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Efficacy of pembrolizumab and oncolytic viral therapy in stage III esophageal cancer: a narrative review

Rajsinh Bhosale[1a], **Lamiya Pirzada**[2b], **Safiyyah Khan**[3], **Aqsa Zainab**[4c], **Shravya Subashini Sivaramakrishnan**[5], **Areeba Mariam Mehmood**[6d] and **Pawan Sapkota Upadhya**[7e]

[1]Independent Researcher, Mumbai 410206, India
[2]Jinnah Sindh Medical University, Karachi 75510, Pakistan
[3]Rajiv Gandhi University of Health Sciences, Bengaluru 560041, India
[4]Allama Iqbal Medical College, Lahore 54700, Pakistan
[5]Gandhi Medical College, Secunderabad, Telangana 500003, India
[6]Dr. Faisal Masood Teaching Hospital, Sargodha 40100, Pakistan
[7]NPI Gorkha Hospital, Gorkha 34000, Nepal
[a] https://orcid.org/0009-0000-4333-9424
[b] https://orcid.org/0009-0009-7464-8831
[c] https://orcid.org/0009-0004-3372-8644
[d] https://orcid.org/0009-0002-8291-7287
[e] https://orcid.org/0000-0002-2182-6616

Abstract

Pembrolizumab and oncolytic viral therapy represent promising therapeutic strategies for improving outcomes in stage III esophageal cancer. This narrative review evaluates current clinical evidence regarding their efficacy and potential role in contemporary treatment paradigms. A comprehensive literature search was conducted using PubMed, Google Scholar and Web of Science to identify relevant studies published between January 2010 and December 2024. Emerging evidence suggests that pembrolizumab combined with chemotherapy demonstrates encouraging pathological response rates, particularly in esophageal squamous cell carcinoma. Oncolytic viral therapy has shown potential in enhancing tumour immunogenicity and improving local tumour control; however, clinical evidence remains limited. Most available data are derived from early-phase and non-randomised studies, underscoring the need for large randomised controlled trials.

Keywords: *esophageal neoplasms*, *pembrolizumab*, *oncolytic virotherapy*, *immunotherapy*, *combined modality therapy*, *esophageal squamous cell carcinoma*

Introduction

Esophageal cancer, including esophageal squamous cell carcinoma (ESCC) and adenocarcinoma, remains one of the most lethal malignancies globally. Stage III disease represents a locally advanced phase characterised by tumour invasion into surrounding structures or regional lymph node involvement. Despite multimodal management incorporating surgery, chemotherapy and radiotherapy, survival outcomes remain suboptimal [1,3].

Review

Correspondence to: Rajsinh Bhosale
Email: raj0133j@gmail.com

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Immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as pembrolizumab, has demonstrated clinically meaningful responses in metastatic and locally advanced settings [2,4]. Similarly, oncolytic viral therapy, which selectively infects and lyses tumour cells while stimulating antitumour immunity, is gaining attention.

This review provides a descriptive narrative synthesis rather than a comparative evaluation of pembrolizumab and oncolytic viral therapy. The focus is predominantly on ESCC, as most of the available clinical evidence included in this review is ESCC-specific rather than adenocarcinoma-specific.

Methods

A narrative literature review was conducted using PubMed, Google Scholar and Web of Science. The literature search covered publications from January 2010 to December 2024. Search terms included 'pembrolizumab,' 'oncolytic viral therapy,' 'esophageal cancer,' 'ESCC,' 'ICIs,' 'neoadjuvant immunotherapy,' 'OBP-301' and 'telomelysin.' Only English-language studies involving human participants were included.

Studies were eligible if they reported clinical outcomes relevant to stage III or locally advanced esophageal cancer, neoadjuvant pembrolizumab or clinical oncolytic virotherapy. Case reports, opinion articles and preclinical-only studies were excluded. A total of 18 studies were included after title, abstract and full-text screening. Data extracted included study design, phase, sample size, treatment regimen, objective response rate (ORR), major pathological response (MPR), pathological complete response (pCR) and safety-related findings when available.

Stage III esophageal cancer was defined using the American Joint Committee on Cancer (AJCC) Tumor–Node–Metastasis staging system. When individual trials did not explicitly define stage III disease, studies involving locally advanced, resectable disease consistent with AJCC stage III criteria were considered. Preclinical studies were excluded to ensure clinical applicability and to focus on evidence relevant to patient-level outcomes.

