treated with intensity-modulated radiotherapy (IMRT), and 1 patient (2.9%) was treated with 3-dimensional conformal radiotherapy (3D-CRT). The oral cavity was the most prevalent primary tumor site, accounting for 21 cases (60%). The most common recurrence patterns were local recurrence in 16 patients (45.7%) and locoregional recurrence in 11 patients (31.4%).

The adherence to the study protocol was commendable, with most patients successfully completing the proposed treatment regimen. Specifically, the median RT doses and fractions administered were 50 Gy and 22 fractions, respectively. Nine patients were administered radiation therapy doses exceeding the protocol's recommended levels, based on physicians' observations of potential suboptimal tumor responses during treatment, as permitted by the protocol. A substantial number of patients adhered to the concurrent chemotherapy regimen as outlined in the protocol. Merely 3 patients did not receive cisplatin, and another 8 patients eventually did not receive docetaxel. Nevertheless, all patients received at least one of the chemotherapy agents defined by the protocol. Remarkably, the median count of weekly hyperthermia sessions was 6, with a

Table 2 Treatment details ($n=35$)

Radiotherapy	
Dose, Gy, median (range)	50 (48–64)
Fraction number, median (range)	22 (21–29)
Duration, days, median (range)	36 (30–53)
Chemotherapy	
Weekly cycles, median (range)	6 (1–6)
6 cycles	22
5 cycles	7
3 to 4 cycles	5
1 to 2 cycles	1
Cisplatin (yes: no)	32:3
Docetaxel (yes: no)	26:8
Hyperthermia	
Weekly cycles, median (range)	6 (4–6)
6 cycles	31
5 cycles	3
4 cycles	1

Values are number unless otherwise noted

Table 3 Tumor response ($n=35$)

Complete response (CR)	19 (54.3%)
Partial response (PR)	10 (28.6%)
Stable disease (SD)	4 (11.4%)
Progressive disease (PD)	2 (5.7%)
Overall response rate (CR + PR), %	82.9%
Disease control rate (CR + PR + SD), %	94.3%

Values are number (percentage) unless otherwise noted

minimum of 4 sessions recorded (Table 2). Specifically, 31 patients successfully completed the full course of 6 hyperthermia sessions, while 3 patients received 5 sessions, and only 1 patient underwent 4 sessions.

The treatment outcomes were promising, with an impressive ORR of 82.9% (Table 3). Among these responses, 54.3% achieved a CR, while 28.6% experienced a PR. Additionally, 11.4% of patients had SD, and only 5.7% exhibited PD. After a median follow-up duration of 2.7 years, the median OS reached 32.8 months (95% confidence interval [CI], 16.7 – 48.9), with the 1-year OS rate of 80.0% (95% CI, 66.7 – 93.3) and the 2-year OS rate of 57.1% (95% CI, 40.6 – 73.6) (Fig. 1a). The study also reported a median progression-free survival (PFS) of 14.9 months (95% CI, 5.7 – 24.1), with a 2-year PFS of 34.3% (95% CI, 18.6 – 50.0) (Fig. 2). The median time to progression (TTP) was found to be 34.9 months. Interestingly, the 2-year rates of local–regional failure and distant metastasis were identified as 41.5% and 17.2%, respectively. The median survival of patients who achieved a CR was not reached, in contrast to the median survival of 12.2 months observed in non-CR patients ($p < 0.001$) (Fig. 1b).

