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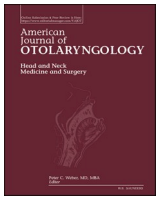

Cost evaluation in head and neck cancer clinical trials: implications for high-value care

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ABSTRACT

Background: Clinical trials are crucial in advancing novel therapeutic interventions for head and neck cancer. Given the increased cost of modern healthcare, cost considerations in clinical trials are important yet remain limited.

Methods: A search of ClinicalTrials.gov identified all head and neck cancer studies including cost in the trial description or as a study outcome. Data collected included study type, duration, completion status, enrollment, funding type, cost outcomes, and cost-effectiveness analyses.

Results: Among 2290 head and neck cancer-focused clinical trials, only 76 (3.3 %) mentioned cost in any capacity. Among the trials mentioning cost, 53 (70 %) included cost outcomes and 26 (34 %) included cost effectiveness analyses. Cost was reported as a primary outcome in 5 (0.2 %) clinical trials, a secondary outcome in 32 (1.4 %) trials, and an exploratory outcome in 16 (0.7 %) trials. Most trials (87 %) were interventional, and the most common primary interventions were procedures (25 %) or drugs (14 %). The mean enrollment was 206 participants, and mean duration of the trials was 50 months (SD 47). 73 (96 %) studies have not yet reported results.

Conclusion: The inclusion of cost in head and neck cancer clinical trials is limited, with <3 % of trials including cost endpoints and < 2 % including cost-effectiveness analyses. The paucity of available study results hinders the assessment of the ultimate impact on patients, insurance companies, and healthcare systems. Given the rising cost pressures in modern healthcare systems, the low prevalence of cost endpoints and cost-effectiveness analyses underscores the need for increased awareness and investment in this domain.

1. Introduction

Head and neck cancer (HNC) is the seventh leading cause of cancer worldwide and accounts for >660,000 new cases and 325,000 deaths annually [1,2]. Given the increasing incidence, shifting patient demographics, and overall disease burden of HNC clinical trials have played an integral role in patient care with 560 trials actively recruiting participants worldwide as of April 2023 [3].

Cancer treatment imposes substantial financial burdens on not only healthcare systems but also individuals. Studies have shown that cancer patients are more prone to decline treatment due to financial concerns compared to other patient [4]. HNC patients encounter considerable total and out-of-pocket costs and face unique long-term treatment-related challenges [5,6]. HNC is associated with the highest post-treatment symptom burden of all common cancers, resulting in additional financial strain due to costs of medications, supplies, travel, and consultations for dental care, physiotherapy, and speech and swallow therapy [5,7]. Thus, costs associated with HNC management have significant implications on quality of life and survival. While clinical endpoints crucially inform advances in evidence-based standards of care, economic endpoints are not commonly reported despite the increasing cost pressures placed on modern health systems [8]. The incorporation of cost endpoints into trials facilitates the evaluation of the economic impact of therapeutic interventions, thus enabling evidence-based decision making and the prioritization of cost-effective treatments. In addition to promoting cost transparency, cost endpoints

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offer insights into resource allocation, patient access to care, and ultimately, patient satisfaction.

Despite the growing emphasis on value-based care, the inclusion of financial endpoints in clinical trials remains limited. This is especially evident in trials assessing specialty oncology medications, which are underrepresented among trials incorporating economic endpoint [9]. To promote high-value care, this study aimed to examine the extent to which cost considerations are incorporated into clinical trial design. The prevalence and characteristics of cost endpoints in HNC clinical trials were assessed using ClinicalTrials.gov. It was hypothesized that financial endpoints remain underreported in HNC clinical trials.

