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REVIEW ARTICLE

Carcinomas of the hypopharynx and cervical esophagus: A systematic review and quality of evidence assessment

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Summary

Purpose: *Hypopharyngeal cervical esophageal carcinoma (HPCEC) is a group of highly malignant entities usually presenting at an advanced stage. Our purpose was to systematically review and synthesize all available data on the management and outcomes of patients with these upper gastrointestinal malignancies.*

Methods: *A systematic literature search of the PubMed and Cochrane databases was performed with respect to the PRISMA statement (end-of-search date: May 1st, 2017). Data on the study design, interventions, participants, and outcomes were extracted by two independent reviewers. Quality assessment of included studies was performed using the tool developed by the National Heart, Lung, and Blood Institute.*

Results: *Thirty-four observational studies were included in this review. Overall, 20,409 patients with HPCECs were included. Mean patient age was 61.3 years. The most widely implemented therapeutic modalities were chemoradiation (38%), radiation alone (16%), and surgery plus radiation (13%). Overall, mean relapse rates were 15±2.6% for local recurrence, 14.7±2.6% for regional recurrence. and 10± 2.3% for distant metastases. Cumulative mean 5- and 3-year survival rates were 20 ± 2.6% and 22 ± 2.6%, respectively, while mean 5-year disease-free survival rates were 22 ± 2.3%. The most common complications were fistulae and pulmonary complications. Mean 30-day mortality rate was 7±2.2% and the mean long-term mortality rate was 22 ± 3.3%.*

Conclusion: *Multimodal approaches are typically needed for the management of HPCECs. Radiotherapy is the mainstay of treatment for local tumors. Locally advanced non-metastatic tumors are typically managed with chemoradiation or a combination of pharyngolaryngoesophagectomy and chemoradiation. For metastatic carcinomas, an arsenal of surgical and medical treatment options can help relieve tumor burden and improve quality of life.*

Key words: *hypopharyngeal cancer, esophageal cancer, pharyngolaryngoesophgectomy, chemotherapy, radiotherapy.*

Introduction

Hypopharyngeal cervical esophageal carcinomas (HPCECs) are challenging to treat [1]. These neoplasms are relatively uncommon and account for approximately 5-6% of all head and neck tumors [2,3]. Staging of HPCECs is performed using the TNM staging system [4]. According to recent guidelines, cases of T1, N0 and selected T2, N0 are considered as early-stage disease, whereas cases of T1, N+, T2-3, Any N, T4a, Any N, T4b, any N and metastatic (M1) disease are considered advanced stage malignancies [4]. Most HPCECs are found at an advanced stage (70-80%) and exhibit a poor prognosis [5]. Over three quarters of patients will develop lymph node metastases during the course

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of their disease. Five-year survival of HPCECs is usually low (20-25%), regardless of the treatment employed [6,7].

A multidisciplinary approach has been applied to treat these tumors including surgery as well radiotherapy and chemotherapy in the definitive, neoadjuvant, and adjuvant setting. Historically, radical surgery with total pharyngolaryngoesophagectomy (PLO) followed by reconstruction with gastric tube, colon interposition graft or free jejunum flap have been the most popular treatment modalities [8]. In recent years, definitive, neoadjuvant, and adjuvant chemoradiotherapy (CRT) have become central in the treatment of HPCECs [8]. When definitive medical treatment fails, salvage surgery is the mainstay of care for residual and recurrent disease [9]. Avoiding post-treatment complications and preserving functions such as voice, swallowing, and respiration are also important considerations when treating HPCECs.

The aim of the present systematic review was to assess the management and outcomes of patients with HPCECs to add to the discussion on how to best treat these rare and aggressive malignancies.

Methods

Search strategy and eligibility of studies

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and in line with the protocol agreed by all authors [10]. Eligible articles were identified through search of the PubMed and Cochrane bibliographical databases (end-

