

Hyperthermia Augments Chemotherapy on Supraglottic Carcinoma: A Case Report

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ABSTRACT: Supraglottic carcinoma is the dominant laryngeal tumor common in India due to chronic alcohol abuse and smoking. Patients often present with non-specific throat pain, dysphagia, and neck lymphadenopathy as the primary disease features of supraglottic carcinoma. In this study, we report a case of a 61-year-old male with a complaint of pain over the right neck with swelling, an open wound with white discharge, and was diagnosed with supraglottis malignancy stage IV with N3 metastasis. The patient was put under the first chemotherapy treatment cycle with paclitaxel, carboplatin, and local hyperthermia (HPT) on the supraglottis. After HPT treatment, the tumor responded and was controlled well, the cancer wound was shrunken, and the pain was reduced significantly. Neoadjuvant chemotherapy and regional HPT have additive antitumor and antimetastatic effects promoting patient recovery. HPT approach has significant merits, especially for treating superficial and deep metastatic sites.

Keywords: Anticancer, carcinoma, chemotherapy, hyperthermia, supraglottic neoplasm.

INTRODUCTION

Laryngeal malignancies are one of the diverse forms of neoplasms that represent one-third of head and neck cancers, causing significant morbidity and mortality. Even though laryngeal neoplasms are globally present, it is one of the most prevalent forms of cancer in India and is often diagnosed in patients with a significant smoking history and the habit of chewing tobacco and tobacco-containing products. The molecular biology of laryngeal malignancy shows either activation of the oncogene, inactivation of tumor suppressor, cellular immortalization, and activation of invasion and metastasis (Cancer Genome Atlas, 2015; Szaumkessel *et al.*, 2017). The disease is highly curable at the early stage with either surgical or radiation therapy to preserve the larynx. At the late stage, the condition is often associated with adverse outcomes, warrants multimodal treatment, and is less likely to allow for the preservation of the larynx. Supraglottic carcinoma is almost exclusively squamous cell carcinoma due to its close association with the glottis and needs to be treated differently from other laryngeal tumors to prevent the function of the larynx, including speech, swallowing, and breathing. Treatment options include surgery, radiation therapy, chemotherapy, or a combination. With the help of an interprofessional team, the present study recognizes laryngeal malignancies and treats the affected patients with hyperthermia (HPT) and chemotherapy. HPT is one of the therapeutic

procedures often combined with other multimodal oncological treatments, in which it works as a sensitizer, thereby increasing the efficiency of curing the disease. HPT is a treatment modality that has shown promise in managing various carcinomas. HPT improves tumor response rates when combined with other cancer therapies, such as radiation and chemotherapy (Kroesen *et al.*, 2019; Rijkhorst *et al.*, 2007). Cancer cells are more sensitive to heat than normal cells, and increased temperatures can lead to the selective destruction of tumor cells. Under this procedure, the temperature is slightly and slowly increased over the cancer-affected area by various methods to achieve the desired temperature. The preclinical studies show a synergistic interaction between hyperthermia and radiation dose in cytostatic treatments (Bull, 1984; Kok *et al.*, 2023).

For the combination of radiotherapy and hyperthermia, the effect is more remarkable for simultaneous application, but this is not feasible in clinical practice. Several types of interaction of heat with chemotherapeutic drugs have been found, six such as supra-additive (alkylating agents, platinum compounds), threshold behavior (doxorubicin), and independent or additive (fluorouracil, taxanes, vinca alkaloids). The synergistic effect *in vitro* can be several powers of ten, even at moderate temperatures (e.g., for cisplatin). At the cellular level, hyperthermia affects the membranes, cytoskeleton and the synthesis of macromolecules, and DNA repair (Dikomey &

Franzke, 1992; Lepock *et al.*, 2001). Hyperthermia increases the permeability of the chemotherapeutic drugs into the tumor cells by altering the fluidity and viscosity of the phospholipid bilayer of the membrane (Meyer *et al.*, 2000; Reinhold & Endrich 1986; Song *et al.*, 2005).