2. Methods

A comprehensive search was conducted using ClinicalTrials.gov for all HNC studies using relevant inclusion terms [10], as shown in Supplemental Table 1. An advanced search was conducted with the following inclusion criteria: "head and neck cancer" as the condition or disease; "all studies" in the status field; and "cost" in the other terms field. Terms closely related to each primary search term were automatically generated and included in the database search. To validate the results, a manual search was conducted for each trial to search for the context in which cost was mentioned. Clinical trial cost data from the 10 most common solid malignancies were similarly extracted from the ClinicalTrials.gov website using the same search methodology for comparison with HNC trials. Trials were included if cost was mentioned in the trial description or listed as a study outcome. In the context of this study, cost outcomes refer to the direct and indirect costs of trial interventions rather than the operating costs associated with managing the trial itself. Data collected included study name, study type, trial start date, duration, completion status, total enrollment, funding type, country of origin, cost outcomes, and cost-effectiveness analyses. Descriptive statistics were collected. Clinical trials were designated as interventional only if the primary treatment modality was oncologic treatment of HNC in the form of surgical resection, radiation therapy, immunotherapy, or chemotherapy; all other clinical trials were designated as non-interventional.

3. Results

Among 2290 HNC-focused trials, only 76 (3.3 %) mentioned cost in the trial description or listed cost as a primary, secondary, or exploratory outcome of the study (Fig. 1). Cost was reported as a primary outcome in 5 (0.2 %) clinical trials, a secondary outcome in 32 (1.4 %) trials, and an exploratory outcome in 16 (0.7 %) trials. Among the trials mentioning cost, 53 (70 %) included cost outcomes and 26 (34 %) included cost-effectiveness analyses. The mean enrollment was 206 participants, and mean duration of the trials was 50 months (Table 1). Of the 76 trials incorporating cost into clinical trial design, the most common countries of origin were the United States (34 %), France (11 %), Canada (9 %), the United Kingdom (9 %), Taiwan (8 %), and the Netherlands (7 %).

Of trials incorporating cost into clinical trial design, 73 (96 %) studies have not yet reported results, and of these 57 (75 %) are closed to accrual. Among the three studies with available results, one study reported safety concerns and patient non-compliance, resulting in no patients completing the intervention arm (NCT03682367). The data collected was found to be unreliable and uninterpretable, and as such, there was no available data on the cost outcomes. The final two studies with available results only mentioned cost in the study description, rather than an outcome measure (NCT01065844, NCT02926573). Thus, the existing results are unable to shed light on cost in HNC clinical trials.

Among HNC clinical trials that mention cost, 49 % ($n = 37$) of the trials included radiation therapy as a component of the treatment regimen, 38 % ($n = 29$) included surgery, 33 % ($n = 25$) included supportive oncology, 7 % ($n = 5$) included chemotherapy, 7 % (n = 5) included imaging, and 3 % (n = 2) included immunotherapy (Table 2).