In terms of treatment-related toxicities (Table 4), the study demonstrated that most patients experienced low-grade acute mucositis, with 68.6% classified as grade 0–1, 25.7% at grade 2, and a small proportion at grade 3 (5.7%). Notably, no patients exhibited severe grade 4–5 mucositis. Acute dermatitis was similarly manageable, with 85.7% of patients graded at 0–1, 14.3% at grade 2, and none at the more severe grade 3–5. Skin erythematous change within the hyperthermia area was often observed for 1 or 2 h following treatment, but no definite burn injury occurred among all patients. Hematological toxicities included grade 3–4 leucopenia in 14.3% of cases, while anemia and thrombocytopenia were each observed at this grade in 14.3% and 8.6% of patients, respectively. Among the patients who experienced grade 3–4 hematological toxicities (leucopenia, anemia, or thrombocytopenia), the median number of days of treatment interruption was 3 days (range: 1–15 days). About late treatment-related toxicities, it is noteworthy that only 12 cases of osteonecrosis were reported, despite all patients having a history of prior radiotherapy. Additionally, severe fibrosis was observed in 9 cases, while 12 cases exhibited local infection. Two unique cases of late toxicities were documented, including one instance of carotid blowout and another of brain necrosis. The patient who experienced a carotid blowout was successfully rescued through embolization treatment and notably achieved a complete response, still being alive at the time of data analysis. The patient with brain necrosis experienced dizziness and was diagnosed via MRI showing temporal lobe necrosis near the re-irradiated field. The symptom improved with steroid therapy, and the patient remains alive with a complete response and no recurrence. Fortunately, no cases of severe grade 5 toxicity were observed throughout the study.

Discussion

Recurrence and metastasis in head and neck cancer pose significant challenges, especially with locoregional recurrence being a prevalent issue. Despite various available options, the prognosis for recurrent head and neck cancer is often poor, with a median overall survival of 6 to 12 months [1–5]. In recent multi-institution cohort studies, salvage re-irradiation utilizing IMRT with a median dose of 60 Gy achieved a median survival of over 1 year and a 2-year survival rate of approximately 40% in patients with unresectable recurrent head and neck cancer [6, 25]. However, there is room for improvement.

In our present study, the introduction of hyperthermia into salvage CCRT utilizing IMRT has yielded remarkable improvements in the treatment of patients with recurrent head and neck cancer. The rationale for selecting the protocol treatment in this phase II study was based on the fact that most patients with recurrent head and neck cancer had a history of prior irradiation, making a total radiation dose of 50 Gy relatively safe for re-irradiation. The study adhered to standard oncology guidelines and previous research endorsing regimens involving cisplatin or carboplatin combined with docetaxel or paclitaxel for recurrent head and neck cancer [21, 26–31]. Weekly cisplatin (20–25 mg/m^2) and docetaxel (10–12 mg/m^2) were selected based on the regimen from a Japanese study [21] that combined hyperthermia with CCRT for advanced head and neck cancer. While the Japanese study used superselective intra-arterial chemotherapy, our study employed intravenous administration. Despite this difference, our study achieved comparable tumor response rates, underscoring that the route of chemotherapy delivery may not significantly influence treatment efficacy when combined with hyperthermia. Considering the conservative doses of chemoradiotherapy, the addition of hyperthermia offered a biologically distinct treatment modality that could potentially enhance oncological outcomes. Even when combined with low-dose CCRT, the tumor response rate in this approach has been impressively high, resulting in a median survival time of 32.8 months and 2-year OS of 57.1%, which substantially outperforms historical outcomes in recurrent head and neck cancer. These results highlight the potential efficacy of adding hyperthermia to CCRT. This significant

