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Optimal management of esophageal cancer in Africa: A systemic review of treatment strategies

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Abstract

Esophageal cancer (EC) is a leading cause of cancer morbidity and mortality in Africa. Despite the high burden of disease, optimal management strategies for EC in resource-constrained settings have yet to be established. This systematic review evaluates the literature on treatments for EC throughout Africa and compares the efficacy and safety of varying treatment strategies in this context (PROSPERO CRD42017071546). PubMed, Embase and African Index Medicus were searched for studies published on treatment strategies for EC in Africa from 1980 to 2020. Searches were supplemented by examining bibliographies of included studies and relevant conference proceedings. Methodological quality/risk of bias was assessed using the Cochrane Risk-of-Bias tool and the Newcastle-Ottawa Scale. Forty-six studies were included. Case series constituted the majority of studies: 13 were case series reporting on outcomes of esophagectomies, 17 on palliative luminal or surgical interventions, four on radiotherapy and three on concurrent chemoradiation. Nine randomized controlled trials were identified, of which four prospectively compared different treatment modalities (one investigating radiotherapy vs chemoradiation, three evaluating rigid plastic stents vs other treatments). This review summarizes the research on EC treatments in Africa published over the last four decades and outlines critical gaps in knowledge related to management in this context. Areas in need of further research include (a) evaluation of the safety and efficacy of neoadjuvant therapy in patients with locally advanced disease; (b) strategies to improve long-term survival in patients treated with definitive chemoradiation; and (c) the comparative effectiveness of modern palliative interventions, focusing on quality of life and survival as outcome measures.

KEYWORDS

Africa, esophageal cancer, quality of life, survival, systematic review, treatment guidelines

Abbreviations: AACR, American Association for Cancer Research; AfrECC, African Esophageal Cancer Consortium; AIM, African Index Medicus; AORTIC, African Organization for Research and Training in Cancer; CT, computed tomography; CUGH, Consortium of Universities for Global Health; EBRT, external beam radiotherapy; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EUS, endoscopic ultrasound; frx, fraction; Gy, Gray; HDRILBT, high-dose-rate intraluminal brachytherapy; HIC, high-income country; NCI, National Cancer Institute; NOS, Newcastle-Ottawa Quality Assessment Scale; OS, overall survival; PET, positron emission tomography; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QOL, quality of life; RCT, randomized-controlled trial; SEMS, self-expandable metallic stent; UCSF, University of California, San Francisco; UICC, Union for International Cancer Control.

1 | BACKGROUND

Esophageal cancer (EC) has been identified as a leading cause of cancer morbidity and mortality in sub-Saharan Africa, with disproportionately high incidence rates along the eastern corridor, extending from Ethiopia to South Africa.[1] Age-standardized incidence rates in Africa's high-risk corridor range from 9 to 47 cases per 100 000.[2,3] Within this region, EC is the third leading cause of cancer mortality.[3] Esophageal squamous cell carcinoma (ESCC) is the dominant histological subtype, accounting for over 90% of all cases across sub-Saharan Africa.[4]

EC is a disease that portends a poor prognosis, with global estimations that 5-year survival is <10%. This is largely due the asymptomatic nature of the disease in early stages, which enables regional or distant spread by the time symptoms develop. This dismal prognosis is likely exacerbated in Africa and other low-resource settings by additional factors, which contribute to delays in diagnosis and barriers to treatment. In Africa, nearly 90% of patients have advanced disease at the time of presentation.[5-7] For patients with localized or locoregional ESCC, chemoradiation with or without surgery offers the best chance for long-term survival.[8] Palliative treatment strategies, however, remain the mainstay of care for most patients presenting with advanced disease.

Optimal management strategies for palliation of advanced EC in resource-limited settings remain unclear due to a lack of randomized controlled trials (RCTs) addressing this question. Palliative treatment modalities include esophageal stenting, radiotherapy, chemoradiotherapy, and brachytherapy, as well as combined treatment approaches. Utilization of different treatment modalities varies widely and may be dictated by resource availability, rather than standards for the best practice. A recent Cochrane analysis on palliative interventions for dysphagia in EC, largely based on studies conducted in high-income countries (HICs), found that esophageal stenting is quick, safe and effective for palliation of dysphagia; however, no single treatment emerged as clearly superior in terms of improving overall survival (OS) or quality of life (QOL).[9] Although this analysis provides some clarity, the unique challenges of delivering care in resource-constrained environments limit the generalizability of these findings to many African settings.

In recent years, there have been several international efforts to develop resource-stratified guidelines for cancer in Africa[10] and other resource-limited settings[11,12]; however, these guidelines have been largely informed by research conducted in HICs. Assessing the evidence for current treatment strategies employed in Africa is an important step toward establishing evidence-based guidelines that are appropriate for the context. To address this knowledge gap, we conducted a systematic review of all studies conducted in Africa evaluating treatment strategies for EC. We aimed to (a) assess and compare the efficacy and safety of varying treatment strategies in this context; and (b) highlight research priorities for improving EC outcomes in Africa.

What's new?

Esophageal cancer is a leading cause of cancer morbidity and mortality in Africa. This systematic review summarizes the research on esophageal cancer treatment strategies in Africa and outlines critical gaps in knowledge related to management in this context. Priority research areas include the comparative effectiveness of modern palliative interventions, the safety and efficacy of neoadjuvant therapy in patients with locally advanced disease, and strategies to improve long-term survival in patients treated with definitive chemoradiation. The identified evidence provides a contemporary benchmark for future research and could help inform international efforts for developing resource-stratified guidelines for cancer in Africa.

2 | METHODS AND ANALYSIS

2.1 | Study design

The protocol for this systematic review was registered a priori with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42017071546). The systematic review was designed and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

2.2 | Eligibility criteria

This systematic review included all primary studies investigating treatment strategies for EC in Africa, including chemotherapy, radiotherapy and procedural or surgical interventions. Criteria for inclusion were as follows: (a) study design was an RCT, nonrandomized trial or case series; (b) study population was adult patients with EC (≥18 years of age); (c) outcome metrics were related to treatment of EC (eg, OS, dysphagia scores and/or adverse events); (d) study was conducted in an African country or with an enumerable subset of participants enrolled in an African country; (e) publication in 1980 or thereafter; and (f) original publication was in English or available with English translation. Of note, due to limited availability of pathology services throughout much of Africa, no diagnostic criteria were specified. Individual case reports were excluded.

The primary outcome of this systematic review was OS. The secondary outcome was posttreatment dysphagia, as measured by either dysphagia scores or dysphagia-free survival.

2.3 | Data sources and search strategy

An electronic literature search of online databases and a manual search of conference proceedings were performed. To search the online databases, we employed a literature search strategy using MeSH terms related to "esophageal cancer," "Africa" and each African country by name (see Appendix for full search strategy). We then searched PubMed, Embase and African Index Medicus (AIM) for any studies

published after 1980. The initial search was performed on 15 June 2017 for PubMed and Embase and on 7 July 2017 for AIM. All searches were updated on 1 April 2020.