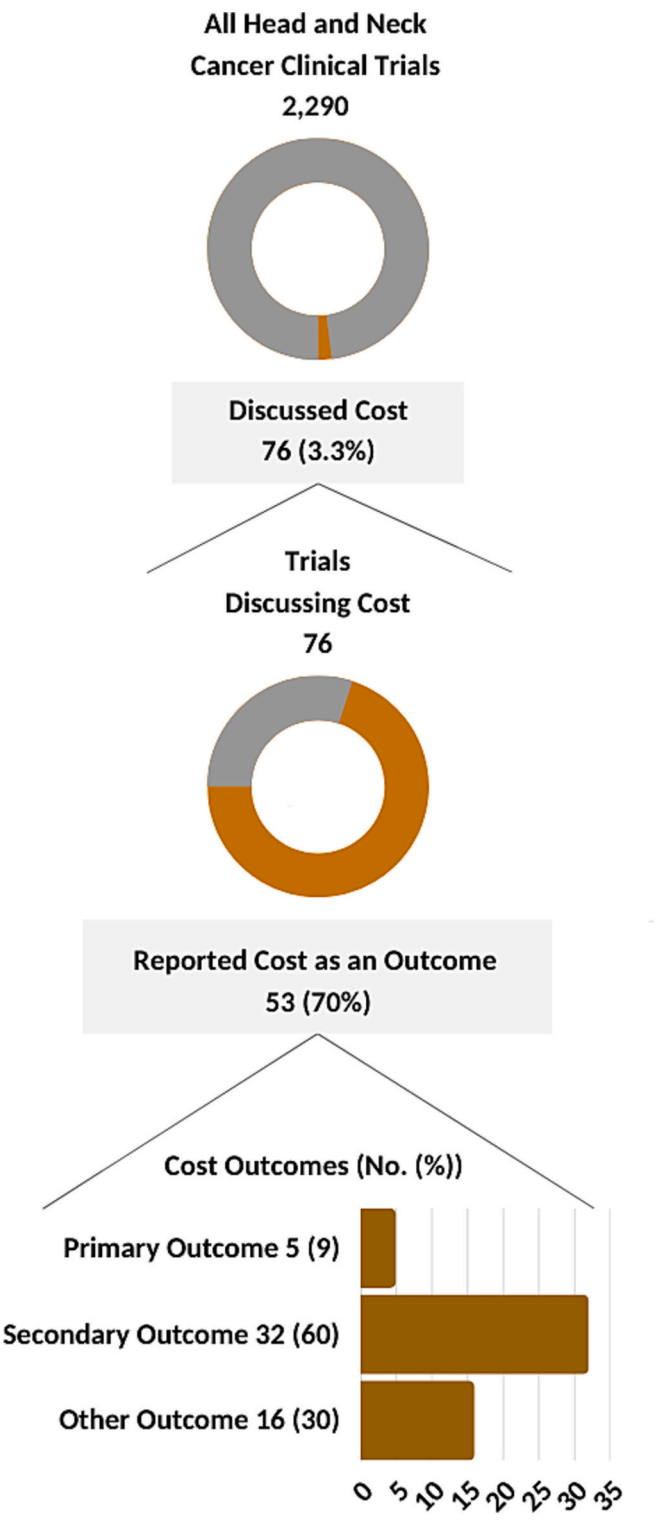

Fig. 1. Head and neck cancer clinical trials incorporating cost outcomes.

Of trials incorporating cost into clinical trial design, 19 (25 %) were interventional and 57 (75 %) were non-interventional. Among interventional trials, the most common primary intervention was surgery ($n = 7$) followed by radiation therapy ($n = 6$), chemotherapy ($n = 4$), and immunotherapy (n = 2; Table 3). Among non-interventional trials, supportive oncology was the primary treatment modality in 25 trials (44 %), diagnostic testing was the primary treatment modality in 9 trials (16 %), medical devices in 5 trials (9 %), and imaging in 1 trial (2 %; Table 4). Commonly investigated treatment modalities in supportive

Table 1
Characteristics of head and neck cancer clinical trials incorporating cost into trial design.

Characteristics	No.	(%)
Country of Origin	76	100 %
USA	26	34 %
France	8	11 %
Canada	7	9 %
United Kingdom	7	9 %
Taiwan	6	8 %
Netherlands	5	7 %
Germany	2	3 %
Ireland	2	3 %
Italy	2	3 %
Sweden	2	3 %
Australia	1	1 %
Belgium	1	1 %
Brazil	1	1 %
Finland	1	1 %
India	1	1 %
Pakistan	1	1 %
Singapore	1	1 %
Switzerland	1	1 %
Vietnam	1	1 %
United States Census Region	26	100 %
Northeast	4	15 %
Midwest	9	35 %
South	8	31 %
West	5	19 %
Funding Source	76	100 %
Other	65	86 %
NIH	9	12 %
Industry	2	3 %
Status	76	100 %
Completed	24	32 %
Recruiting	19	25 %
Not yet recruiting	11	14 %
Active, not recruiting	5	7 %
Withdrawn/Terminated	3	4 %
Unknown	14	18 %
Phase	76	100 %
NA	56	74 %
Phase 1	1	1 %
Phase 2	4	5 %
Phase 3	10	13 %
Phase 4	5	7 %
Enrollment (No. patients)	76	100 %
0-49	16	21 %
50-99	15	20 %
100-499	37	49 %
400-999	7	9 %
1000+	1	1 %
Trial Type	76	100 %
Interventional	19	25 %
Noninterventional	57	75 %

Table 2
Range of treatment modalities employed in head and neck cancer clinical trials that incorporate cost into trial design.

Component of Clinical Trial Design	N	%
Radiation Therapy	37	49 %
Surgery	29	38 %
Supportive Oncology	25	33 %
Chemotherapy	24	32 %
Imaging	5	7 %
Immunotherapy	2	3 %

care trials included speech and swallow therapy, nutrition, pain management, complication prevention, exercise therapy, and postoperative management protocols.