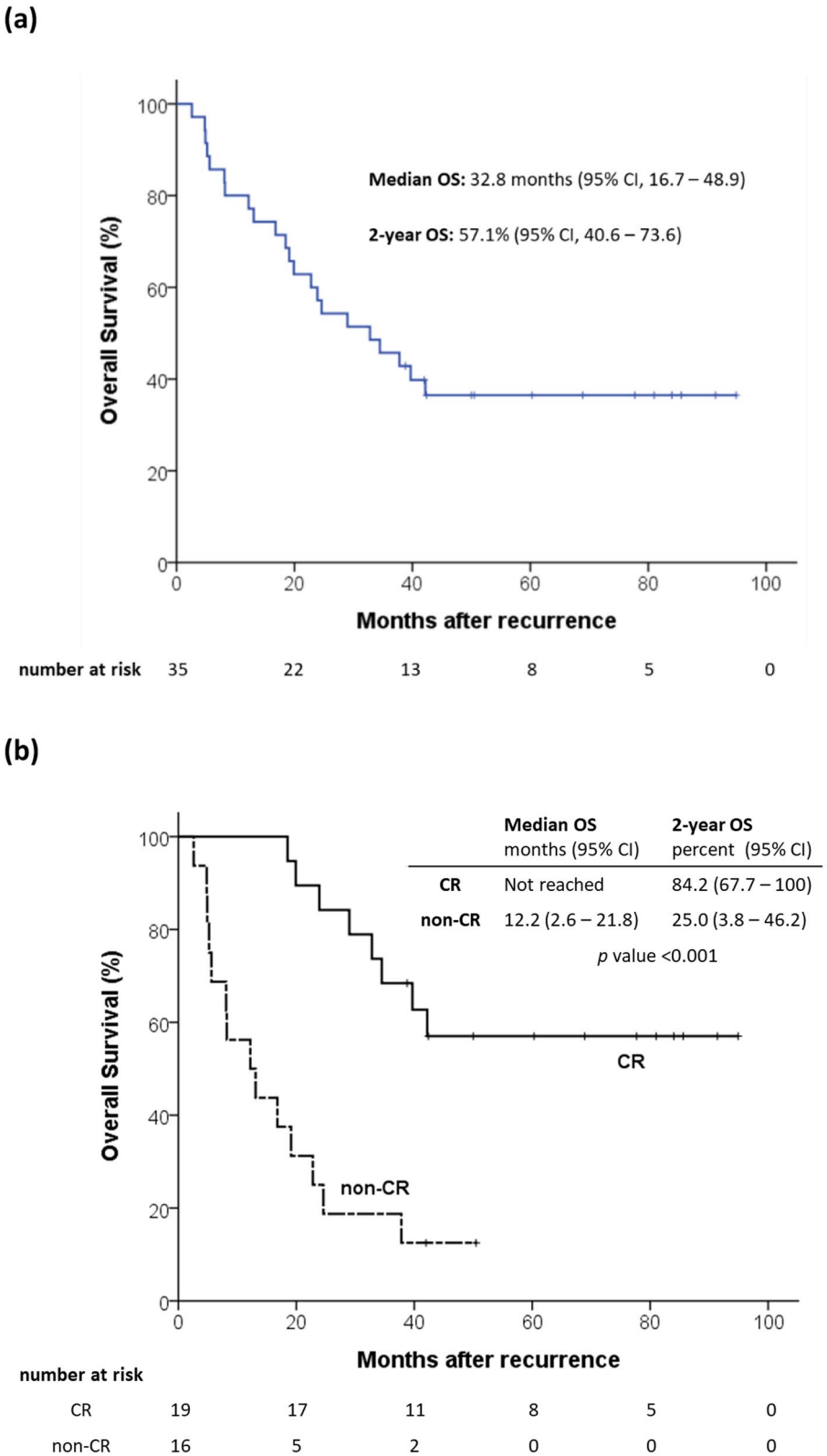

Fig. 1 Overall survival (OS). **a** All patients. **b** Patients with complete response (CR) versus non-CR. OS = overall survival; CR = complete response; CI = confidence interval

