Chemoradiotherapy Combined With Modulated Electro-Hyperthermia (mEHT) Converts Initially Inoperable Esophageal Cancer to Operable Disease

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KEYWORDS

advanced cancer management | chemoradiotherapy | esophageal cancer | modulated electro-hyperthermia | tumor downstaging

ABSTRACT

This case report demonstrated the effectiveness of combining chemoradiotherapy (CCRT) with modulated electro-hyperthermia (mEHT) in converting initially inoperable esophageal cancer into an operable condition. A 60-year- old male with stage IVB lower third esophageal squamous cell carcinoma (cT3N2M1) experienced significant tumor shrinkage (ypT2N0M0) and a notable metabolic response, which enabled successful surgical removal. This treatment approach highlights the potential of mEHT as a valuable addition to the comprehensive management of esophageal cancer.

1. Introduction

Esophageal cancer remains a significant global health challenge due to its high mortality rate and complex management [1]. Despite advancements in medical research and treatment methods, the prognosis for patients with esophageal cancer, particularly those in advanced stages, remains grim [2]. Conventional treatments, such as surgery, chemoradiotherapy, and targeted therapies, often achieve limited success, primarily because of the disease's aggressive nature and its propensity for early metastasis [3]. This highlights the urgent need for more effective treatment strategies to improve patient outcomes.

Modulated electro-hyperthermia (mEHT) is an innovative adjunct therapy that has demonstrated promise in enhancing the efficacy of traditional cancer treatments [4]. By delivering localized heat through electromagnetic waves, mEHT induces cancer cell death via apoptosis and mitotic catastrophe while amplifying the repair of DNA damage caused by chemotherapy and radiotherapy [5]. The therapeutic potential of mEHT lies in its ability to selectively target malignant cells, minimizing harm to surrounding healthy tissues and improving overall treatment effectiveness.

Previous studies have explored the application of mEHT in various cancers, including esophageal cancer. Clinical trials have indicated that mEHT, when combined with chemoradiotherapy, can enhance tumor response rates and improve survival outcomes [4]. However, integrating mEHT into standard treatment protocols for esophageal cancer remains an area of active investigation, with further clinical evidence required to confirm its efficacy and safety.

This case report describes a 60-year- old male diagnosed with initially inoperable stage IVB esophageal squamous cell carcinoma. Through a combination of concurrent chemoradiotherapy (CCRT) and mEHT, the patient achieved a robust pathological response, enabling successful surgical resection. This case underscores the potential of mEHT as an effective adjunct therapy for advanced esophageal cancer, offering renewed hope for patients with limited treatment options.

2. Case Report

A 60-year- old male presented with a three-month history of a left neck mass. On examination at the ear, nose and throat (ENT) outpatient department, the mass was firm, movable, non-tender, and measured 2 × 2 cm, located at level V of the left neck. Ultrasound-guided fine-needle aspiration of the mass confirmed metastatic carcinoma. Further evaluation with neck/chest CT revealed the following findings: a long segmental wall-thickening mass in the lower third of the esophagus, measuring over 7.5 cm in length and 2 cm in thickness, suspicious for esophageal carcinoma; three to six regional metastatic lymph nodes in the left gastric artery and paraesophageal spaces; and non-regional metastatic lymphadenopathy in the left neck levels IV and V.

Endoscopic ultrasound with biopsy further confirmed advanced esophageal squamous cell carcinoma involving the middle and lower esophagus, with extension into the esophagogastric junction (EGJ). 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (PET/CT) revealed a viable tumor in the lower esophagus, regional nodal metastases in the paraesophageal and celiac regions, and distant nodal metastases in the left supraclavicular fossa (SCF) and left neck level V. The SUV max of the largest metastatic node was 7.3. Based on these findings, the patient was diagnosed with lower esophageal squamous cell carcinoma, cT3N2M1, stage IVB.

