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Case Report

Tailored Management of Advanced Esophageal Squamous Cell Carcinoma — Balancing Efficacy and Toxicity with a "Hold Chemotherapy and Keep Immunotherapy" Strategy: A Case Report

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Abstract

Esophageal squamous cell carcinoma (ESCC) is an aggressive malignancy with a poor prognosis in advanced stages. Pivotal trials including ATTRACTION-3, CheckMate 648, and CheckMate 577 have demonstrated that immunotherapy with nivolumab significantly improved survival and maintained disease control. We report a 59-year-old female with a 3-month history of intermittent nausea, vomiting, and unintentional weight loss of approximately 5 kg. A definite diagnosis of ESCC with distant lymph node metastasis (cT2N3M1, Stage IVB) was confirmed by positron emission tomography and esophagogastroduodenoscopy with biopsy. This report details her clinical course, including chemotherapy, immunotherapy, and radiation therapy. Despite initially achieving complete remission, recurrence was detected during follow-up. A "Hold Chemotherapy and Keep Immunotherapy" strategy effectively managed advanced ESCC, balancing efficacy and toxicity while preserving quality of life.

Keywords: Esophageal squamous cell carcinoma, immunotherapy, maintenance therapy

Introduction

Esophageal cancer is the eighth most common malignancy worldwide and the sixth leading cause of cancer-related mortality.[1] Esophageal squamous cell carcinoma (ESCC) accounts for 87% of esophageal cancers, with a high prevalence in Asia.[2] Despite advances in multimodal therapy, advanced ESCC carries a poor prognosis, with a 5-year survival rate below 20%.

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First-line treatment for locally advanced or metastatic ESCC typically involves platinum-based chemotherapy (cisplatin + 5-fluorouracil) with or without immune checkpoint inhibitors (ICIs) such as nivolumab or pembrolizumab,

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particularly in patients with high PD-L1 expression. The CheckMate 648 trial demonstrated that nivolumab plus chemotherapy significantly improved survival in patients with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥1%, establishing immunotherapy as a fundamental component of ESCC treatment.[3] In addition, the ATTRACTION-3 trial confirmed the efficacy of nivolumab as second-line therapy, showing a median overall survival (OS) of 10.9 months compared to 8.4 months with chemotherapy alone.[4]

However, prolonged chemotherapy in patients with metastatic ESCC is associated with significant toxicity, which can limit its long-term feasibility. The challenge of balancing efficacy and adverse effects necessitates the exploration of alternative therapeutic strategies. Here, we present a 59-year-old female with metastatic ESCC (cT2N3M1, Stage IVB, PD-L1 CPS: 40) who initially achieved complete remission (CR) following chemoimmunotherapy. Subsequent imaging showed fluorodeoxyglucose (FDG)-avid uptake in the midthoracic esophagus, raising concerns of recurrence; however, endoscopic biopsy confirmed only high-grade squamous dysplasia. Based on this finding, we opted to continue the "Hold Chemotherapy and Keep Immunotherapy" strategy, emphasizing the long-term feasibility of nivolumab maintenance therapy.

Case Report

A 59-year-old homemaker with no history of smoking presented with a 3-month history of intermittent nausea, vomiting, and unintentional weight loss of approximately 5 kg. Her initial evaluation began with an esophagogastroduodenoscopy (EGD), which revealed an ulcerative lesion 27 cm from the incisor, corresponding to the middle thoracic esophagus. Biopsy confirmed the diagnosis of moderately differentiated ESCC [Figure 1a]. Positron emission tomography/computed tomography (PET/CT) further identified hypermetabolic activity in the midthoracic esophagus with distant lymph node metastases [Figure 2a], leading to a final staging of cT2N3M1, Stage IVB, PD-L1 CPS: 40 [Figure 1b].