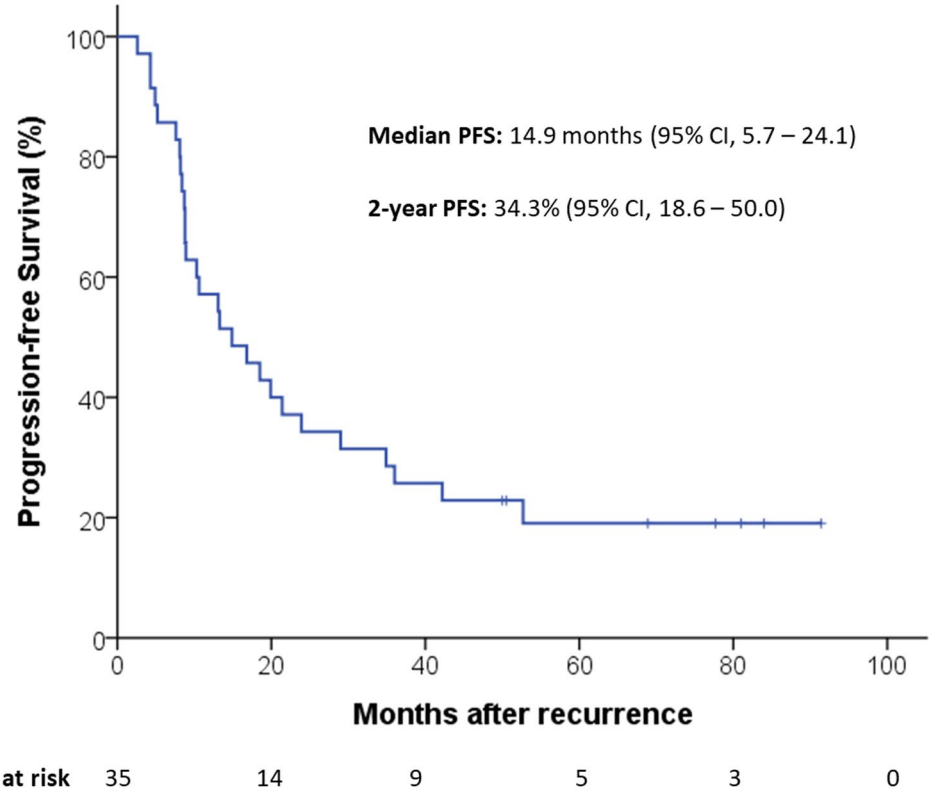

Fig. 2 Progression-free survival (PFS). PFS = progression-free survival; CI = confidence interval

Table 4 Treatment-related Toxicities ($n = 35$)

Acute Toxicities	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
mucositis	10	14	9	2	0
dermatitis	17	13	5	0	0
nausea/vomiting	30	3	2	0	0
leucopenia	13	3	14	4	1
anemia	4	16	10	5	0
thrombocytopenia	28	4	0	1	2
Late Toxicities					**Patient number**
osteonecrosis					12
severe fibrosis					9
local infection					12
carotid blowout					1
brain necrosis					1

Values are number unless otherwise noted

enhancement in treatment efficacy can be attributed to various key factors.

Importantly, the results from our study revealed an ORR exceeding 80%, surpassing outcomes typically achieved with systemic therapy alone. The observed heightened response rate can be conventionally explained by the well-documented phenomenon of chemoradiosensitization induced by hyperthermia [32, 33]. The application of hyperthermia during CCRT likely renders cancer cells more susceptible to the treatment's cytotoxic effects, contributing to the increased response rate. Moreover, the notion of radiosensitization is further

supported by a stronger β-enhancement factor 1.3–7.0 than α-enhancement factor 0.3–1.8 in temperature of 41 °C [34], emphasizing the pivotal role of the upfront boost using 5 Gy per fraction with hyperthermia in augmenting the treatment effectiveness.