When assessing the prevalence of cost reporting in clinical oncology trials, noteworthy variations in the inclusion of cost outcomes were apparent in HNC trials compared with other solid malignancies. Clinical

Table 3
Characteristics of interventional head and neck cancer clinical trials incorporating cost into trial design.

Primary intervention	19	25 %
Surgery	7	37 %
Radiation	6	32 %
Chemotherapy	4	21 %
Immunotherapy	2	11 %

Table 4
Common themes of noninterventional trials head and neck cancer clinical trials incorporating cost into trial design.

Noninterventional trials	57	100 %
Supportive Care	25	44 %
Speech and Swallow Therapy	6	24 %
Nutrition and Hydration	6	24 %
Pain Management	3	12 %
Dermatitis Prevention	2	8 %
Exercise Therapy	2	8 %
Postoperative Management	2	8 %
Infection Prevention	1	4 %
Wound management	1	4 %
Other	2	8 %
Diagnostic Test	9	16 %
Medical device	5	9 %
Imaging	1	2 %
Other	17	30 %

oncology trials with the highest percentage of trials reporting cost as a primary, secondary, or exploratory outcome of the study were uterine cancer (5.6 %), colorectal cancer (4.8 %), breast cancer (3.8 %), thyroid cancer (3.7 %), prostate cancer (3.4 %), and bladder cancer (3.4 %; Supplemental Table 2).

4. Discussion

Given increasingly costly modern healthcare systems and the need to prioritize cost-effective treatments, the incorporation of cost considerations and endpoints in clinical trials is important to inform decision-making, resource allocation, and the delivery of high-value care. However, in this analysis of 2290 HNC clinical trials only 3.3 % mentioned cost in their trial description or listed it as a primary, secondary, or exploratory outcome. This is lower than many other solid malignancies. Of the 76 trials that did incorporate cost, 70 % included cost outcomes and 34 % included cost-effectiveness analyses. Notably, 96 % of trials incorporating costs have not yet reported results, and of these, 75 % are closed to accrual.

As healthcare costs continue to rise, multiple stakeholders are increasingly seeking early evidence of the economic value of interventions ideally tested in clinical trials. The incorporation of cost data in trials may offer early, transparent, and unbiased information regarding value generation, which can be used to inform decision-making, allocation of resources, and ultimately, the delivery of high-value care. The infrequent utilization of cost endpoints and cost-effectiveness analyses in clinical trials may be partially attributed to the complicated nature of cost measurement and resource utilization as well as significant practical design challenges. Data need to investigate the cost to the patient, cost effectiveness, or value may not be available on ClinicalTrials.gov. The controlled environment of clinical trials may not capture the full spectrum of cost information needed by decision-makers, as healthcare costs vary significantly based on geographic location, patient population, and clinical setting, making it difficult to generalize cost data across different trials. Trials are protocol-driven and reflect research aims rather than the cost constraints faced outside of the trial setting, which also limits generalization.

HNC trials (3.3 %) had a lower percentage of trials reporting cost

than other solid malignancies including thyroid (3.7 %), breast (3.8 %), colorectal (4.8 %), and uterine (5.6 %). Differences in cost reporting between HNC and other solid malignancies may stem from HNC's complexity, heterogeneity, and lower prevalence, which can limit trial numbers, sample sizes, and statistical power. The lack of cost reporting in closed trials ($n = 75$, 0 reported) may indicate accrual challenges. Overall, low cost reporting in HNC trials is likely multifactorial, influenced by resource constraints, accrual difficulties, variability in cost measurement, absence of standardized guidelines, and a primary focus on clinical endpoints.

HNC treatment exerts significant cost pressure on the US healthcare system, with aggregated expenditures estimated between $3.79 billion and $5.46 billion in 2020 [11]. HNC disproportionately affects socioeconomically disenfranchised individuals with lower education, income, and baseline health status, making this financially strained population particularly vulnerable to higher financial toxicity given the intensive, multimodal nature of treatment [12]. Higher financial toxicity in HNC treatment has been associated with missing clinic visits, being noncompliant with or rationing recommended medications and supplements, and requiring supportive infusions [13]. HNC survivors experience higher total medical costs relative to other cancer patients and face higher out-of-pocket costs relative to their income. After treatment, nearly half of HNC survivors reduce their workload, of which a third leave the workforce entirely [14]. The nationwide economic impact of HNC coupled with the high financial burden placed on individual patients highlights the importance of integrating cost considerations into the development of cancer interventions.