To address concerns regarding the scarcity of published data on EC treatment in Africa, we sought to identify any citations from relevant conference proceedings that met the predefined eligibility criteria. Conferences relevant to global oncology or EC in Africa were identified (see Supplement Table S1 for complete list of conferences) and published abstracts were downloaded from conference websites when available. When not publicly accessible, we obtained full text of available conference proceedings from conference organizers.

2.4 | Study selection and data collection

All citations identified excluding conference abstracts were uploaded to Covidence (Veritas Health Innovation), a systemic review software.[14] The title and abstract of citations were first screened to assess eligibility, after which the full text of each study was evaluated based on a standardized inclusion/exclusion form. If multiple citations reported data on the same study population, the more recent and complete citation was preferentially included. Reference lists of included studies and any identified review articles were then manually screened to identify studies that may have been missed during the original search.

Data were abstracted using a standardized data collection form. Abstracted data included the following: study characteristics, study population, interventions, outcomes measured, duration of follow-up and results.

2.5 | Quality assessment

The study quality of each of the eligible nonrandomized cohort studies available in full text was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale (NOS; see Appendix).[15] Studies were considered to be of high quality if the NOS score was ≥7. For the eligible RCTs, we evaluated risk of bias using the revised Cochrane Risk-of-Bias Tool (RoB2).[16,17] Two reviewers (G.B. and R.M.) independently evaluated each of the studies. Any domains that differed in scoring were resolved by adjudication between the two reviewers.

3 | RESULTS

3.1 | Study selection

A total of 8339 records were identified; of these, 2503 were from the three electronic databases (PubMed, Embase and AIM), 5785 from conference proceedings and 51 from a review of reference lists (Figure 1). A total of 429 duplicates were excluded, yielding 7910 unique records for inclusion in the initial title and abstract screen. After the initial screen, a total of 165 full-text articles and five conference abstracts were assessed in full; 121 of the full-text articles were excluded due to failure to meet the inclusion criteria. Three abstracts were excluded due to duplication of data in a related manuscript. Overall, 44 full-text articles and two conference abstracts were included in the analysis.[18,19]

3.2 | Study characteristics

Of the 46 studies included, 31 were prospective, 13 were retrospective and 2 reported both retrospective and prospective data. Of the prospective studies, 9 were RCTs, 7 were phase II clinical trials and 17 were observational cohort studies. All retrospective studies were institutional case series, with one designed as a comparative cohort study.[20] ESCC was the predominant histological subtype in 34 of the 36 studies reporting confirmed histological findings. Studies were identified from 10 countries in Africa. Over 50% (n = 27) of all studies were conducted in South Africa with the remaining from Egypt (n = 6), Ethiopia (n = 3), Kenya (n = 2), Nigeria (n = 2), Sudan (n = 2), Algeria (n = 1), Malawi (n = 1), Mozambique (n = 1) and Zimbabwe (n = 1). The total number of participants among included studies by country is presented in Figure 2.

Of the 37 nonrandomized studies, 17 reported on palliative luminal and surgical interventions (Table 1). Ten of these studies reported on self-expandable metallic stents (SEMS)[6,20-28]; five on rigid plastic stents, laser treatment or dilation[29-33]; and two on retrosternal gastric bypass.[34,35] Four studies reported on palliative radiotherapy,[18,20,32,36] six studies on chemotherapy[32,37-41] and three studies on concurrent chemoradiotherapy[32,42,43] (Table 2). Thirteen studies were case series reporting outcomes following esophagectomy (Table 3).[6,7,19,32,44-52]

All nine RCTs were single-center studies conducted in South Africa (Table 4). Three studies compared intubation with plastic stents to other treatments (dilation with bleomycin,[54] retrosternal gastric bypass[53] and SEMS[60]), and two evaluated intubation combined with either chemotherapy, radiotherapy or chemoradiation as compared to intubation alone.[56,57] The remaining four RCTs investigated retrosternal bypass surgery with and without pyloroplasty[55]; high-dose-rate intraluminal brachytherapy (HDRILBT) dosing strategies[59]; chemoradiotherapy vs radiotherapy alone[58]; and HDRILBT with and without external beam radiotherapy (EBRT).[61]

3.3 | Quality assessment and risk of bias within studies

The NOS was used to assess the quality of all 35 nonrandomized studies with full text available (see Supplement Table S2). Of these, six (17%) received scores ≥7, indicating high quality.[24,27,28,36,40,42] Thirteen studies (37%) received scores of 5 or 6, and the remaining 16 (46%) received scores of ≤4. Comparability and outcome biases were most common and observed in 89% and 75% of studies,