It is noteworthy that head and neck cancer often fosters an immunosuppressive microenvironment characterized by impaired tumor-infiltrating T lymphocytes, diminished natural killer (NK) cell activity, and reduced absolute lymphocyte counts. [35–37]. While immunotherapy utilizing immune checkpoint inhibitors has exhibited promise for recurrent and metastatic head and neck cancer [3], its substantial financial burden may pose a constraint for many patients. Hyperthermia has emerged as a promising strategy, not only sensitizing chemoradiotherapy but also demonstrating potential as an immune-stimulating approach, as supported by preclinical data [38, 39]. Hyperthermia has been shown to promote immune responses through several mechanisms. It can enhance the immunogenicity of tumor cells by increasing the expression of heat shock proteins (HSPs), which can facilitate the presentation of tumor antigens to immune cells, thereby enhancing dendritic cell activity and T-cell-mediated immunity. Additionally, hyperthermia can increase tumor perfusion, facilitating immune cell trafficking and delivery of therapeutic agents to the tumor site. The immunomodulatory effects of hyperthermia can create a more favorable microenvironment for the immune system to target and eliminate cancer cells. This immune-stimulating component of hyperthermia could potentially improve response rate and yield unexpected survival benefits. Our study revealed a remarkable survival profile, exhibiting a characteristic plateau in the tail of the overall survival curve comparable to that observed with immunotherapy. Conversely, hyperthermia appears to present a more cost-effective alternative. Future studies could explore biomarkers to predict response to hyperthermia and its role in immune modulation. Elevated levels of heat shock proteins (e.g., HSP70) may indicate enhanced immune activation, while the density of tumor-infiltrating lymphocytes, such as cytotoxic T lymphocytes and regulatory T cells, could reflect the immune response to treatment. Serum cytokine profiles, including IL-6, TNF-α, and IFN-γ, might provide insights into inflammatory and immune activation. Additionally, evaluating PD-L1 expression could help identify patients who may benefit from combining hyperthermia with immunotherapy.

A study by Saba et al. [40] on IMRT reirradiation combined with nivolumab for recurrent or second primary head and neck squamous cell carcinoma, including more than 70% of their patients undergoing salvage surgery before reirradiation, has shown promising results in improving outcomes, with 1- and 2-year and PFS rates of 61.7% and 43.2% respectively, whereas 1- and 2-year OS rates were 84.4% and 48.4% respectively. This suggests that reirradiation, coupled with immune checkpoint inhibitors, may enhance treatment efficacy. However, considering our trial enrolled only patients with unresectable diseases, our 2-year PFS of 34.3% and 2-year OS of 57.1% were still deemed comparable. While we focused on hyperthermia as an adjunct, future studies could investigate the potential synergistic effect of combining hyperthermia with immunotherapy agents such as nivolumab to further improve outcomes in this challenging population.

Our findings should be considered within the context of evolving reirradiation strategies, including high-dose CCRT [1, 5, 6], stereotactic body radiotherapy (SBRT) [25, 41], and particle therapy [42–45], which reported median survival times ranging from 8 to 26 months. Proton therapy, in particular, provides a precise dose distribution with reduced exposure to surrounding healthy tissues, making it a promising option for patients with prior radiation. In a recent study by Lee et al. [45], proton therapy reirradiation was evaluated in 242 patients with recurrent head and neck squamous cell carcinoma, 40.5% of whom underwent salvage surgery prior to reirradiation. Among those treated with fractionated proton therapy, 1-year local control and overall survival rates were 71.8% and 66.6%, respectively, with higher performance status and prior salvage surgery correlating with improved survival. Our study demonstrated impressive efficacy by incorporating hyperthermia into salvage CCRT, achieving a median OS of 32.8 months and a 1-year OS rate of 80%. This approach offers comparable survival outcomes and represents a practical alternative in resource-limited settings where advanced treatment modalities may not be readily available. Future trials should explore the potential synergy between hyperthermia and advanced radiotherapy techniques like proton therapy to further optimize outcomes and minimize toxicities in this challenging patient population.