Incorporating cost endpoints in trials may provide early economic value with high internal validity to payers, offer less biased estimates of key model parameters in healthcare resource utilization, and enhance the methodological quality of cost-effectiveness analyses [9,15]. The low prevalence and visibility of cost endpoints and cost-effectiveness analyses in HNC trial design underscores the need for increased awareness and investment in this domain. Further research should explore effective ways to integrate cost considerations into clinical trials and their impact on treatment outcomes, patient quality of life, and healthcare costs, including challenges across trial phases and treatment types. Additionally, there may be utility in developing standard guidelines or best practices for incorporating cost considerations in clinical trial design as most trials do not report results [16]. It is also important to increase the transparency of regulatory and logistical considerations for incorporating cost considerations into clinical trial design, such as specialized staff with expertise in economic evaluation and considering the costs indirectly related to trial interventions (managing adverse events, follow-up care, etc.). Ultimately, the goal of incorporating cost endpoints in clinical trial design is to ensure that patients have access to effective and affordable treatments. Identifying gaps in the current approach is crucial for developing strategies that enhance cost transparency in clinical trial design, integrating clinical and economic endpoints to improve patient outcomes and high-value care.

The study design has limitations, particularly regarding the scope of data available from ClinicalTrials.gov. This registry primarily captures prospective interventional studies and may not comprehensively include studies focused on cost to the patient, cost-effectiveness, or value, which are often explored through post-hoc analyses, health technology assessments (HTA), or non-interventional study designs. This study is also limited by the inclusion of “cost” as the primary search term rather than all possible related economic or financial search terms. Furthermore, given the regulatory pathway for drug approval and subsequent price establishment, it is unsurprising that radiation and surgical studies more frequently address cost, as these treatments are often linked to established CPT codes and reimbursement structures. This remains an important area for future research to better capture the evolving landscape of value-based care in HNC.

Future research should address these limitations by incorporating broader data sources beyond ClinicalTrials.gov, such as HTAs and real-world cost-effectiveness studies, and expanding search strategies to include additional economic and financial terms could improve study scope. Additionally, a systematic review of published cost-effectiveness and value-based care studies in HNC, including retrospective cost analyses and real-world evidence studies, could provide further insight into how cost factors influence treatment decision-making.

5. Conclusion

The underreporting of cost considerations in HNC clinical trials highlights a significant gap in the field, particularly as healthcare costs continue to rise and impact patient access to care. Our findings suggest the need for greater emphasis on incorporating economic endpoints in clinical trial design, particularly to enhance decision-making, inform resource allocation, and promote value-based care. Future research should focus on addressing the challenges of measuring and reporting cost in trials, developing standardized guidelines for integrating cost considerations, and exploring the impact of cost data on patient outcomes and healthcare systems. Ultimately, integrating cost endpoints into clinical trial design will better inform healthcare providers, payers, and policymakers, contributing to improved patient care and more sustainable healthcare practices.

CRediT authorship contribution statement

Rachel G. Collins: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ina A. Lee:** Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Daniel R.S. Habib:** Writing – original draft, Writing – review & editing. **Desmond C. Garner:** Conceptualization, Supervision, Writing – review & editing. **Douglas B. Johnson:** Supervision, Writing – review & editing. **Priyesh N. Patel:** Supervision, Writing – review & editing. **Michael C. Topf:** Supervision, Writing – review & editing.

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Declaration of competing interest

DBJ has served on advisory boards or as a consultant for BMS, Catalyst Biopharma, Iovance, Jansen, Mallinckrodt, Merck, Mosaic ImmunoEngineering, Novartis, Oncosec, Pfizer, Targovax, and Teiko, has received research funding from BMS and Incyte, and has patents pending for use of MHC-II as a biomarker for immune checkpoint inhibitor response, and abatacept as treatment for immune-related adverse events.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjoto.2025.104655.

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