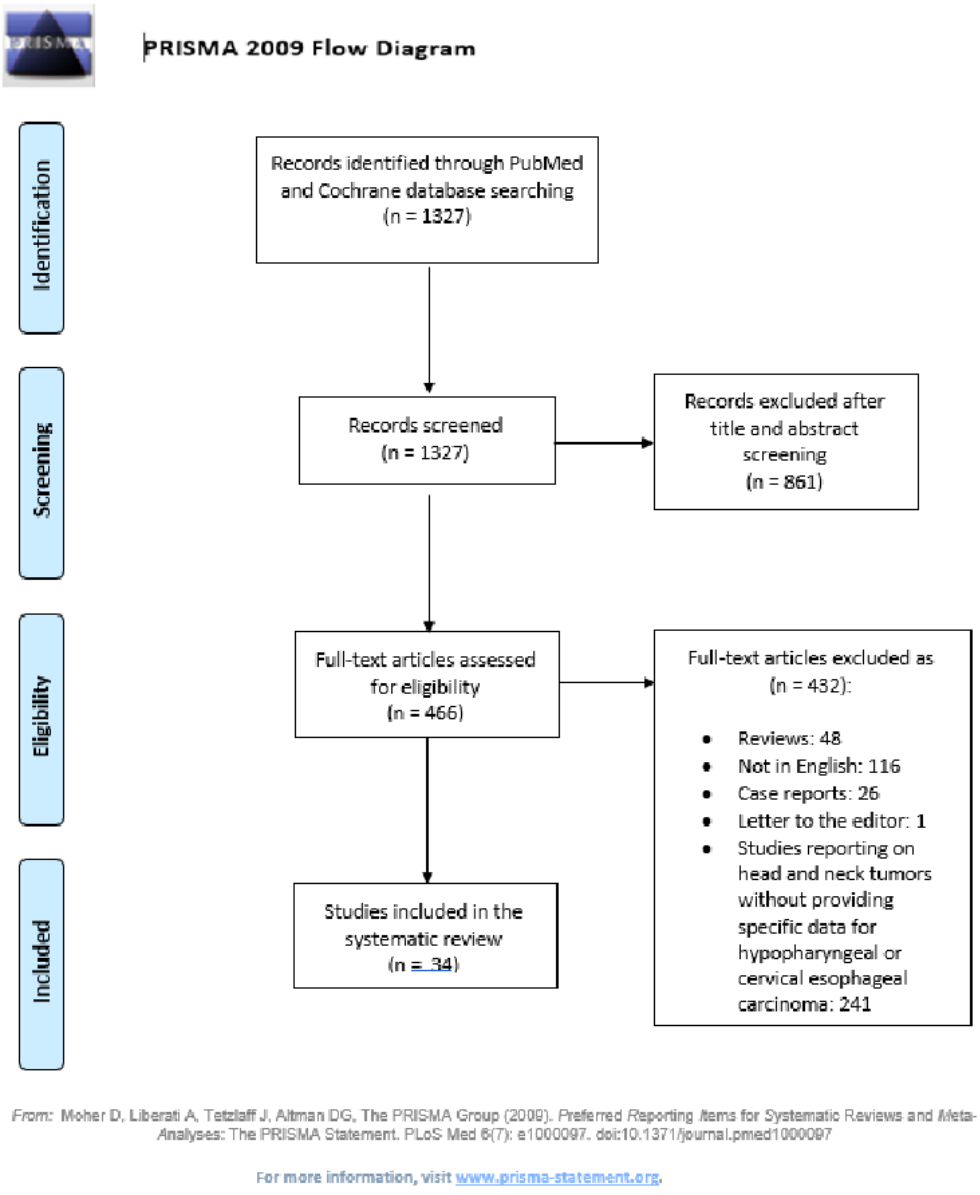

Figure 1. PRISMA flow chart.

Table 1. General characteristics of eligible studies

Authors	*Year*	*Country/ Region*	*Age*	*Number of patients with carcinoma of hypopharynx*	*Number of patients with carcinoma of upper esophagus*
Inoue et al	1973	Japan	NR	180	0
Carpenter et al	1976	USA	NR	162	0
Razack et al	1977	USA	NR	120	0
Vanderbrouck et al	1977	France	NR	49	0
Horwitz et al	1979	USA	NR	80	0
Ahmad et al	1984	USA	60*(35-87)	199	0
Van den Bogaert et al	1985	Belgium	NR	88	0
Sadeghi et al	1986	USA	NR	10	0
Kajanti et al	1990	Finland	63*(SD=12)	162	0
Vikram et al	1991	USA	61*	9	10
Frank et al	1994	USA	62*	110	0
Jones et al	1996	UK	62*	647	47
Zelefsky et al	1996	USA	61#(36-80)	56	0
Kraus et al	1997	USA	60#(42-79)	132	0
Kim et al	1998	Korea	61*(30-80)	62	0
Tsujinaka et al	1999	Japan	61*(SD=6.8)	0	64
Saito et al	2000	Japan	61*(40-72)	0	13
Triboulet et al	2001	France	55*(33-81)	131	78
Denham et al	2003	Australia	66#(38-83)		67
Chu et al	2004	Taiwan	61#(36-80)	104	0
Bova et al	2005	Australia	62*(29-85)	180	0
Nakamura et al	2005	Japan	65#(42-80)	43	0
Vandersteen et al	2005	France	62*(SD=10.5)	100	0
Wang et al	2006	Taiwan	60*(43-76)	26	15
Iseli et al	2007	Australia	69*(51-87)	16	1
Kao et al	2008	USA	NR	647	0
Lee et al	2008	Taiwan	62*(43-76)	74	0
Milisavljenic et al	2009	Serbia	NR	89	0
Chedid et al	2010	Brazil	56*	174	0
Daiko et al	2011	Japan	58#(40-70)	0	34
Ida et al	2014	Japan	63*(41-72)	13	1
Kesski-säntti et al	2014	Finland	61#(51-84)	45	0
Bussu et al	2015	Italy	61#(42-84)	123	0
Kuo et al	2016	USA	63*	16248	0