METHODOLOGY

A 61-year male patient reported severe chronic pain in the right neck. The patient was admitted to the hospital (Indira Gandhi Medical College, Pondicherry), and his pain was managed with NSAIDs and opioids but was not adequately controlled. The patient also reported dysphagia and irritation while passing urine. Initial observation showed swelling over the supraglottis, an open wound with white discharge, a lesion (size: 6.8 CM × 4.4 CM × 6.2 CM), and right lymph node swelling. With the help of a visual analogue scale (VSA), the patient's pain was rated 10 on the 10-point pain scale over the right neck.

Diagnosis: The patient had carcinoma supraglottic malignancy stage IV (T4a N3 Mx). The Eastern

Cooperative Oncology Group (ECOG) showed 1 on a performance status scale that describes a patient's level of functioning in terms of his ability to care for himself in day-to-day activity. The patient's history also showed an open wound with white discharge, a foul smell on the right neck wound, and lymph node swelling. The left neck region appeared normal.

Treatment: The patient was admitted to the hospital (Indira Gandhi Medical College and Hospital, Pondicherry) and started the first cycle of chemotherapy with paclitaxel (230 mg) and carboplatin (300 mg) injections. In the neoadjuvant therapy, the patient was put under hyperthermia (Device Name: Remission 1°C hyperthermia, AdipoLABs Healthcare India Pvt. Ltd, Seoul, Republic of Korea) 3 days/week along with chemotherapy (paclitaxel injection 230 mg) as given in Table 1. Remission 1° C hyperthermia device, a therapeutic apparatus, generates high-frequency thermotherapy to the body tissue without stimulating sensory and motor nerves, causing no physical inconvenience or muscular contraction.

Table 1: Hyperthermia and chemotherapy dosing regimen.

Hyperthermia Chart					
			Diagnosis: Carcinoma of the supraglottis		
Age / Gender: 61 years/male			Type of Rx: hyperthermia + chemotherapy		
Session #	Duration (Minutes)		Radio Frequency (RF) Hz		Temperature achieved (°C)
	Regional (Abdomen)	Targeted (Supraglottis)	Regional (Abdomen)	Targeted (Supraglottis)	
Session (1-5)	40 min	20 min	40 RF	36 RF	40°C
Session (6-10)	40 min	20 min	40 RF	37 RF	40°C
Session (11-15)	40 min	20 min	40 RF	38 RF	41°C
Session (16-22)	40 min	20 min	40 RF	38 RF	42°C

RESULTS AND DISCUSSION

Investigations: Supraglottic carcinoma was studied using contrast-enhanced computed tomography, and the following criteria were investigated. Before hyperthermia and chemotherapy showed heterogeneously enhancing neck mass involving the right para-pharyngeal, right submandibular, and right parotid space with intrusion into the oropharynx, hypopharynx, epiglottis, and right supraglottis.

Observation following hyperthermia and chemotherapy: During the first session, the patient exhibited pain over the supraglottis (10/10 on the VSA scale) and an open wound over the tumor site with white discharge and swelling over the supraglottis (Fig. 1a). In the fifth session, the patient's pain reduced to some extent (7/10) swelling subsided; however, pus collection was present

on the open wound that also started to shrink to some degree (Fig. 2b). After the fifteenth session, the pain was reduced significantly (3/10) open wound lesion was decreased to some extent (3×2×3 cm) with no blood discharge or pus collection over the lesion (Fig. 3c). His dysphagia reduced, and food intake improved and also his overall well-being. At the twenty-second session of hyperthermia and chemotherapy, the patient's pain was relieved significantly (1/10), the tumor wound shrunk to some extent (2×1×1.5 cm), and the swelling reduced (Fig. 4d). At the end of the twenty-fifth session of hyperthermia and chemotherapy, the pain reduced significantly, the swelling subsided, and tumor responded well, and skin started to grow over the tumor area (Fig. 5).