The patient was initiated on combination chemoimmunotherapy consisting of cisplatin (60–70 mg/m²) and 5-fluorouracil (600–1000 mg/m²) administered every 3 weeks, with a total cumulative dosage of 600 mg/m² of cisplatin and 6800 mg/m² of 5-fluorouracil administered across 10 chemotherapy cycles, depending on cycle-specific adjustments, alongside nivolumab (240 mg IV every 2 weeks) following the ATTRACTION-3 protocol. Subsequent imaging demonstrated a favorable response to treatment, and follow-up PET/CT indicated CR with the resolution of all previously detected FDG-avid lesions [Figure 2b]. EGD revealed tumor regression grade of 0, and a subsequent CT scan showed no detectable residual disease.

However, routine follow-up PET/CT in May 2024 revealed new FDG-avid uptake in the midthoracic esophagus [Figure 2c], raising the suspicion of recurrence. Definitive concurrent chemoradiotherapy was not administered in this case, and systemic chemotherapy had been discontinued after December 2023. The patient had previously achieved PET-confirmed CR on December 21, 2023, and the new FDG-avid lesion was identified on May 30, 2024, marking a disease-free interval of approximately 160 days (~5 months) since the last chemotherapy exposure and the initial remission. EGD biopsy confirmed only high-grade squamous dysplasia rather than invasive carcinoma. Given the absence of confirmed malignant recurrence, the decision was made to continue with the "Hold Chemotherapy and Keep Immunotherapy" strategy without reinitiating cytotoxic chemotherapy. In addition, she was referred for radiation therapy for advanced local control.[5]

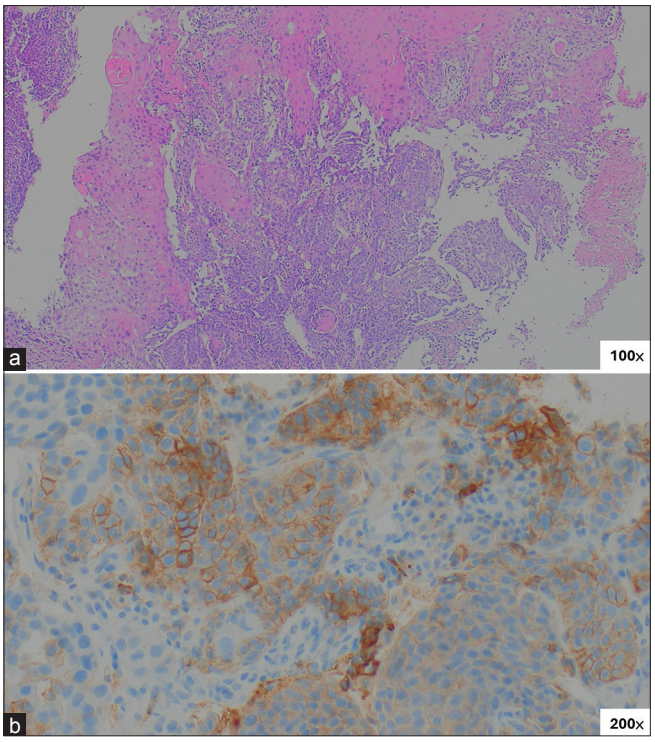

Figure 1: Histopathologic and programmed death-ligand 1 (PD-L1 analysis. (a) H and E (×100): Grade 2 squamous cell carcinoma with keratinizing epidermoid nests, desmoplastic stroma, and tumor necrosis (p40 positive), (b) PD-L1 IHC (×200): CPS: 40, assessed using 22C3 pharmDx Assay (Agilent/Dako), indicating a high PD-L1 expression level

To ensure continued disease control, she remained on maintenance nivolumab therapy. Additional surveillance included regular imaging and endoscopic evaluation. Follow-up CT imaging showed stable disease, and EGD revealed an unremarkable squamous epithelium, further supporting the decision to maintain the current treatment approach. The patient remains under close observation with the disease under control and showing tolerance to long-term immunotherapy, and she has not received further chemotherapy.