NR: not reported, SD: standard deviation, *mean, #median

Table 2. Types of chemotherapy

Author	*Regimens*
Vikram et al	Cisplatin 100mg/m^2 and 5-FU 900mg/m^2/day (3 cycles)
Zelefsky et al	Cisplatin and 5-FU or Cisplatin and or Cisplatin and bleomycin (or vinblastine) ‡
Kim et al	Cisplatin 100mg/m^2 and 5-FU 1000mg/m^2/day (3 cycles)
Tsujinaka et al	Cisplatin 75mg/m^2 and 5-FU 350mg/m^2/day (4 cycles)
Denham et al	Cisplatin 80mg/m^2 and 5-FU 500mg/m^2/day (2 cycles)
Bova et al	Methotrexate, vincristine, bleomycin, 5-FU, hydrocortisone* / Cisplatin and 5-FU#
Nakamura et al	5-FU 250mg/day
Lee et al	Cisplatin 20mg/m^2 and 5-FU 1000mg/m^2/day (4 cycles)
Daiko et al	Cisplatin 20mg/m^2 (2 cycles)
Ida et al	Cisplatin and 5-FU or monotherapy of 5-FU or oral S-1
Kesski-säntti et al	Cisplatin 40mg/m^2 (6 cycles) or Mitomycin 10mg/m^2 once
Bussu et al	Cisplatin or cetuximab

5-FU: 5-fluorouracil, *until 1986, #after 1986, ‡17 patients received 3 cycles, 7 patients received 2 cycles, 2 patients received 1 cycle

of-search date on May 1st, 2017) by two independent reviewers (NT and KSM). The following MeSH terms were utilized in combination with Boolean operators (AND, OR, NOT): "upper", "esophagus", "neoplasms", "hypopharynx", "chemotherapy", "radiotherapy", "chemoradiotherapy", "surgery", "pharyngolaryngoesophgectomy", "pharyngolaryngectomy", "laryngectomy". Reference lists were systematically searched for relevant articles in a "snowball" procedure.

Eligible studies: (1) were primary research papers, (2) published in English, (3) reported outcomes in humans, and (4) included only adult patients (≥18 years old) who were treated for HPCECs. Excluded studies met at least one of the following criteria: (1) not published in English, (2) experimental studies in animals, (3) *in vitro* basic science studies, (4) reviews and meta-analyses, (5) editorials, perspectives and letters to the editor, (6) papers irrelevant to HPCECs.

Data extraction and tabulation

Two reviewers, blind to each other (NT, KSM), independently reviewed the full papers of eligible studies and performed the data extraction and tabulation. All disagreements were resolved with discussion and final decision was reached by consensus with a third reviewer (DS). Particularly, the following data were extracted for all studies included in the present systematic review: first author, year of publication, country of enrollment, study interval, study type, number of patients with carcinoma of the hypopharynx or upper esophagus, patient age, treatment modalities, recurrence rates, disease-free survival, 3-year survival, 5-year survival, mortality (30-day, one-year, long-term [defined as mortality after one year of treatment]), postoperative complications.

Statistics

Data on outcomes of interest were extracted, tabulated, analyzed cumulatively and expressed as unweighted means and standard deviations (SDs) whenever possible. Continuous variables were summarized as medians and range. We applied the formula proposed by Hozo et al to estimate the respective means and SDs [11]. All relative rates were estimated based on available data for each variable of interest.

Assessment of study quality

The quality of included case series was assessed using the tool developed by the National Heart, Lung, and Blood Institute (NHLBI) based on work from the Agency for Healthcare Research and Quality, the Cochrane Collaboration, the United States Preventive Services Task Force, the Scottish Intercollegiate Guidelines Network and the National Health Service Centre for Reviews and Dissemination [12,13]. The NHLBI scale ranges from 1-9; with a score of 1-3 denoting poor quality, 4-6 fair quality and 7-9 suggesting good quality. Two independent reviewers (KSM, NT) rated the quality of eligible studies and all discrepancies were resolved through discussion and consensus. Ultimately, a synthesis of the two reports was performed. The mean and SD for the NHLBI score of the entire systematic review were calculated.