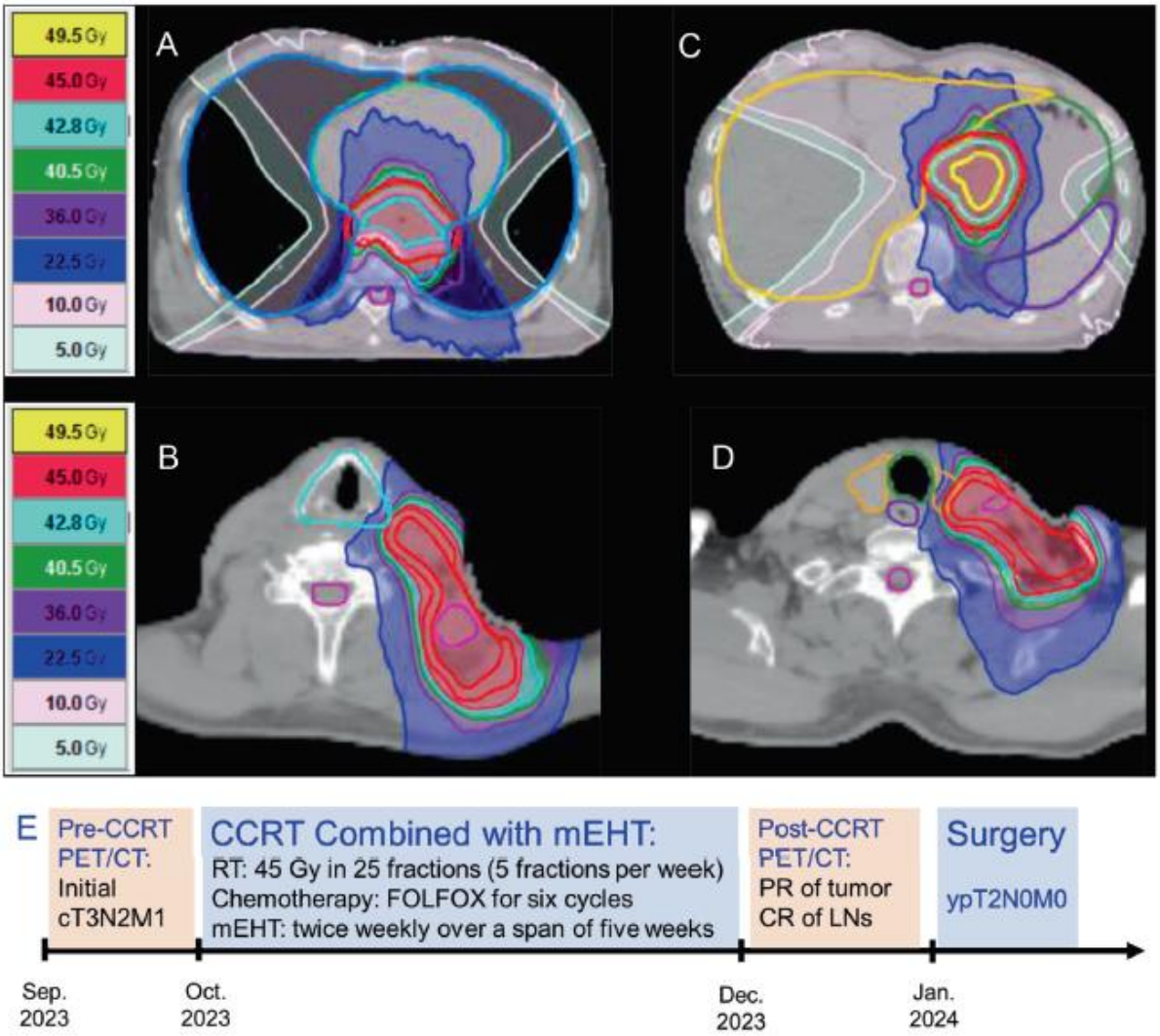

FIGURE 1 | Radiation dose distribution from the radiotherapy treatment plan and an overview of the clinical course for a 60-year- old male diagnosed with lower esophageal squamous cell carcinoma, cT3N2M1, stage IVB. The planning target volume (PTV) of 45 Gy (red area) is focused on the primary esophageal tumor in the lower third of the esophagus (A), the left neck level V nodal metastasis (B), the celiac nodal metastasis (C), and the left supraclavicular fossa nodal metastasis (D). This distribution targets both the primary tumor and regional as well as distant metastatic lymph nodes identified on PET/CT and CT imaging. (E) an overview of the patient's clinical course. CCRT: Concurrent chemoradiotherapy. mEHT: Modulated electro-hyperthermia. PET/CT: Positron Emission Tomography/Computed Tomography. PR: Partial response. CR: Complete response.