Discussion

The treatment of advanced ESCC has evolved significantly with the introduction of ICIs. While traditional chemotherapy

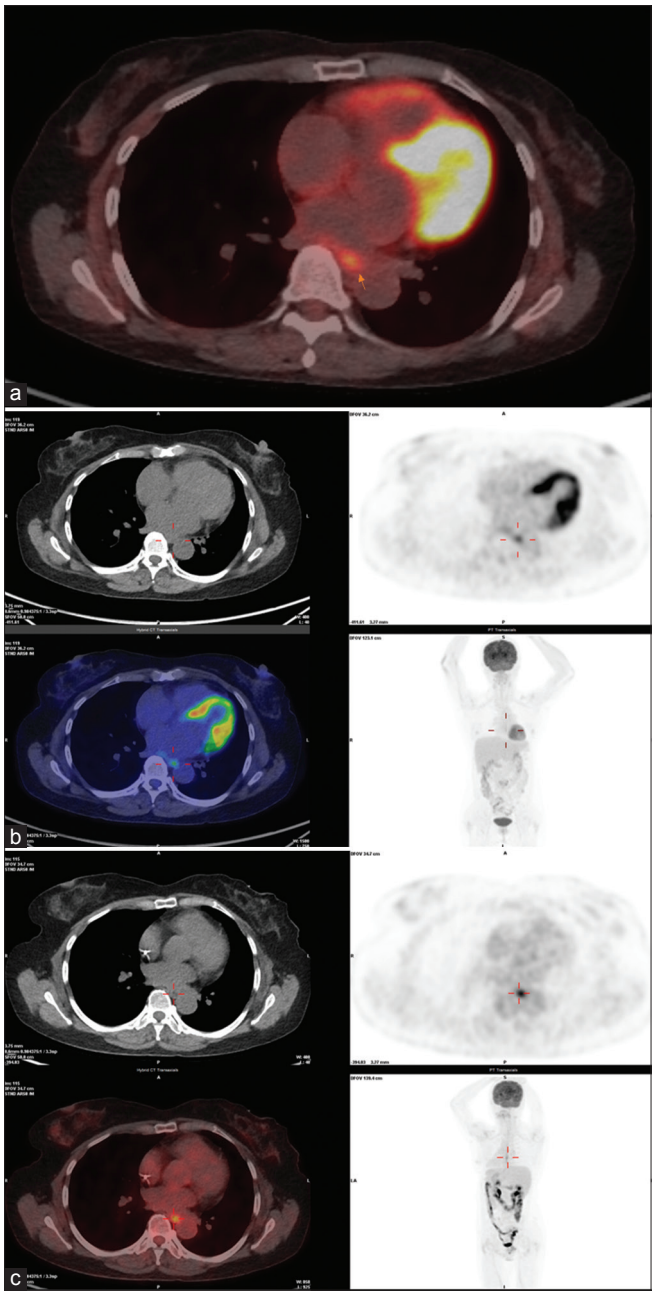

Figure 2: Positron emission tomography/computed tomography (PET/CT) imaging before and after treatment. (a) Baseline (pretreatment, August 2023): High-grade fluorodeoxyglucose (FDG)-avid lymphadenopathy in multiple regions, including the middle thoracic esophagus (arrow), gastrohepatic ligament, hepatoduodenal ligament, celiac, right retrocrural, paraaortic, aortocaval, paracaval, and bilateral common iliac regions, consistent with metastatic lymph node involvement, (b) Posttreatment (December 21, 2023): Complete metabolic response (CR) in prior FDG-avid lymph nodes. Low-grade FDG uptake in the lower esophagus suggested posttherapeutic inflammation rather than recurrence (~4-month interval), (c) PET/CT (May 30, 2024): New focal high-grade FDG uptake (maximum standardized uptake value: from 6.3 to 8.0) in the midthoracic esophagus (arrow), raising the suspicion of recurrence (~5-month interval from prior CR)

remains the backbone of systemic therapy, the integration of ICIs has improved survival outcomes, particularly in PD-L1-positive tumors. However, challenges remain regarding optimal treatment duration, management of recurrence, and balancing efficacy with toxicity. This case highlights the feasibility of long-term nivolumab maintenance therapy in a patient with advanced ESCC and emphasizes the importance of biopsy confirmation before altering the treatment strategy.