Protocol registration

This study is registered with the Research Registry (http://www.researchregistry.com/) and its unique identifying number is: reviewregistry340.

Results

Eligible studies

466 studies were assessed for eligibility and 34 were ultimately were included in the present systematic review (Figure 1). Of these, 11 studies were from North America [14-24], 10 from Asia [25-34], 9 from Europe [35-42], 3 from Australia [43-5] and one from South America [46]. All studies were retrospective and published in the last 40 years.

Quality of evidence assessment

Twenty-four studies were of good quality, while the remaining 10 were of fair quality. The mean NHLBI score was 7 (SD:1.3) and detailed quality assessment for each study is provided in Supplementary Table 1.

Patient characteristics

A total of 20,409 patients diagnosed with HPCECs were included in our systematic review. Among them 20,079 were diagnosed with hypopharyngeal carcinoma and 330 with carcinoma of the upper esophagus. The mean patient age was 61.3 years (Table 1).

Treatment modalities

Several treatment modalities were used in the studies included in our review. Overall, 1325 (8%) patients underwent treatment with surgery alone [15-18,21-23,27-34,40,41,45,46], 3187 (20%) received only radiation therapy [15,16,19,22,24,25,27,28,35,40,42,47], while chemotherapy alone was administered in 117 (0.7%) patients [27,35]. Furthermore, 7508 (48%) patients received both radiation therapy and chemotherapy [14,16,20,25–27,35,39,41,44] (Table 2), 1242 (8%) underwent preoperative radiation therapy followed by surgery [16,19,22,25,28,31,34,36,37,41,42], 15 (0.1%) patients received chemotherapy followed by surgery [37], whereas 834 (5%) received both radiation therapy and chemotherapy and then underwent surgery [16,25,29,32,33,37,41,43-45]. Surgery followed by postoperative radiation therapy was employed in 1490 (10%) patients 15,17,18,21-24,26-28,31,36-38,42,43,46,47], surgery followed by postoperative CRT in 35 (0.2%) patients [30,35,39] and preoperative radiation therapy followed by surgery and then postoperative radiation therapy in 2 (0,01%) patients [42]. All surgical procedures were PLOs

Table 3. Number of treatment modalities of eligible studies

Authors	*Surgery alone*	*Surgery + preoperative CRT*	*Surgery + preoperative + postoperative RT*	*Surgery + preoperative RT*	*Surgery + preoperative CT*	*Surgery + postoperative RT*	*CT alone*	*RT alone*	*Surgery + postoperative CRT*	*CT +RT*
Inoue et al	61	0	0	24	0	5	0	82	0	0
Carpenter al	82	0	0	18	0	8	0	39	0	0
Razack et al	37	0	0	0	0	44	0	28	0	0
Vanderbrouck et al	0	0	0	17	0	23	0	0	0	0
Horwitz et al	0	0	0	0	0	24	56	0	0	0
Ahmad et al	0	0	0	65	0	0	0	87	0	0
Van den Bogaert et al	0	0	2	15	0	5	0	66	0	0
Sadeghi et al	3	0	0	0	0	7	0	0	0	0
Kajanti et al	0	0	0	0	0	29	0	106	0	0
Vikram et al	0	0	0	0	0	0	0	0	0	19
Frank et al	65	0	0	0	0	45	0	0	0	0
Jones et al	14	0	0	0	0	0	0	12	0	0
Zelefsky et al	0	0	0	0	0	30	0	0	0	26
Kraus et al	26	0	0	0	0	106	0	0	0	0
Kim et al	1	0	0	0	0	17	7	7	0	30
Tsujinaka et al	37	27	0	0	0	0	0	0	0	0
Saito et al	9	4	0	0	0	0	0	0	0	0
Triboulet et al	0	22	0	5	15	145	0	0	0	0
Denham et al	0	10	0	0	0	0	0	0	0	57
Chu et al	35	0	0	2	0	67	0	0	0	0
Bova et al	0	82	0	0	0	169	0	0	0	0
Nakamura et al	0	10	0	1	0	0	0	3	0	29
Vandersteen et al	0	0	0	0	0	0	54	10	20	14
Wang et al	14	0	0	6	0	21	0	0	0	0
Iseli et al	13	5	0	0	0	0	0	0	0	0
Kao et al	103	0	0	0	0	544	0	0	0	0
Lee et al	0	0	0	0	0	44	0	0	0	30
Milisavljenic et al	0	0	0	0	0	89	0	0	0	0
Chedid et al	106	0	0	0	0	68	0	0	0	0
Daiko et al	25	0	0	0	0	0	0	0	9	0
Ida et al	5	9	0	0	0	0	0	0	0	0
Kesski-säntti et al	0	0	0	0	0	0	0	0	6	39
Bussu et al	2	59	0	4	0	0	0	0	0	58
Kuo et al	687	606	0	1085	0	0	0	2738	0	7206
Total (%)	1325 (8%)	834 (5%)	2 (0.01%)	1242 (8%)	15 (0.1%)	1490 (10%)	117 (0.7%)	3178 (20%)	35 (0.2%)	7508 (48%)