Given the extent of the disease and distant nodal metastases, surgery was not recommended by the thoracic surgery team. Consequently, the treatment plan included concurrent chemoradiotherapy (CCRT). Over a two-month period, the patient received six cycles of FOLFOX chemotherapy and radiotherapy, delivering a total dose of 4500 cGy in 25 fractions, targeting the primary esophageal tumor and the metastatic nodes in the paraesophageal, celiac, and left SCF regions. The goal of mEHT in oncology is to elevate the tumor temperature within the 39°C–42.5°C range, thereby enhancing its susceptibility to oncologic therapies [4]. The mEHT procedure for this patient was conducted using the EHY2030 device, administered twice weekly over a span of 5 weeks. Each session lasted 60 min, following a gradual escalation protocol to optimize treatment efficacy. The patient was positioned supine, with a 30 cm circular electrode applicator placed on the chest wall, precisely targeting the esophageal tumor. The stepwise power adjustment began at 80 W for the initial 10 min, progressively increasing to 100 W for the subsequent 10 min, and further escalating to 180 W for another 10 min. During the final 30 min of treatment, the power output was modulated based on the patient's tolerance and subjective discomfort, ensuring safety while maintaining therapeutic efficacy, with a maximum threshold of 240 W. Figure 1 illustrates the radiation dose distribution, with a planning target volume (PTV) of 45 Gy covering the primary tumor and metastatic lymph nodes, along with an overview of the patient's clinical course.

A follow-up PET/CT scan, performed approximately 6 weeks after completing CCRT and mEHT, demonstrated a partial metabolic response (PMR) in the primary esophageal tumor and a complete metabolic response (CMR) in the nodal metastases. The initial PET/CT had revealed a 54-mm mass in the anterior mediastinum with an SUVmax of 9.4. Following treatment, the SUVmax of the primary tumor decreased to 5.4, indicating PMR https://www.youtube.com(Figure 2A,B). Significant metabolic reductions were observed in the nodal metastases, including the left SCF node (SUVmax reduced from 4.8 to 1.3; Figure 2C,D), the celiac node (SUVmax reduced from 3.5 to 1.3; Figure 2E,F), and the left neck level V nodes (SUVmax reduced from 7.3 to 0.6; Figure 2G,H).

Two months after completing CCRT and mEHT, the patient underwent video-assisted thoracoscopic surgery (VATS) esophagectomy with gastric tube reconstruction, VATS lymph node dissection, and feeding jejunostomy. Postoperative pathology revealed ypT2N0M0, indicating no residual nodal involvement and significant tumor downstaging. This outcome represented a successful conversion of an initially inoperable stage IVB disease to an operable condition.