Clinical implications of immunotherapy in esophageal squamous cell carcinoma

The emergence of ICIs has transformed the treatment paradigm for advanced ESCC, particularly in patients with high PD-L1 expression. The CheckMate 648 trial reported that nivolumab plus chemotherapy significantly improved OS, especially in patients with a PD-L1 CPS ≥1%, with superior efficacy over chemotherapy alone.[5] Given that our patient had a PD-L1 CPS of 40, continuing nivolumab maintenance therapy after achieving CR was a clinically reasonable decision.

The ATTRACTION-3 trial further validated nivolumab monotherapy as an effective second-line option, demonstrating a median OS of 10.9 months, superior to standard chemotherapy alone.[6] These results emphasize that ICI-based therapies can provide a durable response, suggesting that long-term immunotherapy can be a viable alternative to chemotherapy-based regimens in appropriately selected patients.

A key consideration in our case was the continuation of nivolumab monotherapy following initial CR. While discontinuing chemotherapy may raise concerns about tumor relapse, emerging evidence suggests that prolonged ICI therapy alone may be sufficient to sustain disease control, particularly in patients with a strong PD-L1 expression and an initial deep response. This strategy minimizes chemotherapy-induced toxicity and preserves the patient's quality of life, supporting its role in the long-term management of advanced ESCC.

Managing potential recurrence and treatment toxicity

A critical challenge in managing metastatic ESCC is differentiating true recurrence from posttreatment inflammatory changes. In our case, FDG-avid uptake in the midthoracic esophagus on PET/CT initially raised concerns of tumor recurrence. However, a subsequent EGD biopsy confirmed only high-grade squamous dysplasia rather than invasive carcinoma, highlighting the necessity of histopathological confirmation before adjusting the treatment strategy.

Continuing nivolumab maintenance therapy while discontinuing chemotherapy allowed our patient to avoid unnecessary cytotoxic exposure. This decision aligns with real-world clinical data. Evidence of adjuvant nivolumab treatment for "resected" esophageal or gastroesophageal junction cancer was provided in the CheckMate 577 trial,[6] although further evidence was needed for "unresected" ESCC. The reduced tumor burden with long-term nivolumab maintenance also reduces the risk of immune-related adverse events, which is a growing concern with the extended use of ICIs.

Furthermore, our patient demonstrated stable disease on follow-up CT without histopathological evidence of

recurrence, supporting the continuation of nivolumab without reinitiating chemotherapy. This highlights the need for individualized treatment, where real-time imaging and histopathological findings guide treatment adjustments to ensure that the patients receive the most appropriate and least toxic therapeutic regimen.

Medical criteria for the initiation and termination of immune checkpoint inhibitor regimens in patients with esophageal squamous cell carcinoma

The initiation and termination of ICI therapy in patients with advanced ESCC follow standardized clinical criteria to optimize efficacy while minimizing toxicity. The initiation criteria depend on tumor stage, prior treatment history, and PD-L1 expression, while the termination criteria depend on disease progression, treatment-related toxicity, and clinical deterioration.[7]

The criteria for initiating and discontinuing ICI therapy are summarized in Tables 1a and b, which outlines the current standard of care based on major phase III clinical trials.[8]

In our case, continued nivolumab maintenance therapy was justified given the absence of confirmed recurrence and patient stability. This highlights the importance of individualized treatment decisions, ensuring that therapy is tailored based on ongoing clinical, imaging, and histopathological findings.