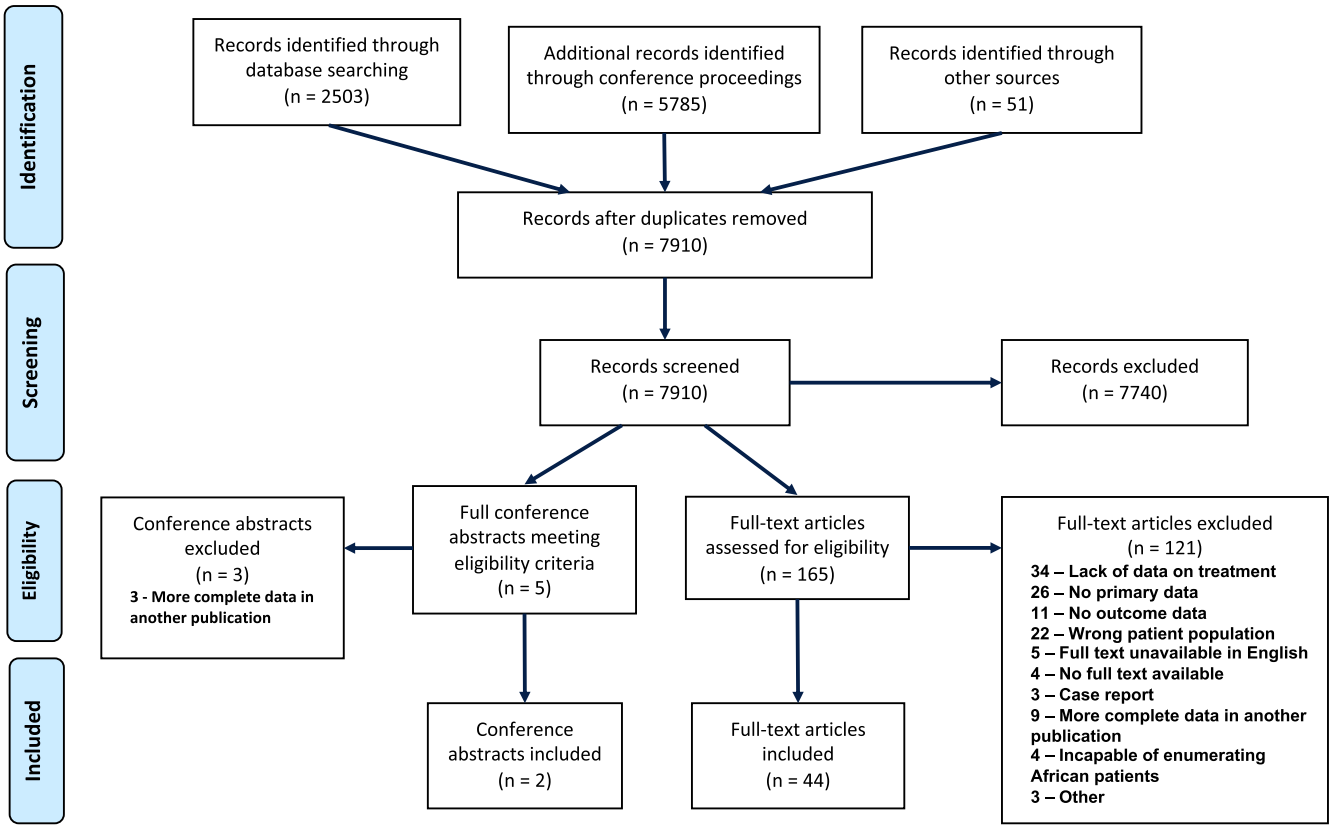

FIGURE 1 PRISMA flow chart of study selection and screening process, including reasons for exclusion

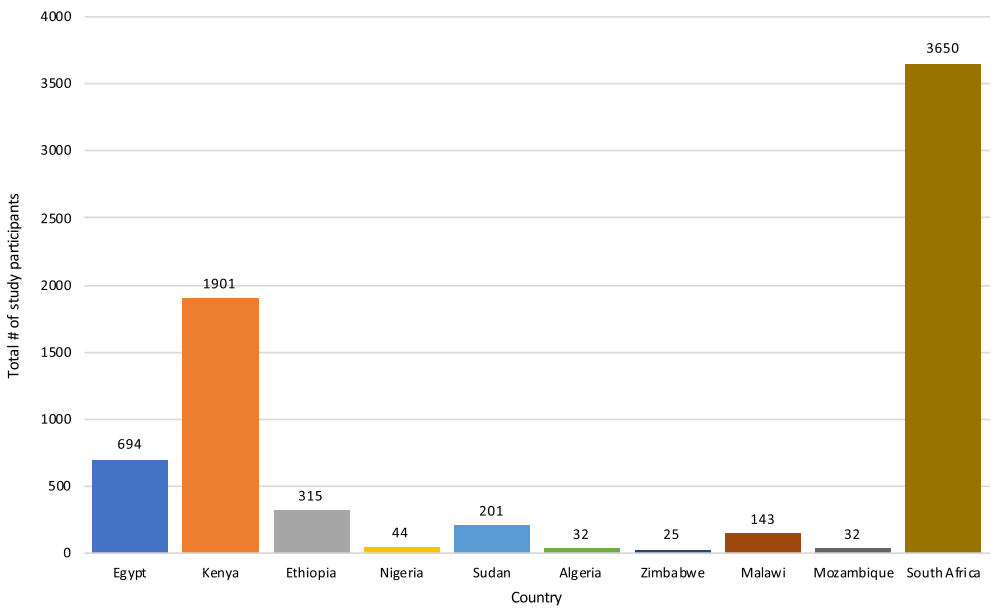

FIGURE 2 Total number of study participants by country

respectively. The Cochrane RoB2 tool was used to assess risk of bias in the nine RCTs identified (Figure 3A,B). One study (11%) was determined to be at "high risk" of overall bias due to missing data.[58] The remaining eight studies (89%) raised "some concerns" for bias, most commonly due to risk of bias arising from the randomization process and in selection of the reported results.

3.4 | Summary of evidence by intervention

3.4.1 | Esophagectomy

Thirteen studies reported outcomes for patients who underwent esophagectomy (Table 3). Five of the studies reported data on

TABLE 1 Nonrandomized studies reporting on treatment outcomes for palliative luminal and surgical interventions

Study	Country	Design	Study period	Patient population	n	Histology (%)	Intervention	Procedure-related mortality	Dysphagia score after treatment (mean change)[a,b]	Overall survival[c] (weeks)	Comments
Self-expandable metallic stents (SEMS)											
Motilall et al[21]	South Africa	Prospective	2002–2005	EC with TEF	21	SCC 100	SEMS	10%	Postprocedure: −2.1 ($P < .001$)	9	
				EC with no TEF	37	SCC 100	SEMS	3%	Postprocedure: −1.9 ($P = .013$)	13	
Elsharkawy et al[22]	Egypt	Retrospective	1999–2007	Inoperable EC	124	SCC 56 Adeno 44	SEMS	0%	Postprocedure: −2.3 ($P < .05$)[d]	7	
White et al[23]	Kenya	Prospective	1999–2008	Inoperable EC	951	SCC 94[e] Adeno 5 Other 1	SEMS	0.30%	Long-term: −2.3[f] At death: −1.3	36	
Liakos et al[20]	South Africa	Retrospective	2005–2008	Inoperable EC	18	SCC 100	SEMS	6%	NR	15	
Thumbs et al[24]	Malawi	Prospective	2009–2010	Inoperable EC	143	SCC 83[e] Adeno 2 Other 15	SEMS	2%	Postprocedure:−3.0 1-year: −3.0[d]	30	
Govender et al[25]	South Africa	Retrospective	2007–2011	Inoperable EC	453	NR	SEMS	0%	NR	NR	9% were undergoing repeat SEMS
Cotton et al[6]	Kenya	Prospective	2010–2012	Inoperable EC	875	NR	SEMS	NR	At death: dysphagia score 0–2 - 100%	39	
Shaker et al[26]	Egypt	Retrospective	2010–2012	Inoperable EC	31	NR	SEMS	0%	Postprocedure: −2.9 ($P < .001$)	25[g]	
Loots et al[27]	South Africa	Prospective	2013–2014	Stage III + IV EC	105	SCC 91[e] Adeno 7 Other 2	SEMS	NR	NR	12	Subset received chemotherapy ± XRT
Abdelshafy et al[28]	Egypt	Prospective	2012–2017	Inoperable EC	350	SCC 58 Adeno 40 Other 2	SEMS	0%	Postprocedure: −2.0 ($P < .001$)	20	8% received prior XRT, 7% chemotherapy, 3% chemoXRT
Other luminal therapies											
Kneebone et al[29]	South Africa	Retrospective (1979)/ prospective (1980–1981)	1979–1981	Inoperable EC	135	NR	Plastic stent, or dilation + bleomycin	NR	NR	6-month: 20%[h] 1-year: 1% 2-year: 0%	
Cotton et al[30]	South Africa	Prospective	1985	Any EC with malignant stricture	190	NR	Plastic stent	27%	NR	NR	

(Continues)

TABLE 1 (Continued)