Table 4. Recurrence, survival and mortality of patients of eligible studies

Author	*Recurrence*			*Survival*		*Mortality*		
	Local	*Regional*	*Distant*	*Overall*	*Disease-free*	*Early (30days)*	*Within 1 year*	*Late (>1 year)*
Inoue et al	17*	3*	2*	24	NR		76	
Carpenter et al	12#	25#	1b	47	25		46	
	31*	10*	3*					
	47*#	13 *#	0*#					
	17 #‡	22 #‡	5 #‡					
	12 #§	25 #§	13#§					
Razack et al	33		14	34	NR		72	
Vandenbrouck et al	NR	NR	NR	36‡	NR	10	24	NR
				56§				
Horwitz et al	21*	21*	17*	13*	NR	NR	NR	NR
	23¥	8¥	23¥	15¥				
	27¶	9¶	27¶	56¶				
Ahmad et al	51	8	10	36	NR	1	16	NR
Van den Bogaert et al	NR	NR	NR	18	NR	NR	67*	82*#
Sadeghi et al	NR	NR	NR	NR	NR		NR	NR
Kajanti et al				28*#	NR	NR	NR	88
		56		16*				
Vikram et al	NR	NR	NR	NR	NR	26	NR	11
Frank et al	57#	NR	18#	NR	NR	NR	NR	
	14*#		48*#					NR
Jones et al	32#	20#	NR	NR	NR	NR	NR	1#
	21*	11*#						4*
Zelefsky et al	42*Δ	38*Δ	23*Δ	15*Δ	30*Δ	27*Δ	NR	NR
	30*#	30*#	40*#	22*#	42*#	23*#		
Kraus et al	18	17	12	30	41	2	NR	8
Kim et al	10 *Δ	7*Δ	0*Δ	NR	NR	NR	NR	NR
	6 *#	6*#	20*#					
Tsujinaka et al	10*#Δ	NR	5*#Δ	42*#Δ	NR	6	NR	NR
	16#		5#	27#				
Saito et al	NR	NR	NR	33	NR	NR	NR	NR
Triboulet et al	22	23	11	29↓	NR	5	NR	NR
				14◊				
Denham et al	30	NR	26	50	NR	NR	NR	NR
Chu et al	12	21	12	47	62	4	NR	NR
Bova et al	17		23	33	53	3	39	
Nakamura et al		14		NR	NR		21	
Vandersteen et al	17	88	9	37Δ	NR	NR	NR	50
				30*Δ				
Wang et al	12	15	20	39↓	NR	10	44	
				13◊				
Iseli et al	24	NR	12	NR	NR	NR	NR	39
Kao et al	NR	NR	NR	NR	NR	NR	NR	NR
Lee et al	NR	NR	NR	NR	NR		5	
Milisavljenic et al	NR	NR	NR	NR	NR	NR	NR	NR
Chedid et al	9	9	10	28	NR	6	NR	NR
Daiko et al	3		9	67	NR	0	0	0
Ida et al	14		NR	50	NR	7	NR	NR
Kesski-säntti et al	9		10	31	45		69	
Bussu et al	7		9	NR	NR		27	
Kuo et al	NR	NR	NR	32*Δ	NR	NR	NR	NR
				25*				
				34*#Δ				
				34*#				

All values are in %. *:radiotherapy, #:surgery, ‡: preoperative radiotherapy, §: postoperative radiotherapy, ¥: unplanned radiotherapy and surgery, ¶: planned radiotherapy and surgery, Δ: chemotherapy, ↓: hypopharyngeal cancer, ◊: cervical esophagus cancer, NR: not reported

(Table 3). Our systematic review showed that up until the late 1990s, radical surgery with total PLO followed by reconstruction was the most popular modality. In more recent years, CRT became an important component of the management that these patients receive.