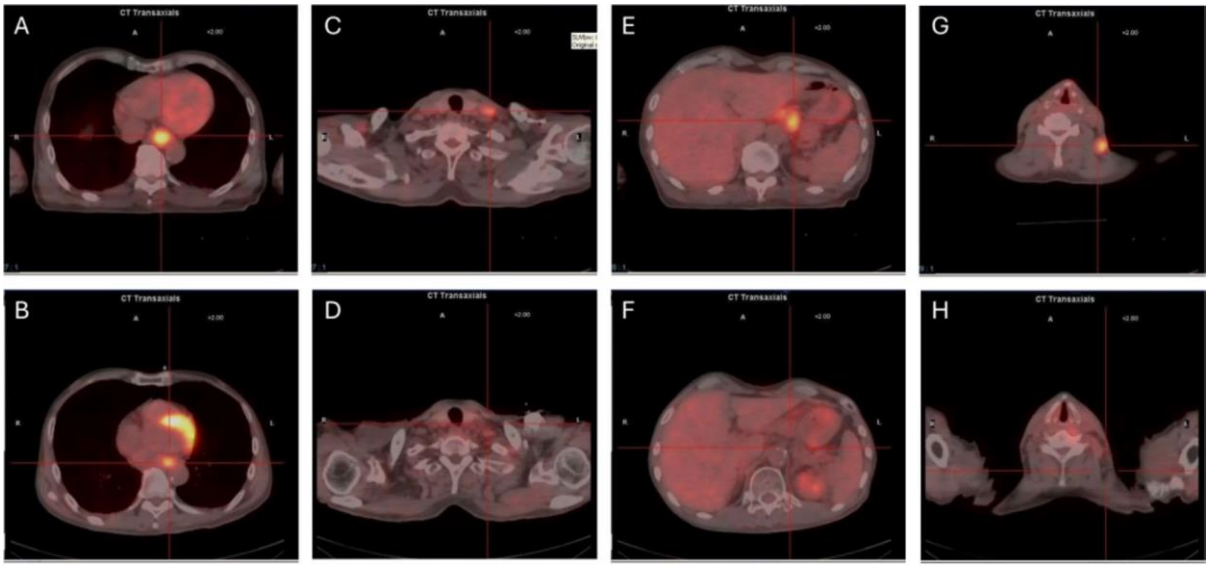

FIGURE 2 | PET-CT images illustrating the metabolic response of the primary esophageal tumor and nodal metastases before and after treatment with chemoradiotherapy and modulated electro-hyperthermia. (A, B) Primary esophageal tumor before treatment (A, SUVmax 9.4) and after treatment, showing a partial metabolic response (B, SUVmax 5.4). (C, D) Left supraclavicular fossa nodal metastasis before treatment (C, SUVmax 4.8) and after treatment, showing a complete metabolic response (D, SUVmax 1.3). (E, F) Celiac nodal metastasis before treatment (E, SUVmax 3.5) and after treatment, showing a complete metabolic response (F, SUVmax 1.3). (G, H) Left neck level V nodal metastasis before treatment (G, SUVmax 7.3) and after treatment, showing a complete metabolic response (H, SUVmax 0.6).

3. Discussion

Esophageal cancer classified as cT3N2M1, stage IVB, is widely regarded as unsuitable for surgical intervention at diagnosis due to its advanced stage and extensive lymph node metastasis, with outcomes remaining poor even after CCRT [2, 3]. This case highlights the effectiveness of combining mEHT with CCRT in treating advanced esophageal cancer. The integration of mEHT significantly enhanced the patient's response to CCRT, successfully converting an initially inoperable stage IVB disease into an operable condition. The observed downstaging from cT3N2M1 to ypT2N0M0 underscores mEHT's potential to achieve remarkable tumor control and improve overall outcomes, even though mEHT was used alongside a suboptimal CCRT dose of 45 Gy administered with palliative intent.

One remarkable feature of mEHT is its ability to trigger an immune response, which enhances the effectiveness of chemotherapy, particularly in reducing lymph node metastasis. By inducing the release of heat shock proteins (HSPs), mEHT generates danger signals that activate the immune system [6]. These HSPs promote the presentation of tumor antigens to immune cells, thereby eliciting a robust anti-tumor immune response [7]. This immune activation contributes to the targeted elimination of cancer cells, including those that have metastasized to lymph nodes [8]. In this case, the CMR of previously affected lymph nodes suggests that the combination of mEHT and CCRT effectively stimulates the immune system to combat metastatic disease.

The complete response (CR) observed in lymph node metastases and tumor downstaging from cT3N2M1 to ypT2N0M0 following CCRT combined with mEHT is consistent with prior evidence highlighting the synergistic effects of hyperthermia. A meta-analysis on hyperthermia combined

with chemoradiotherapy for esophageal cancer demonstrated a notably higher CR rate compared to standard CCRT alone (odds ratio 2.00, $p < 0.00001$), indicating that hyperthermia substantially augments tumor radiosensitization and immune activation [9]. Furthermore, previous studies have demonstrated the capacity of mEHT to enhance the efficacy of conventional cancer therapies, including its application in esophageal cancer [10]. These mechanisms are likely integral to the observed therapeutic effect, reinforcing the role of mEHT as a promising adjunct to CCRT in the multimodal treatment of esophageal cancer.

This case further corroborates these findings, suggesting that mEHT could be a valuable adjunct in the treatment regimens of patients with advanced esophageal cancer, especially for those deemed ineligible for surgery. The patient's favorable outcome underscores the importance of exploring multimodal treatment approaches to improve the prognosis for patients with advanced cancers. Future research should prioritize larger cohort studies and randomized controlled trials to validate the efficacy of mEHT when combined with CCRT and other therapeutic strategies.

In conclusion, this case emphasizes the potential of mEHT in advancing the therapeutic response for advanced esophageal cancer. By enabling the conversion of inoperable disease to operable disease, mEHT provides a promising avenue for enhancing patient outcomes. Continued research and clinical trials are essential to fully establish its role in the comprehensive management of esophageal cancer.

Author Contributions

Deng-Yu Kuo: Conceptualization; Resources; Writing original draft. Pei-Wei Shueng: Methodology; Supervision; Writing original draft. Shan-Ying Wang: Supervision; Writing – review and editing. Cheng-Hung How: Supervision; Writing – review and editing. Chen-Xiong Hsu: Conceptualization; Project administration; Supervision; Writing – review and editing.

Acknowledgments

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present case report was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital (approval number: 113227-C). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author. Due to patient privacy regulations and ethical restrictions, the raw clinical data cannot be publicly shared but may be provided in a de-identified format upon institutional review board approval.

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