Study	Country	Design	Study period	Patient population	n	Histology (%)	Intervention	Procedure-related mortality	Dysphagia score after treatment (mean change)[a,b]	Overall survival[c] (weeks)	Comments
Abdel-Wahab et al[31]	Egypt	Prospective	1994–1997	Any EC with malignant stricture	104	SCC 71 Adeno 29	Dilation + laser treatment	6%	Postprocedure: −1.5	32	6% received prior XRT
Dandara et al[32]	South Africa	Retrospective	1977–2007	Inoperable EC	448	SCC 90[i] Adeno 4 Other 6	Plastic stent	NR	NR	12	12% received XRT, 2% chemotherapy, 4% chemoXRT
Sur et al[33]	South Africa	Prospective	NR	EC with stricture post-HDRILBT	41	NR	Dilation	NR	Postprocedure dysphagia: 0: 68%, −1.0: 32% 6-month dysphagia score: 0: 50%, −1.0: 50%	NR	20% received brachytherapy 4- to 5-month postdilation
Palliative surgical procedures											
Angorn et al[34]	South Africa	Retrospective	1980–1982	Inoperable EC	60	NR	Retrosternal gastric bypass	8%	Postprocedure score 0: 100%	NR	
Mannell et al[35]	South Africa	Retrospective	1980–1986	Inoperable EC	124	SCC 100	Retrosternal gastric bypass	11%	Postprocedure dysphagia score: 0: 89%, 2: 8%	20	Subset received chemotherapy and/or XRT

Abbreviations: Adeno, adenocarcinoma; EC, esophageal cancer; HDRILBT, high-dose-rate intraluminal brachytherapy; NR, not reported; SCC, squamous cell carcinoma; SEMS, self-expandable metallic stents; TEF, tracheo-esophageal fistula; XRT, radiotherapy.

[a]Dysphagia assessed by either Oglivie's, Atkinson or Mellow and Pinkas' Dysphagia Score, which define 0 to 4 as follows: 0, able to swallow a normal diet; 1, able to swallow some solids; 2, able to swallow semi-solids only; 3, able to swallow only liquids; 4, unable to swallow saliva (Oglivie's), complete obstruction (Atkinson's) or complete dysphagia with failure to swallow anything (Mellow and Pinkas').

[b]Dysphagia score reported as mean change from baseline unless otherwise specified; *P* value included if reported.

[c]Median survival unless otherwise specified.

[d]Dysphagia score reported as median change from baseline.

[e]Total number of histologically confirmed cases out of total number with documented histology.

[f]Timing of follow-up not specified.

[g]Mean survival.

[h]Composite outcome for patients undergoing intubation with rigid plastic stent or dilation with bleomycin.

[i]Histological distribution reflects total case series of 1868 subjects.

esophagectomies performed with curative intent, each of which included a subset of patients who received perioperative chemotherapy and/or radiation.[6,7,32,47,51] All reported availability of computed tomography (CT) scans for preoperative staging. Median OS was largely consistent across all five studies, ranging between 1 and 2 years. Operative mortality was 10% and 12% in the two studies evaluating this metric. [47,51] Long-term outcomes were reported by two studies, with 13% and 21% of patients alive at 5 years.[47,51]

One phase II trial investigated neoadjuvant chemoradiation prior to esophagectomy.[42] Due to the focus of the study, limited surgical details were reported. In this study, neoadjuvant chemoradiation with capecitabine and oxaliplatin was well tolerated with no treatment-related deaths. Median OS was 1.5 years, similar to other esophagectomy case series. One-third of patients achieved progression-free survival at 2 years; however, OS data beyond 2 years were not reported.

In many of the remaining studies on esophagectomies, surgical resection was a first-line intervention due to few alternative treatment options.[44-46,48-50,52] In these studies, advanced preoperative imaging (CT, endoscopic ultrasound [EUS] or positron emission tomography [PET]) was largely unavailable, and >90% of patients were found to have advanced disease at the time of operation. Operative mortality varied widely, ranging from 16% to 50%.[45,46,48-50,52] OS data were inconsistently reported (see Table 3).

3.4.2 | Concurrent chemoradiation

Three studies reported outcomes of concurrent chemoradiation.[32,43,58] Two of the studies, both from South Africa, evaluated chemoradiation with curative intent. One was a case series,[32] and the other was an RCT comparing chemoradiation vs radiotherapy in locally advanced, inoperable disease.[58] Median OS in the chemoradiation arm of the RCT was 24 weeks, which was comparable to the 30 weeks observed in the case series. Findings from the RCT showed 5-fluorouracil and cisplatin with EBRT (40 Gray (Gy)/10 fractions (frx)) offered no survival benefit over EBRT alone and caused greater toxicity. This RCT is the only study to report long-term survival data for definitive chemoradiation in Africa, with 3-year OS of 3%.

One study reported outcomes of palliative chemoradiation. A prospective study from Egypt evaluated the efficacy of 5-fluorouracil and cisplatin with EBRT (40 Gy/22 frx) in patients with locally advanced and metastatic disease.[43] Most patients (76%) had improvement in dysphagia following treatment. Median OS was 30 weeks.

3.4.3 | Radiotherapy

Seven studies investigated palliative radiotherapy, four of which included data on outcomes of EBRT alone.[18,32,36,58] A variety of dosing and fractionation regimens were used including 8–10 Gy/1 frx,[18] 12 Gy/4 frx,[36] 20 Gy/5 frx[18] and 40 Gy/10 frx.[58] Median OS values were similar across the studies, ranging from 20 to 41 weeks. Only one study evaluated QOL outcomes. In a phase II clinical trial from Ethiopia, a short course of 12 Gy/4 frx given over 2 days led to a majority of patients experiencing improvement in dysphagia, regurgitation, odynophagia and chest or back pain with stable or improved performance status.[36]

Limited data were available on brachytherapy. Sur and colleagues reported results from two South Africa RCTs evaluating HDRILBT.[59,61] The first of these RCTs investigated three HDRILBT regimens, 12 Gy/2 frx, 16 Gy/2 frx and 18 Gy/3 frx.[59] Although this study found no significant difference in OS or dysphagia-free survival between the three groups, there was a trend toward longer OS with higher dosing. This was balanced against more strictures in the highest dose group. A follow-up RCT evaluated 16 Gy/2 frx with and without EBRT and found that the addition of EBRT offered no benefit as measured by OS or dysphagia-free survival over HDRILBT alone.[61] Median OS for HDRILBT with and without EBRT was 30 and 29 weeks, respectively.

3.4.4 | Chemotherapy

Six studies reported outcomes on palliative chemotherapy (see Table 2).[32,37-41] Five of these studies were phase II clinical trials.[37-41] Median OS was similar in each of the studies, ranging from 10 to 15 weeks. None of the studies evaluated QOL outcomes.

3.4.5 | Palliative luminal and surgical interventions

Limited data are available from Africa on both dilation and endoscopic laser ablation. A case series from South Africa evaluated the use of dilation for brachytherapy-related strictures and demonstrated sustained improvement in dysphagia following dilation.[33] A case series from Egypt examined outcomes of dilation with laser ablation and found this combination to be safe and effective for improving dysphagia in a subset of patients with obstructive tumors.[31] Operative mortality in this study was 6% with a median OS of 32 weeks.