Recurrence & survival

Twenty-five of the 34 studies included in our review reported recurrence after treatment [14,15,19,22-25,27-31,33-35,37-41,43,44,46,47]. The mean recurrence rates were: 15% (SD=2.6%) for local recurrence, 14.7% (SD=2.6%) for regional recurrence and 10% (SD=2.34%) for distant metastases. Twenty-three clinical studies reported 5-year survival [14,15,19,22-24,28-37,39,42-44,46,47], 3 reported 3-year survival rates [27,40,46] and 2 did not include overall survival in their primary outcomes. Specifically, the mean 5- and 3- year survival rates were 20% (SD=2.6%) and 22% (SD=2.6%) respectively. Disease-free survival was reported in 6 out of 34 studies included in our review [14,22,23,31,41,43] and the mean rate was 22% (SD=2.3%) (Table 4).

Complications & mortality

Eighteen studies reported postoperative complications [14,15,18-20,22,23,29,31-34,36-38,41,43,45,47]. 156 (0.7%) patients developed fistulae [14,18-20,22,23,31,36,38,41,43,45,47],

Table 5. Number of postoperative complications

Author	*Anastomotic leakage*	*Fistulae*	*Strictures*	*Pulmonary complications*	*Cardiovascular complications*	*Bleeding*	*Carotid rupture*	*Larynx necrosis*	*Local wound infection*
Inoue et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Carpenter et al	0	10	10	0	0	0	1	0	0
Razack et al	0	0	0	0	0	0	1	0	0
Vanderbrouck et al	0	15	0	0	0	6	0	8	0
Horwitz et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ahmad et al	0	4	0	11	0	0	1	0	0
Van den Bogaert et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sadeghi et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kajanti et al	0	2	1	0	0	0	1	0	0
Vikram et al	0	1	1	1	0	0	0	1	0
Frank et al	NR	24	14	0	0	0	0	0	18
Jones et al	NR	NR	NR	R	NR	NR	NR	NR	NR
Zelefsky et al	0	5	0	0	0	0	0	0	2
Kraus et al	0	34	12	1	0	0	3	0	29
Kim et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tsujinaka et al	11	0	0	26	0	0	0	0	0
Saito et al	0	0	0	1	0	0	0	1	3
Triboulet et al	47	0	0	30	3	0	0	7	0
Denham et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chu et al	0	15	0	0	0	NR	0	0	9
Bova et al	3	18	0	7	0	0	0	0	12
Nakamura et al	0	0	0	0	0	0	0	0	0
Vandersteen et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang et al	9	0	0	10	0	3	0	3	4
Iseli et al	0	6	6	0	0	0	0	0	0
Kao et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Milisavljenic et al	0	15	0	0	0	0	0	0	0
Chedid et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Daiko et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ida et al	1	0	0	0	0	2	0	0	0
Kesski-säntti et al	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bussu et al	0	7	0	0	0	0	0	0	0
Kuo et al	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR=not reported

87 (0.4%) developed pulmonary complications [19,20,23,32-34,37,43], 78 (0.3%) local wound infections [14,18,23,31,32,34,43], 71 (0.3%) anastomotic leakage [29,33,34,37,43], 44 (0.2%) strictures [29,33,34,37,43], 11 (0.05%) postoperative bleeding [29,34,36], 7 (0.03%) rupture of the carotid artery [15,19,22,23,47] and 3 (0.01%) cardiovascular complications [37] (Table 5). Mean 30-day mortality rate was 7% (SD=2.2%) in the included studies [19,20,23,29,33,34,36,37,43,46] whereas the mean long-term mortality (>1 year) rate was 22% (SD=3.7%) [20,23,35,40,42,45,47].

Discussion

HPCEC is a heterogeneous group of malignant tumors which tend to present at an advanced stage [48]. Several therapeutic modalities have been implemented to manage these insidious carcinomas. We systematically reviewed 34 studies enrolling a total 20,409 patients and summarized all available data on the epidemiology, management and outcomes of HPCECs.