Results

Pembrolizumab in stage III esophageal cancer

Several studies have investigated pembrolizumab as part of neoadjuvant therapy in resectable or locally advanced esophageal cancer, particularly ESCC. Reported outcomes include ORR, MPR and pCR, as summarised in Table 1.

Oncolytic viral therapy in stage III esophageal cancer

Oncolytic viruses selectively replicate within tumour cells, leading to direct oncolysis and stimulation of antitumour immunity. Clinical data specific to stage III esophageal cancer remain limited. The available clinical studies are summarised in Table 2.

Table 1. Clinical studies evaluating pembrolizumab.

Study	Phase/Design	Sample size	Treatment	ORR (%)	MPR (%)	pCR (%)
Lin *et al* [5]	Retrospective	Not reported	Pembrolizumab + chemotherapy	87.2	68.2	45.5
Duan *et al* (PEN-ICE) [6]	Open-label, single-arm	18 enrolled; 13 proceeded to surgery	Pembrolizumab + chemotherapy	Not reported	69.2	46.2
Duan *et al* multicentre study [7]	Open-label, multicentre, single-arm	Not reported	Pembrolizumab + chemotherapy	50.0	82.3	47.1
Wu *et al* [8]	Observational	Not reported	Chemo-immunotherapy	Not reported	42.11	34.21

Table 2. Clinical studies evaluating oncolytic viral therapy.

Study	Virus	Phase/Design	Sample size	Combination therapy	Outcome reported
Fujiwara *et al* [9]	OBP-301 (telomelysin)	Phase I dose-escalation	Not reported	Radiotherapy	ORR 84.6%
Tanabe *et al* [10]	OBP-301 (telomelysin)	Early-phase clinical study	Not reported	Radiotherapy	Complete response rate reported; ORR not reported
Middleton *et al* [11]	RP1 (HSV-1)	Phase I/II	Not esophageal-cancer specific	Nivolumab	Activity across tumour types; esophageal-specific ORR not reported

Discussion

Current evidence suggests that pembrolizumab combined with chemotherapy can produce encouraging pathological response rates in locally advanced ESCC. However, the available evidence should be interpreted cautiously because much of it derives from small studies, single-arm designs and regional cohorts, particularly studies conducted in Asian populations. This may limit the generalisability of findings to broader patient populations, including patients with esophageal adenocarcinoma.

The reported ORR, MPR and pCR rates are clinically notable, but pathological response should not be interpreted as equivalent to long-term survival benefit. While MPR and pCR are useful early indicators of treatment activity, their relationship with durable survival outcomes in this setting remains uncertain and requires validation in larger randomised controlled trials.

Oncolytic viral therapy is an emerging modality with a mechanistic rationale for synergy with immune checkpoint inhibition. Nevertheless, clinical data in stage III esophageal cancer remain sparse, and most evidence comes from early-phase studies or conference abstracts. Several cited references are conference abstracts, reflecting the developing nature of this field; therefore, their findings should be interpreted as preliminary until confirmed in full peer-reviewed publications and prospective randomised studies.

Future trials should focus on biomarker-driven patient selection, including programmed death-ligand 1expression, tumour mutational burden and immune microenvironment characteristics. Studies evaluating pembrolizumab in combination with oncolytic viral therapy may help define whether these approaches have additive or synergistic roles in stage III esophageal cancer treatment algorithms.

Conclusion

Pembrolizumab and oncolytic viral therapy represent promising immunotherapeutic strategies in stage III esophageal cancer, particularly in ESCC. Pembrolizumab-based neoadjuvant therapy has demonstrated encouraging pathological response rates, whereas oncolytic viral therapy remains an emerging approach with limited clinical data. Larger randomised controlled trials and biomarker-guided studies are required to establish their definitive roles in clinical practice.

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List of abbreviations

AJCC, American Joint Committee on Cancer; ESCC, Esophageal squamous cell carcinoma; HSV-1, Herpes simplex virus type 1; ICI, Immune checkpoint inhibitor; MPR, Major pathological response; ORR, Objective response rate; pCR, Pathological complete response; TMB, Tumour mutational burden.

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

Rajsinh Bhosale: Conceptualisation, Literature Review, Drafting, Editing, Supervision

Lamiya Pirzada: Literature Review, Drafting

Safiyyah Khan: Literature Review

Aqsa Zainab: Manuscript Writing

Shravya Subashini Sivaramakrishnan: Formatting, References, Proofreading

Areeba Mariam Mehmood: Manuscript Writing

Pawan Sapkota Upadhya: Editing.

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