Retrosternal gastric bypass was investigated in two case series[34,35] and two RCTs from South Africa.[53,55] Early studies demonstrated the palliative benefit of this procedure, with operative mortality of 8% to 11%.[34,35,53,55] As rigid plastic stents became available, an RCT evaluated retrosternal gastric bypass as compared to intubation with plastic stents and found that plastic stents caused fewer complications with comparable palliation and operative mortality.[53]

Two case series[30,32] and five RCTs[53,54,56,57,60] reported outcomes of intubation with plastic stents. Operative mortality rates ranged from 0% to 27%[30,53,54,60] with median OS ranging from 12 to 19 weeks.[32,54,56,57] Among the RCTs, early studies examined rigid plastic stents as compared to plastics stents with chemotherapy,[57] with radiotherapy[57] and with concurrent chemoradiation.[56] These

TABLE 2 Nonrandomized studies reporting on treatment outcomes for chemotherapy, radiotherapy and concurrent chemoradiation

Study	Country	Design	Study period	Patient population	n	Histology (%)	Treatment[a]	Treatment intent	Dysphagia score after treatment (mean change)	Overall survival (weeks)[b]	Comments
Chemotherapy											
Alberts et al[37]	South Africa	Prospective phase II trial	NR	Inoperable EC	24	SCC 100	Trimetrexate	Palliative	NR	12	
Ansell et al[38]	South Africa	Prospective phase II trial	NR	Inoperable EC	17	SCC 100	Ifosfamide	Palliative	NR	10	
Alberts et al[39]	South Africa	Prospective phase II trial	NR	Inoperable EC	35	SCC 100	5-Fluorouracil + leucovorin	Palliative	NR	14	
Mannell et al[40]	South Africa	Prospective phase II trial	1987–1988	Locally advanced + metastatic EC	11	SCC 100	Carboplatin	Palliative	NR	12	
Slabber et al[41]	South Africa	Prospective phase II trial	1993–1995	Inoperable EC	17	SCC 100	13-*cis*-retinoic acid + interferon alpha 2a	Palliative	NR	15	
Dandara et al[32]	South Africa	Retrospective	1977–2007	Inoperable EC	20	SCC 90[c] Adeno 4 Other 6	Chemotherapy	Palliative	NR	14	
Radiotherapy											
Dandara et al[32]	South Africa	Retrospective	1977–2007	Inoperable EC	570	SCC 90[c] Adeno 4 Other 6	EBRT	Palliative	NR	20	
Liakos et al[20]	South Africa	Retrospective	2005–2008	Inoperable EC	12	SCC 100	• Brachytherapy (n = 5) • EBRT (n = 7)	Palliative	NR	20[d]	
Messaoud et al[18]	Algeria	Retrospective	2010–2014	Locally advanced + metastatic EC	32	SCC 24 Adeno 76	EBRT (20 Gy/5 frx or 8–10 Gy/1 frx)	Palliative	NR	41	
Deressa et al[36]	Ethiopia	Prospective phase II trial	NR	Locally advanced + metastatic EC	17	SCC 65 Adeno 35	EBRT (12 Gy/4 frx over 2 days)	Palliative	1-month posttreatment: 76% complete or partial improvement	24	35% received 5-fluorouracil-based chemotherapy after EBRT
Concurrent chemoradiation											
Dandara et al[32]	South Africa	Retrospective	1977–2007	Inoperable EC	231	SCC 90[c] Adeno 4 Other 6	Concurrent chemoradiotherapy	Curative	NR	30	
Wahba et al[42]	South Africa	Prospective phase II trial	2006–2008	Locally advanced EC	42	SCC 36 Adeno 55 Other 10	EBRT (45 Gy/25 frx) + capecitabine/ oxaliplatin	Curative (neoadjuvant therapy)	NR	80	Resection performed 4–6 weeks after chemoradiation
Akl et al[43]	Egypt	Prospective	2010–2012	Locally advanced + metastatic EC	25	SCC 88 Adeno 12	EBRT (40 Gy/22 frx) + cisplatin/5-FU	Palliative	Posttreatment: −0.76[e], any improvement: 72%, median duration improved 5 months	30	

Abbreviations: Adeno, adenocarcinoma; EC, esophageal cancer; EBRT, external beam radiotherapy; frx, fractions; Gy, Gray; MS, median survival; NR, not reported; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil.

[a]Treatment regimen (ie, chemotherapy regimen, radiotherapy dosing/fractions) not reported unless specified.

[b]Median survival unless otherwise specified.

[c]Histological distribution reflects total case series of 1868 subjects.

[d]Combined median survival for patients receiving EBRT or brachytherapy.

[e]Dysphagia score based on 0 to 4 scale: 0, normal swallowing; 1, difficulty swallowing some hard solids but can swallow semisolids; 2, unable to swallow any solids but can swallow liquids; 3 difficulty swallowing liquids; 4, unable to swallow saliva.

studies demonstrated that the addition of chemotherapy or radiotherapy to rigid plastic stents offered no benefit in terms of OS or palliation and that chemoradiation caused substantial toxicity. A subsequent RCT compared rigid plastic stents to SEMS and found SEMS to be superior with fewer complications and improved palliation but similar OS.[60] Since this RCT, 11 case series have published outcomes of SEMS for malignant dysphagia (Table 4). These studies have consistently demonstrated the safety and efficacy of SEMS across a variety of settings in Africa. Procedural mortality with SEMS has ranged from 0% to 10%,[20-26,28] mean improvements in dysphagia scores from 1.9 to 3.0,[21-24,26,28] and median OS from 7 to 39 weeks.[6,20-24,26-28]

4 | DISCUSSION

Our systematic review provides a comprehensive and rigorous assessment of the published literature on EC treatment strategies in Africa. We summarized data on a total of 46 studies from 10 countries, evaluating outcomes across the care continuum. Our findings demonstrated a paucity of literature from Africa on EC treatment, despite the high burden of disease. With the exception of southern Africa, limited data have been reported from most other regions in Africa. We identified only six studies from eastern Africa, two studies from western Africa and seven from northern Africa. Many of the included studies highlight notable gaps in diagnostics, specifically with regard to the advanced imaging (CT, PET and EUS) needed to identify patients with potentially curable disease. Among the studies reporting outcomes of palliative interventions, we observed considerable heterogeneity in access to and routine use of SEMS, EBRT, brachytherapy and chemoradiation across various settings. Overall, prognosis remains poor for the vast majority of patients, with reported OS ranging from 7 to 41 weeks after treatment with modern palliative interventions.

A previous review on this topic published a descriptive summary of studies that reported data on treatment outcomes as well as incidence rates and risk factors.[62] Our study differs from this previous review in several important ways. First, we identified 12 additional studies on treatment outcomes across Africa. Second, we evaluated key details on study populations to contextualize findings, including histological subtype, staging and treatment intent. Finally, our review is the first to undertake a rigorous evaluation of methodological quality, risk of bias and an appraisal of existing evidence comparing EC treatment strategies within Africa.