The management of hypopharyngeal cancer depends largely on staging. In early stage hypopharyngeal cancer, surgery may be considered for patients who have disease that is technically resectable with a laryngeal-sparing approach. This category includes upper pyriform sinus and posterior pharyngeal wall tumors. Such approaches are generally not indicated for early-stage patients with transglottic tumor extension, postcricoid invasion, and deep pyriform sinus invasion. Although excellent local control (70-90%) and functional outcome have been reported, most of the series using conservative surgical procedures utilized induction chemotherapy and/or adjuvant radiotherapy. It is unclear whether conservative surgery alone would achieve a comparable outcome [49-51]. Importantly, radiotherapy alone has been shown to be effective as the mainstay treatment for local disease and no significant difference in the 5-year cancer-specific survival rates has been found between radiotherapy alone and surgery plus radiotherapy [25]. Indeed, definitive radiotherapy with a minimum dose of 70 Gy in 2 Gy fractions to the primary tumor and 46-50 Gy to elective nodal regions is feasible for T1 and small T2 hypopharyngeal cancers. Definitive radiotherapy has resulted in variable rates of laryngeal preservation, ranging from 41 to 100 percent for T1 tumors and from 41 to 86% for T2 tumors [19,52]. Tumors that persist or recur after radiotherapy can be treated with salvage surgery with or without adjuvant chemotherapy [16]. Positive surgical margins and extracapsular extension seem to be two important factors dictating the need for adjuvant chemotherapy [16]. Induction chemotherapy has also shown favorable results, especially in terms of preserving the larynx [35]. For many decades, primary surgical resection with adjuvant radiotherapy has been the gold standard of treatment for advanced cancers of the hypopharynx [22,42,53]. In recent years though, managing advanced hypopharyngeal carcinomas with CRT has been proven to be an equally effective treatment while resulting in preservation of the larynx [16]. Survival analysis using the National Cancer Database, revealed that overall 5-year survival rates were higher for chemoradiotherapy compared with radiotherapy alone in the definitive setting, but were comparable between surgery with chemoradiotherapy and surgery with radiotherapy. These findings were replicated when controlling for year of diagnosis, age, insurance status, comorbidity, T classification, and N classification in multivariate analysis. Recent studies have also shown similar results [16,39,41].

Cervical esophageal cancer, on the other hand, usually exhibits a significantly worse prognosis than hypopharyngeal carcinomas (18% 3-year survival vs 33% 3-year survival, respectively) [40]. There seems to be no significant difference in survival rates between patients treated with surgery versus those treated with irradiation for cervical esophageal carcinoma [40]. Malignancies located below the pharyngo-esophageal junction have a worse prognosis compared to lesions above the pharyngoesophageal junction, with surgery yielding encouraging results only for the latter [34]. These findings may be attributed to the earlier spread of this malignancy. In general, cervical esophageal cancer tends to spread early both cephalically and caudally, so routine dissection of deep cervical and cervical paratracheal, as well as upper mediastinal lymph nodes is recommended [30]. Larynx-preserving resection is recommended to improve postoperative function, but only when there is no tracheal invasion. If further invasion has occurred, neck and upper mediastinum lymph node dissection as well as proximal trachea resection are usually performed [32]. On the other hand, Triboulet et al [37] reported that the postoperative implementation of radiation improves the survival of patients with HPCECs. Daiko et al [30] suggested that postoperative CRT may result in even better outcomes. Larynx-preserving cervical esophagectomy may also be feasible in patients with disease that has metastasized to upper mediastinal lymph nodes. Hence, the benefits of introducing chemotherapy in the multimodal treatment of cervical-esophageal cancer are well substantiated especially when it comes to achieving loco-regional control [44].

Irrespective of the treatment method employed, 5-year survival for HPCECs is usually low (20-25%). In this systematic review mean 5 and 3-year survival rates were 20% (SD=2.6%) and 22% (SD=2.6) respectively while disease free survival was reported only in 6 studies and the mean rate was 22% (SD=2.3).

Despite substantial progress in the way we manage HPCECs, the recurrence rates still remain as high as 56%. Specifically, in the studies included in our review the mean recurrence rates for local and regional recurrence were 15% (SD=2.6) and 14.7% (SD=2.6) respectively, while the mean recurrence rate for patients with distant metastases was 10% (SD=2.3). Due to "field cancerization" [54] metachronous HPCEC may also occur in patients that previously received CRT and/or esophagectomy. In these patients, PLO with gastric tube, colon interposition graft or free jejunal transfer seems to be a feasible and safe technique [29].

Methodological strengths of the present paper include: 1) comprehensive literature search using rigorous and systematic methodology; 2) detailed data extraction; and 3) quality assessment of eligible studies. The limitations of this systematic review reflect the limitations of the included studies, which can be summarized as follows: 1) only papers published in English were eligible; 2) despite our comprehensive literature research, no eligible randomized-controlled trials were identified; 3) the discrepancies of the TNM staging system during the last 40 years together with the incomplete reporting of the staging of disease included in the original studies precluded us from pooling available treatment data per cancer-stage; 4) We analyzed carcinomas of the hypopharynx and esophageal esophagus together because they are in many ways similar including anatomic location, risk factors, clinical presentation, biology, as well as diagnostic and treatment options. Nevertheless, subtle differences between these two malignancies do exist and therefore our combined analysis may suffer to some extent from selection bias; 5) Finally, the heterogeneity of the included studies and 6) the scarcity of events in several variables did not allow us to deduce meaningful conclusions on certain outcomes of interest.