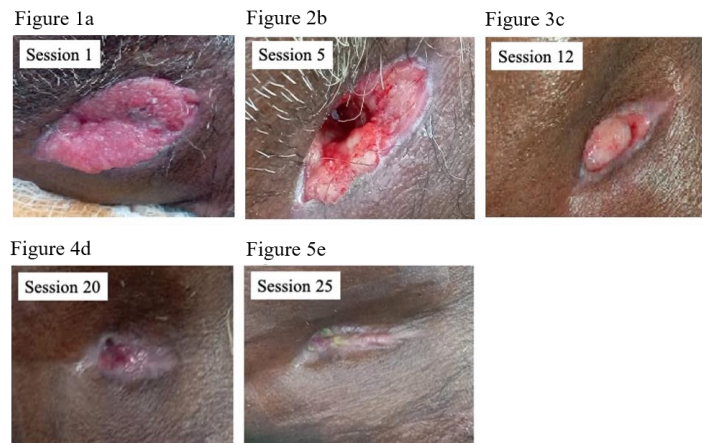


Fig 1-5. The photographs of a 61-year-old male with supraglottic carcinoma showing recovery after neoadjuvant chemotherapy and hyperthermia.

The photograph of a 61-year-old male with supraglottic carcinoma, in the first session, the patient exhibited severe pain over the supraglottis on the VSA pain scale of 10 out of 10. The open wound over the tumor site with the white discharge and swelling over the supraglottis were observed. During session 5 of hyperthermia and chemotherapy, the patient's pain reduced to some extent (7/10) swelling subsided; however, pus collection was present on the open wound that also started to shrink to some extent. At the 12th session, the pain was reduced significantly (3/10); the open wound lesion was decreased to some extent ($3 \times 2 \times 3$ cm) with no blood discharge or pus collection over the lesion. After the 20th session, the patient's pain was relieved significantly (1/10), the tumor wound shrunk to some extent ($2 \times 1 \times 1.5$ cm), and swelling was reduced. After the 25th session, the patient exhibited a significant reduction of pain, the swelling subsided, the tumor responded well, and skin started to grow over the tumor area.

After hyperthermia and chemotherapy, the CECT image showed endoscopy-status posterior right glottis-edematous cryptical fold and mild narrowing in post cricoid area - scope negotiated across; the esophagus, 39 cm; stomach - erythematous mucosa; duodenum-normal. The results suggested that the tumor responded well after receiving non-regional chemotherapy and local hyperthermia.

Challenges of the Study: The present study was really challenging case, as the patient had a raw open ulcer and need to apply heat over it. First, hyperthermia was delivered without patients' discomfort, and at the same time, the tumor was needed to get the required heat dose. So hyperthermia technique was used as a marginal heating on the skin and used a biofilm to cover the wound and delivered hyperthermia. The protocol was designed in such a way that the patient was given neoadjuvant chemotherapy and concurrent hyperthermia. The required heat to the tumor was prescribed by indigenous techniques to deliver heat to the ulcer and the patient was followed for the tumor response and the management of chemotherapy-related side effects.

CONCLUSIONS

The present study investigated the most promising treatment modalities for supraglottic carcinoma using a combination of hyperthermia and chemotherapy. The cancers in the supraglottic region are usually superficial compared to other forms of deep organ malignancies, and it is very appropriate to use hyperthermia along with chemotherapy to control cancer. The synergistic effect of hyperthermia and chemotherapy also augments the rate of wound healing, pain reduction, and swelling, suggesting that chemotherapy and regional HPT have additive antitumor and antimetastatic effects promoting patient recovery. HPT approach has significant merits, especially for treating superficial as well as deep metastatic sites. However, it should be noted that hyperthermia is not suitable for all types of cancer, and several factors, such as tumor location, stage, and patient comorbidities, can influence its effectiveness. Therefore, its use in cancer treatment should be evaluated case-by-case.

FUTURE SCOPE

The case report on treating supraglottic carcinoma using neoadjuvant chemotherapy and regional hyperthermia (HPT) presents a promising approach. The future scope of this study includes further refinement of treatment protocols; continuous refinement of treatment protocols is essential to optimize the combination of neoadjuvant chemotherapy and regional HPT, such as determining the optimal dosage, frequency, and duration of chemotherapy and hyperthermia sessions to achieve the best treatment outcomes. Combinatorial approaches may enhance treatment response, overcome resistance, and improve patient outcomes. Finally, evaluating the cost-effectiveness and resource utilization will assist in healthcare resource allocation and reimbursement decision-making. By exploring these future scopes, researchers can advance the understanding and application of neoadjuvant chemotherapy and regional HPT in supraglottic carcinoma, ultimately improving treatment outcomes and patient care.

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Conflict of Interest. None.

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