The existing data on long-term survival following esophagectomy are limited. The two studies that evaluated 5-year OS after potentially curative resection in South Africa and Sudan reported survival rates of 13% and 21%, respectively, which are substantially lower than those reported in HICs, ranging from 30% to 60%.[47,51,63] This gap is likely due to several factors, including limited use of neoadjuvant therapy, more advanced disease and challenges with preoperative patient selection given limited availability of advanced imaging. Among the esophagectomy case series we identified, only one reported access to EUS, which was available for 15% of the patients undergoing esophagectomy in Sudan, and none reported availability of PET.[51] In this study, CT and EUS results were concordant with intraoperative findings in 55% and 69% of patients, respectively. Further work is needed to optimize patient selection given imaging constraints at many African centers.

Studies from multiple centers in Africa report operative mortality rates following esophagectomy that are comparable to contemporary outcomes in HICs over the last two decades.[64,65] However, recent case series identify major challenges related to perioperative supportive care, specifically preoperative nutritional support[52] and perioperative pulmonary care to prevent respiratory complications.[51,52] Limited availability of critical care services is also a major challenge. In addition, more research is needed to investigate the benefit and safety of neoadjuvant therapy in this context. Although trimodality therapy with neoadjuvant chemoradiation followed by surgery has become standard of care in many settings, the risks and benefits of this approach have not yet been established in settings with limited supportive care.

Use of definitive chemoradiation for locally advanced disease is another area warranting further study. Across many HICs, definitive chemoradiation is generally considered to be an acceptable alternative to esophagectomy for patients with ESCC and the standard of care for patients with locally advanced EC or poor functional status who are ineligible for surgery. In the sole study, we identified which reported long-term outcomes after definitive chemoradiation, only 3% of patients survived three years,[58] considerably lower than that reported in HICs.[66] Notably, this RCT found no difference in OS between chemoradiation and radiation alone and observed worse toxicity in the chemoradiation arm. These findings conflict with results from the landmark RTOG 85-01 trial, which established chemoradiation as superior to radiotherapy for locally advanced disease.[67] This may be due to differences in study populations, with more advanced disease, dysphagia and weight loss among participants in the South African trial, as well as higher rates of therapy discontinuation. Overall, the results from these studies highlight the challenges of extrapolating treatment strategies developed in HICs to many African centers and the importance of developing locally adapted approaches. Although concurrent chemoradiation may benefit a subset of patients with inoperable disease, access to specialized oncological services is limited throughout much of Africa. In many African countries, chemotherapy and radiotherapy are only available at national referral centers and therefore access to care is limited to a minority of patients living nearby and those able to travel long distances.

Palliative treatment strategies for advanced EC have been an active area of research across African countries over the last four decades. Several palliative interventions have fallen in and out of favor during this time period, including surgical resection, rigid plastic stents and dilation procedures. As these modalities became obsolete, SEMS, EBRT, chemoradiation and HDRILBT emerged as the most broadly accepted options for palliation though access to each remains limited throughout much of the continent. Overall findings from our

TABLE 3 Nonrandomized studies reporting surgical outcomes for esophagectomies

Study	Country	Design	Study period	Total EC pts evaluated (n)	n (%) operable	Resected/ total patients explored (%)	Advanced stage (III/IV)%[a]	Procedure	Procedure-related mortality (%)	Overall survival	Comments
Ihekwaba et al[44]	Nigeria	Retrospective	1970–1979	61	NR	10/13 (76)	NR	Esophagectomy NOS (n = 10)	NR	6-month: 80% 3-year: 20%	
Lazarus et al[45]	South Africa	Prospective	1983–1984	100	NR	4/NR (N/A)	NR	• ILE (n = 2) • 3-stage esophagectomy (n = 1) • Bypass (n = 1)	25[b]	4-month: 100%	
Sinzobahamvya et al[46]	Zimbabwe	Retrospective	1985–1986, 1988–1989	339	32 (9)	25/32 (78)	92	• ILE (n = 19) • Left thoracotomy esophagectomy (n = 6)	16	NR	
Mannell et al[47]	South Africa	Prospective	1978–1989	NR	NR	127 / NR (N/A)	80	• ILE (n = 34) • ME (n = 93)	12	1-year: 56% 2-year: 31% 5-year: 13%	85% were curative intent, 15% palliative intent; 62% received adjuvant XRT
Ahmed et al[48]	Sudan	Retrospective	1986–1991	101	69 (68)	61/69 (88)	93	• ILE (n = 61)	28	1-year: 60% 2-year: 40%	
Ahmed et al[49]	Ethiopia	Retrospective	1992–1996	142	79 (56)	34/74 (46)	93[c]	• ILE (n = 30) • Partial esophago-gastrostomy (n = 4) • Bypass esophago-gastrostomy (n = 18) • Gastrotomy/ Jejunostomy (n = 10)	28[b]	NR	
Adegboye et al[50]	Nigeria	Prospective	1986–1987	NR	NR	10/NR (N/A)	100	THE (n = 10)	50	MS 34 weeks	
			1989–1996	NR	NR	21/NR (N/A)	100	THE (n = 21)	14	6-month: 100% 1-year: 39% 18-months: 19%	
Dandara et al[32]	South Africa	Retrospective	1977–2007	1868	NR	103/NR (NR)	NR	Esophagectomy NOS (n = 103)	NR	MS 85 weeks	7% received chemoXRT, 5% chemotherapy, 28% radiotherapy
Ahmed et al[51]	Sudan	Prospective	2003–2007	NR	103 (N/A)	100/103 (97)	55	• ILE (n = 67)	10	1-year 71%	

TABLE 3 (Continued)

Study	Country	Design	Study period	Total EC pts evaluated (n)	n (%) operable	Resected/ total patients explored (%)	Advanced stage (III/IV)%[a]	Procedure	Procedure-related mortality (%)	Overall survival	Comments
								• ME (n = 27) • Total gastrectomy + distal esophagectomy (n = 6)		2-year 52% 5-year 21% 10-year 8%	34% received neoadjuvant chemotherapy and/or XRT
Alemu et al[52]	Ethiopia	Retrospective	2006–2011	NR	156 (NA)	139/156 (89)	91	THE (n = 139)	19	NR	
Denewer et al[19]	Egypt	Prospective	NR	NR	60 (N/A)	47/60 (78)	NR	Minimally invasive esophagectomy[d] (n = 47)	2	NR	
Cotton et al[6]	Kenya	Prospective	2010–2012	1341	141	75/NR (N/A)	NR	Esophagectomy NOS (n = 75)	NR	Stage I/II: MS 96 weeks[e] Stage III/IV: MS 56 weeks[e]	.7% received adjuvant chemotherapy and/or XRT
Come et al[7]	Mozambique	Retrospective (2012–2014)/ prospective (2014–2016)	2012–2016	522	NR	32/NR (N/A)	19	ILE (n = 32)	NR	MS 35 weeks	3% received neoadjuvant chemotherapy; % receiving adjuvant therapy NR

Abbreviations: EC, esophageal cancer; ILE, Ivor Lewis esophagectomy; ME, McKeown esophagectomy; MS, median survival; N/A, not applicable; NOS, not otherwise specified; NR, not reported; THE, transhiatal esophagectomy; XRT, radiotherapy.