Conclusions

Although in a period of 40 years many approaches have been proposed and investigated, there is still no definitive indication on the best treatment for patients with HPCECs. That said, a multidisciplinary treatment approach is needed when dealing with malignant cancer of the hypopharynx and cervical esophagus. In local, non-metastatic disease, radiotherapy or larynx-preserving surgery may be used to preserve vital structures. Locally advanced and metastatic tumors are usually treated with chemoradiation or a combination of PLO and neoadjuvant or adjuvant chemotherapy and radiation.

Authors' contributions

Study concept and design: Schizas, Mylonas, Economopoulos, Theochari, Ziogas
Acquisition of data: Theochari, Mylonas, Ziogas, Schizas, Economopoulos
Analysis and interpretation of data: Theochari, Mylonas, Ziogas, Schizas, Economopoulos
Drafting of the manuscript: Schizas, Theochari, Ziogas, Mylonas, Economopoulos
Critical revision of the manuscript for important intellectual content: Schizas, Economopoulos, Mylonas, Ziogas, Theochari

Conflict of interests

The authors declare no conflict of interests.

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Supplementary Table 1. NHLBI Quality Assessment Scale for case series

First Author	*Was the study objective clearly stated?*	*Was the study population clearly and fully described, including a case definition?*	*Were the cases consecutive?*	*Were the subjects comparable?*	*Was the intervention clearly described?*	*Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?*	*Was the length of follow-up adequate? (5 years)*	*Were the statistical methods well-described?*	*Were the results well-described?*	*Total score*	*Quality rating*
Inoue et al	1	0	1	1	1	1	1	0	1	7	High
Carpenter et al	1	1	1	0	1	1	1	0	1	7	High
Razack et al	1	0	1	1	1	1	1	0	1	7	High
Vanderbrouck et al	1	0	1	0	1	1	1	0	1	6	Fair
Horwitz et al	1	0	1	1	1	1	1	0	1	7	High
Ahmad et al	1	1	1	1	1	1	1	1	1	9	High
Van den Bogaert et al	0	0	1	0	1	1	1	0	1	5	Fair
Sadeghi et al	1	1	1	1	1	1	1	0	1	8	High
Kajanti et al	1	1	1	0	1	1	1	1	1	8	High
Vikram et al	1	0	1	0	1	1	1	0	1	6	Fair
Frank et al	1	0	1	1	1	1	1	1	1	8	High
Jones et al	1	0	1	1	1	0	0	1	1	7	High
Zelefsky et al	0	0	1	1	1	1	1	0	1	6	Fair
Kraus et al	1	0	1	0	1	1	1	1	1	7	High
Kim et al	0	0	1	0	1	1	0	0	1	4	Fair
Tsujinaka et al	1	0	1	1	1	1	1	1	1	8	High
Saito et al	1	0	1	0	0	1	1	1	0	5	Fair
Triboulet et al	1	1	1	1	1	1	1	1	1	9	High
Denham et al	1	1	1	1	1	1	1	0	1	8	High
Chu et al	0	0	1	1	1	1	1	0	1	6	Fair
Bova et al	1	1	1	1	1	1	1	1	1	9	High
Nakamura et al	1	1	1	1	1	1	1	1	1	9	High
Vandersteen et al	1	1	1	1	1	1	1	0	1	8	High
Wang et al	1	0	1	0	1	1	1	0	1	6	Fair
Iseli et al	0	1	1	1	1	1	1	0	1	7	High
Kao et al	1	1	1	1	1	1	1	1	1	9	High
Lee et al	0	0	1	1	1	1	0	1	1	6	Fair
Milisavljenic et al	1	0	1	0	1	1	1	1	1	7	High
Chedid et al	1	1	1	1	1	0	1	0	1	7	High
Daiko et al	0	1	1	1	1	1	1	1	1	8	High
Ida et al	0	0	1	0	1	1	1	0	1	5	Fair
Kesski-säntti et al	1	1	1	0	1	1	1	1	1	8	High
Bussu et al	1	1	1	0	1	1	1	1	1	8	High
Kuo et al	1	1	1	1	1	1	1	1	1	9	High