In our study, the high proportion of oral cavity cases (60%) likely reflects the predominance of head and neck cancers originating in the oral cavity in our region, influenced by prevalent risk factors such as betel nut chewing, smoking, and alcohol consumption. These factors significantly contribute to the elevated incidence of oral cavity tumors in our patient population. Additionally, inoperability was a notable factor, as many patients with recurrent oral cavity tumors presented with advanced disease involving critical structures or had significant comorbidities, making them unsuitable candidates for salvage surgery. Managing recurrent tumors in the oral cavity poses unique difficulties, including issues with achieving

uniform heat distribution due to anatomical constraints and potential discomfort for patients. Despite these challenges, we optimized hyperthermia delivery using customized applicators and closely monitored patient tolerance during treatment sessions. Our results indicate that the integration of hyperthermia was feasible and effective even for oral cavity tumors.

Furthermore, the treatment-related toxicities observed in our study were manageable, enhancing the attractiveness of this therapeutic approach. The acute toxicities during the treatment course were tolerable, with the majority of patients completing the protocol treatment, underscoring the practicality of this approach. Although it was common to observe erythematous skin reaction shortly after hyperthermia, we did not notice definite skin burn injury or exacerbation of radiation dermatitis caused by hyperthermia. Notably, the compliance with hyperthermia was outstanding, as 97% of patients successfully completed 5 to 6 cycles of sessions, surpassing that observed with chemotherapy. Despite all patients having a history of prior radiotherapy, the incidence of osteonecrosis and severe late complications was lower than anticipated. Our study also highlighted the acceptable tolerance among patients with a history of intensive treatments. To address the increased risk of osteonecrosis associated with re-irradiation in the head and neck region, we emphasize the need for comprehensive monitoring and preventive strategies, which can guide future studies and clinical practice. These strategies include regular imaging for early detection, periodic bone density assessments, and optimizing radiation fields using advanced techniques such as proton therapy. A multidisciplinary approach involving radiation oncologists and other specialists is crucial for effective management and better patient outcomes.

The study is subject to several limitations, including its single-arm design, a restricted follow-up duration, and a relatively small sample size. Challenges in patient accrual may be attributed to strict adherence to the protocol, underscoring the importance of maintaining study quality. A more comprehensive interpretation will be possible with long-term follow-up or through the execution of a randomized study. Indeed, we are currently engaged in a randomized controlled phase 3 study that directly compares salvage CCRT with or without hyperthermia for patients with previously irradiated non-metastatic recurrent head and neck cancer. This endeavor necessitates a significantly larger number of participants.

Conclusion

In conclusion, the combination of hyperthermia with CCRT initiated with an upfront boost represents a promising approach for recurrent head and neck cancer, offering a high response rate, manageable side effects, and an encouraging survival benefit. This strategy holds potential as a valuable addition to the armamentarium against this challenging disease, providing hope for patients with limited treatment options and poor prognoses. Further research is warranted to validate these findings and explore their broader applicability in clinical practice.

Abbreviations

CCRT	Concurrent chemoradiotherapy
RT	Radiotherapy
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
CI	Confidence interval
GTV	Gross tumor volume
CTV	Clinical target volume
CT	Computed tomography
PTV	Planning target volume
IMRT	Intensity-modulated radiotherapy
RF	Radiofrequency
ECOG	Eastern Cooperative Oncology Group
CR	Complete responses
PR	Partial responses
PD	Progressive disease
SD	Stable disease
SE	Standard error
3D-CRT	3-Dimensional conformal radiotherapy
TTP	Time to progression
NK	Natural killer
HSP	Heat shock protein
SBRT	Stereotactic body radiotherapy

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Author contributions

KLY and KHC designed the study; KLY, MSC, HLK and KHC arranged radiotherapy and collected study data; CYH and SPH made diagnosis, staged the diseases and collected study data; YYH and RHW performed hyperthermia and collected study data; HCL and YCL administrated chemotherapy and collected study data; KLY performed statistical analyses, interpreted data and wrote manuscript; KHC provided critical review and revision of manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This phase II study was approved by the institutional review board of Shin Kong Wu Ho-Su Memorial Hospital (No. 20150205D).

Consent for publication

Consent for publication was obtained.

Competing interests

The authors declare no competing interests.

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