[a]Postsurgical staging unless otherwise specified.

[b]Represents composite operative mortality of all procedures.

[c]Staging for 92 of 142 EC patients evaluated.

[d]Thoracoscopic radical esophagectomy with laparoscopic gastric tube reconstruction and anastomosis through neck incision.

[e]Median survival for patients who underwent surgery alone; patients receiving adjuvant chemotherapy and/or XRT were excluded.

TABLE 4 Study details of included randomized controlled trials (all conducted in South Africa)

Author	Patient population	n	Histology (%)	Treatment	Overall survival[a] (weeks)	Treatment	Overall survival[a]	Treatment	Overall survival[a] (weeks)	*P* value	
Angorn et al[53]	Locally advanced + metastatic, inoperable EC	106	NR	Plastic stent	NR	Retrosternal gastric bypass	NR	—	—	—	• Comparable operative mortality (plastic stent 6%, gastric bypass 8%) • More complications with gastric bypass • No difference in immediate palliation
Mannell et al[54]	Locally advanced + metastatic, inoperable EC	170	NR	Plastic stent	13[b]	Dilation + bleomycin	15[b]	—	—	.155	• Worse operative mortality with plastic stent (18% vs. 6%) • More complications with plastic stent • Dilation + bleomycin better palliation
Mannell et al[55]	Locally advanced EC	40	SCC 100	Retrosternal gastric bypass	NR	Retrosternal gastric bypass + pyloroplasty	NR	—	—	—	• Operative mortality with and without pyloroplasty (15% vs. 5%) • Fewer symptoms of postoperative gastric stasis with pyloroplasty • No difference in 1-month and 3-month gastric emptying studies
Alberts et al[56]	Locally advanced, inoperable EC	20	SCC 100	Plastic stent	19	Plastic stent followed by 5-FU + cisplatin + EBRT	11	—	—	.03	• More toxicity with chemoradiation (trial terminated early)
Schmid et al[57]	Locally advanced, inoperable EC	127	SCC 100	Plastic stent	15	Plastic stent + EBRT	9	Plastic stent + chemotherapy	11	.70	• No difference in palliation across the three groups
Slabber et al[58]	Locally advanced, inoperable EC	70	SCC 100	EBRT	21	EBRT +5-FU + platinum	24	—	—	.42	• More toxicity with chemoradiation
Sur et al[59]	Locally advanced + metastatic EC	172	SCC 95 Adeno 5	HDRILBT (12 Gy/2 frx)	NR	HDRILBT (16 Gy/2 frx)	NR	HDRILBT (18 Gy/3 frx)	NR	—	• No difference in 12-month survival (12 Gy/2 frx 10%, 16 Gy/2 frx 22%, 18 Gy/3 frx 35%, $P > .05$) • No difference in dysphagia-free survival at 12 months • More strictures with 18 Gy/3 frx
Sanyika et al[60]	Locally advanced + metastatic, inoperable EC	40	SCC 100	SEMS	NR	Plastic stent	NR	—	—	—	• No difference in 3-month survival (90% in both groups) • More complications with plastic stent • Improved post-operative palliation, 1-month and 3-month patency with SEMS
Sur et al[61]	Locally advanced, inoperable EC	60	SCC 100	HDRILBT	29	HDRILBT + EBRT	30	—	—	>.05	• No difference in dysphagia-free survival at 6 or 12 months • More strictures in HDRILBT group (n = 7 vs. n = 4), otherwise no difference in adverse effects

Abbreviations: Adeno, adenocarcinoma; EBRT, external beam radiotherapy; EC, esophageal cancer; frx, fraction; HDRILBT, high-dose-rate intraluminal brachytherapy; NR, not reported; SCC, squamous cell carcinoma; SEMS, self-expandable metallic stents; 5-FU, 5-fluorouracil.

[a]Median survival unless otherwise specified.

[b]Mean survival.