Novelty and clinical relevance of the strategy

While maintenance immunotherapy has been validated in other solid tumors, such as durvalumab in NSCLC (PACIFIC trial)[9] and avelumab in urothelial carcinoma (JAVELIN Bladder 100 trial),[10] the application of a similar concept in ESCC remains largely unexplored. Most pivotal ESCC trials (e.g. CheckMate 648, ATTRACTION-3) continued systemic therapy until disease progression. However, this may not reflect the needs of patients who achieve deep or complete responses and wish to avoid cumulative toxicity.

In our case, we adopted a tailored "Hold Chemotherapy and Keep Immunotherapy" strategy following clinical remission. Although this case involves a single patient, it illustrates the potential feasibility and tolerability of treatment de-escalation in carefully selected ESCC patients. This real-world example adds to the evolving discussion around response-adapted, biomarker-guided treatment strategies in immuno-oncology.

Table 1a: Medical criteria for the initiation and termination of each immune checkpoint inhibitors regimen trial for esophageal squamous cell carcinoma esophageal squamous cell carcinoma

Regimen (trial name)	Line	Initiation criteria	Termination criteria
Nivolumab + chemo (CheckMate 648)	1st	Unresectable, advanced, recurrent, or metastatic ESCC (no prior systemic therapy)	Disease progression per RECIST v1.1, unacceptable toxicity, or death
Nivolumab + ipilimumab (CheckMate 648)	1st	Same as above	Same as above
Pembrolizumab + chemo (KEYNOTE-590)	1st	Unresectable, recurrent, or metastatic EAC/ESCC, PD-L1 CPS ≥10% preferred but not required	Disease progression, severe IRAEs, or patient withdrawal
Camrelizumab + chemo (ESCORT-1st)	1st	Advanced or metastatic treatment-naïve ESCC	Disease progression, unacceptable toxicity, or patient refusal
Toripalimab + chemo (JUPITER-06)	1st	Locally advanced, unresectable, or metastatic treatment-naïve ESCC	PD, IRAEs, or physician decision based on clinical deterioration
Sintilimab + chemo (ORIENT-15)	1st	Unresectable, locally advanced, recurrent, or metastatic treatment-naïve ESCC	Disease progression, SAEs, or patient request
Tislelizumab + chemo (RATIONALE-306)	1st	Stage III–IV, unresectable, recurrent, or metastatic ESCC without prior systemic therapy	Progressive disease, severe toxicity, or clinical deterioration
Nivolumab monotherapy (ATTRACTION-3)	2nd	Prior fluoropyrimidine/platinum-based therapy failure in unresectable or metastatic ESCC	Radiological/clinical progression, immune-related toxicity, or patient request

ESCC: Esophageal squamous cell carcinoma, CPS: Combined positive score, SAEs: Severe adverse events, PD: Progressive disease, IRAEs: Immune-related adverse events, EAC: Esophageal adenocarcinoma, RECIST: Response Evaluation Criteria in Solid Tumors

Table 1b: Regulatory approval status of selected progressive disease-1 inhibitors for advanced esophageal squamous cell carcinoma across NMPA, FDA, and EMA

Drug	NMPA (China)	FDA (USA)	EMA (EU)
Camrelizumab	Approved for ESCC	Not approved	Not approved
Toripalimab	Approved for ESCC	Approved (NPC only)	Approved for ESCC
Sintilimab	Approved for ESCC	Not approved	Not approved
Tislelizumab	Approved for ESCC	Approved for ESCC	Approved for ESCC

All four agents – Camrelizumab, toripalimab, sintilimab, and tislelizumab – have demonstrated statistically significant survival benefits in large, randomized Phase 3 trials in Chinese populations. While these regimens are NMPA-approved, they are not yet all approved by the FDA or EMA for use in esophageal cancer. ESCC: Esophageal squamous cell carcinoma, NPC: Nasopharyngeal Carcinoma

Further case discussion

Potential role of local radiotherapy in biopsy-negative, metabolically active lesions

Definitive concurrent chemoradiotherapy was not administered in this case, and systemic chemotherapy was discontinued after December 2023. Recurrence was suspected based on PET/CT findings in May 2024, marking an interval of approximately 5 months since the last exposure to chemotherapy.