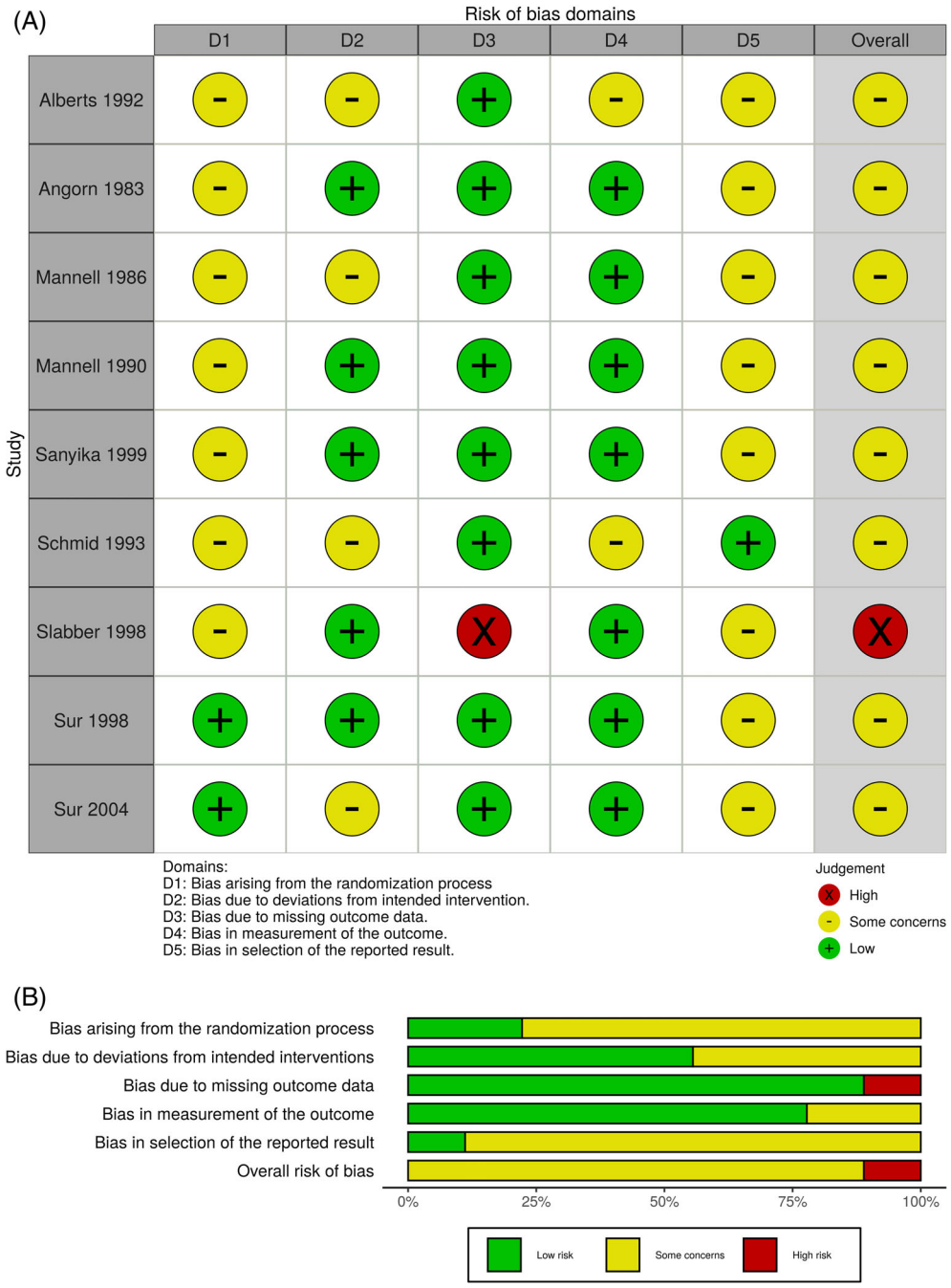

FIGURE 3 Quality of randomized, controlled trials as assessed by the Cochrane risk-of-bias tool. A, Risk of bias summary: review authors' judgements about each risk of bias item for each included study. B, Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

review suggest that each of these modern interventions have evidence supporting its safety and efficacy for treatment of dysphagia. Moreover, data on survival outcomes are comparable but limited by the absence of comparative RCTs.

SEMS are the most widely studied of the contemporary palliative interventions in Africa. More limited data are available on palliative EBRT, chemoradiation and HDRILBT. We identified a paucity of studies reporting QOL outcomes across all palliative interventions. Head-to-head studies are also notably absent, with only one published study which compared SEMS and radiotherapy through retrospective chart review at a single institution in South Africa.[20] Although retrospective analyses have limitations, the authors reported longer OS with radiotherapy but shorter delays until treatment and lower healthcare utilization with SEMS. None of the studies prospectively compared interventions, either as observational studies or as part of RCTs.

Tradeoffs between SEMS and radiation therapies for advanced EC are an area of active investigation. SEMS are well known to provide immediate dysphagia relief but pose risks for recurrent dysphagia and need for re-intervention. By contrast, the effects of brachytherapy and EBRT are not immediate but often provide more durable symptom control. These findings have been demonstrated in several RCTs in HICs.[68,69] Steyerberg et al developed and validated a prognostic score using European trial data to help guide treatment decisions, favoring SEMS for those with short life expectancy and brachytherapy for those with longer life expectancy.[70] A study to evaluate use of this prognostic score within a South African patient

population reported poor predictive value, however, further highlighting the challenges of extrapolating data to African settings.[27]

Based on existing evidence, many questions remain with regard to the role of SEMS vs radiation-based therapies for palliation of EC in Africa. The paucity of prospective, comparative studies that evaluate OS and QOL is a major gap in existing knowledge on this topic. In addition, further research is needed on patient preferences on the acceptability of various treatment modalities in this context. Given the resource constraints and long distances traveled for cancer care in Africa, secondary outcomes may take on added importance, including time to initiation of treatment, resource utilization and cost. A multicenter prospective observational study conducted through the African Esophageal Cancer Consortium (AfrECC)[71] is currently underway in Tanzania, Kenya and Malawi, which will begin to answer some of these questions. This study aims to evaluate the effects of SEMS; EBRT; and chemoradiation on QOL, OS and healthcare utilization.

Additional research is needed on combination therapies in Africa, including SEMS with EBRT or brachytherapy, which have demonstrated promise in other settings.[72,73] Although RCTs remain the gold standard, randomization within the context of a clinical trial may pose ethical dilemmas in this patient population, as many patients are severely malnourished and in poor condition. Pragmatic trials that incorporate clinician discretion and patient needs into treatment allocation have been used in other settings[74] and may offer a more appropriate study design within this context.

Although many questions remain with regard to optimal treatment strategies for patients with advanced disease, access to palliative interventions remains a major challenge in many African settings. Key barriers include the high costs and limited access to specialized oncological services, including diagnostic pathology services, chemotherapy, and radiotherapy, as well as diagnostic and therapeutic endoscopy. In particular, the high cost of SEMS has proven to be a prohibitive barrier in many settings. AfrECC is currently leading a promising initiative to establish multisector partnerships to improve access to SEMS throughout eastern Africa countries, including Kenya, Malawi, Tanzania and Zambia. Further work is needed to expand this initiative and to improve access to other essential services for EC management as well.

4.1 | Limitations

Our study has several limitations. Many of the studies included in this review differed in study design, patient populations and reported endpoints. We noted inconsistency in reporting details of treatments and a lack of standardization in outcome data. Many of these factors limit the comparability of treatments across studies. Another limiting factor was the regional variability in access to many of the treatments, which can lead to potential differences in wait times for treatments and patient groups receiving interventions. Although there are two unique histologies of EC, we did not restrict inclusion of studies based on histological subtype. Few of the studies, however, included patients with adenocarcinoma and of those that did, ESCC accounted for the majority of cases in all but two studies. We identified studies from a total of 10 countries, representing <20% of all African countries. A majority of published studies on EC originate from South Africa. Furthermore, our systematic review was limited to studies published in English, which excluded relevant data published in other languages. Finally, few studies available in the existing literature were of high quality or without risk of bias.

BOX 1 Priorities for future research on esophageal cancer treatment in Africa

1. Comparative effectiveness of modern palliative interventions, with a focus on quality of life and overall survival as outcome measures.
2. Strategies to improve long-term survival in patients treated with definitive chemoradiation.
3. Safety and efficacy of neoadjuvant therapy in patients with locally advanced disease.

5 | CONCLUSIONS

This review summarizes the research investigating treatment outcomes in EC in Africa published over the last four decades. Findings from this study highlight that EC remains a deadly disease in Africa, associated with high morbidity and mortality. Further research is needed to define optimal treatment strategies in this context. Moreover, given the high proportion of patients who present with advanced disease, the importance of identifying risk factors for primary prevention and developing cost-effective strategies for early detection must also be acknowledged.

In this review, we identified critical gaps in knowledge related to the management of EC in Africa. Additional research is needed throughout most African regions; however, eastern Africa stands out in particular given the paucity of data and disproportionate burden of EC within this region. In addition, we identified the following as areas in need of further research: (a) evaluation of the safety and efficacy of neoadjuvant therapy in patients with locally advanced disease; (b) strategies to improve long-term survival in patients treated with definitive chemoradiation; and (c) the comparative effectiveness of modern palliative interventions, with a focus on QOL and OS as outcome measures (see Box 1). The existing evidence identified in this review provides a contemporary benchmark for future research.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in this study, and data sources and handling of these data are described in Tables 1 to 4 and in the Methods and Analysis section, respectively. Further information is available from the corresponding author upon request.

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