While EGD-guided biopsy revealed only high-grade squamous dysplasia, the presence of a focal FDG-avid lesion with maximum standardized uptake value ranging from 6.3 to 8.0 raised concerns over possible oligoprogression. In the current immunotherapy era, localized radiotherapy has emerged as a rational approach for managing biopsy-negative but metabolically active lesions, particularly when systemic disease remains otherwise controlled. This aligns with emerging evidence that such lesions may represent resistant subclones amenable to local treatment while continuing immunotherapy.

Importantly, such PET/CT findings may also reflect posttreatment inflammation, submucosal recurrence, or paraesophageal nodal involvement not accessible by endoscopic biopsy. This underscores the need for multimodality assessments and cautious interpretation before modifying systemic therapy.

Alternative interpretations and the nature of "remission"

While the decision to continue immunotherapy in our patient was based on a favorable prior response and biomarker status (PD-L1 CPS: 40), we recognize that the observed remission may have been durable regardless of continuing ICI therapy. In addition, the PET-avid lesion in May 2024 may have represented a false-positive result due to posttreatment inflammation or paraesophageal nodal activity, particularly in a previously irradiated field. The high-grade dysplasia observed on biopsy may reflect radiation-induced mucosal atypia, residual premalignant epithelium, or incomplete sampling of a submucosal lesion. These possibilities underscore the need for careful longitudinal evaluation and histologic correlation before modifying the treatment strategy in the post-ICI setting.

Radiotherapy considerations

In our case, localized external beam radiation therapy was administered from July 3 to August 21, 2024, delivering a total dose of 5800 cGy in 29 daily fractions over a 6-week period to the midthoracic esophagus, as determined by PET/CT-guided planning. The rationale was twofold: (1) to manage suspected oligoprogression in the setting of biopsy-equivocal findings, and (2) to provide local disease control without interrupting systemic ICI therapy. Radiation therapy may also modulate the local tumor immune microenvironment and facilitate durable control in previously treated fields. Whether the observed dysplasia was a residual lesion or radiation effect remains unclear; however, no progression was seen on follow-up imaging or endoscopy.

Management of high-grade squamous dysplasia

High-grade squamous dysplasia is widely recognized as a precursor to invasive esophageal cancer. Standard management strategies – particularly in untreated patients – include endoscopic mucosal resection or radiofrequency ablation, both of which have shown efficacy in reducing the risk of cancer progression, as outlined in the ASGE guidelines.[11]

In our case, however, the biopsy-confirmed high-grade squamous dysplasia occurred within a posttreatment field after intensive chemoradiotherapy and immunotherapy. The lesion was nonmass-forming, with no ulceration or deep infiltration on EGD. In addition, subsequent endoscopic evaluation was unremarkable. Given the potential for radiation-induced mucosal atypia and the technical difficulty or risk of complications with endoscopic mucosal resection in irradiated fibrotic tissue, we opted for close surveillance rather than immediate endoscopic ablation. This reflects a pragmatic approach balancing histopathological findings, treatment history, and patient-specific risks.

Conclusion

This case demonstrates that long-term maintenance nivolumab therapy can be an effective strategy in patients with advanced ESCC, particularly in those who achieve initial CR. Careful interpretation of imaging and biopsy findings is critical to avoid unnecessary further chemotherapy. This approach highlights the evolving role of immune-based maintenance strategies in the treatment paradigm of advanced ESCC.

Limitations

As a single-patient case report, this study is inherently limited in its ability to establish efficacy due to the lack of statistical power, generalizability, and the possibility of selection bias. The findings should be interpreted with caution and considered hypothesis-generating rather than conclusive.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent form. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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