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REVIEW ARTICLE

Patient-reported outcomes evaluating palliative radiotherapy and chemotherapy in patients with oesophageal cancer: A systematic review

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Abstract

Background. Patient-reported outcomes (PROs) and assessments of treatment-related toxicity provide important information on the effect of palliative chemotherapy and/or radiotherapy. The aim of this study was to review the effect of palliative radiotherapy and/or chemotherapy on symptoms and quality of life assessed by PROs and measurement of toxicity for patients with oesophageal cancer. *Methods.* The Central, Medline and Embase databases (1990 to November 2011) were systematically searched for prospective studies of palliative chemotherapy and/or radiotherapy in patients with advanced oesophageal cancer with PRO- and/or toxicity outcomes. The risks of bias were assessed. *Results*. Of 2677 records identified, only 32 included PROs, of which eight were randomised controlled trials. In studies with sufficient standard of PRO (n = 18), either Health Related Quality of Life (HRQL) (n = 14) or patient-reported dysphagia (n = 4), were assessed. Docetaxel added to cisplatin + fluorouracil (CF) improved HRQL compared to CF only, even though toxicity increased. Epirubicin added to CF resulted in longer preserved HRQL than its comparator in two trials, and non-inferiority in one. All phase II chemotherapy studies reported maintained HRQL or improved dysphagia combined with low level of toxicity. Brachytherapy resulted in better HRQL compared to stent placement in two trials, and external radiotherapy relieved dysphagia. The quality of the HRQL methodology and the interpretation and presentation of the PRO results varied, and clinical significance was seldom discussed. *Conclusion.* PRO endpoints are seldom used and further studies of homogenous patient groups with valid measures and methodology of PROs should be encouraged in the evaluation of palliative treatment. Brachytherapy, external radiotherapy and combination chemotherapy improved HRQL and dysphagia in the few identified studies with sufficient PRO methodology.

According to the literature, no studies of oesophageal cancer patients have shown a survival benefit of palliative chemotherapy or radiotherapy [1,2]. Therefore, the treatment is given to prevent or palliate symptoms, and relevant endpoints must be considered when evaluating the effect of the palliative treatment.

Both the disease and the treatment have major impact on these patients' symptoms, including dysphagia, functional well-being and health related quality of life (HRQL) [3]. These concepts are best known by patients, and are therefore assessed using patient-reported outcome (PRO). During the last two decades guidelines to ensure sufficient quality of PRO methodology have been developed [4,5]. The use of PROs has increased significantly and they are now recognised as valuable endpoints in clinical trials [6]. The traditional evaluations of survival, tumour response and time to progression, seem to be less appropriate. However, these endpoints are still often assessed in palliative studies.

Toxicity is another important issue when evaluating palliative treatment. Observer-rated toxicity of treatment is included in most clinical trials, e.g. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) [7]. Observer-rated patients' performance status (ECOG/WHO or Karnofsky performance status) may also be regarded as a measure of toxicity of treatment.

The aim of this study was to systematically review the effect of palliative chemotherapy and/or

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radiotherapy for patients with advanced cancer of the oesophagus by assessing PROs, including HRQL, and toxicity after treatment. The primary outcome was the effect of palliative radiotherapy and chemotherapy assessed by PROs after treatment. The secondary outcome was treatment toxicity evaluated by health workers. In addition, the quality of the PRO methodology and to what extent the authors included results of the PROs in their conclusions, were evaluated.

Materials and methods

A protocol was written in accordance with the guidelines of the Cochrane handbook for systematic reviews [5] in collaboration with The Norwegian Knowledge Centre for the Health Services.

Criteria for inclusion of studies

Prospective studies on patients with carcinoma of the oesophagus and oesophagogastric junction treated with chemotherapy and/or radiotherapy with palliative intent were included if PRO and/or toxicity were part of the treatment evaluation. Both randomised controlled trials (RCTs) and non-randomised trials were included to ensure sufficient data on the outcome measures. Studies of high-dose radiotherapy (≥ 40 Gy with concomitant chemotherapy or ≥ 50 Gy alone) were defined as treatment with curative intent if not stated otherwise, and were not included. Chemotherapy applied without surgery or radiotherapy was defined as treatment with palliative intent if not stated otherwise.

Questionnaires completed by the patients themselves or filled in by study personnel based on interviews of the patients (not observer-rated) were regarded as valid measurements. PROs regarding patient's satisfaction with care, mood disturbances and coping strategies, and toxicity not recognisable by the patients (e.g. haematological or nephrological toxicity), were not included.

Search methods for identification of studies

Searches were conducted in accordance with the guidelines of the Cochrane library [5]. Two healthcare librarians with experience in search strategies performed the search in cooperation with the first author.

The Cochrane Central Register of Controlled Trials (Central), Medline and Embase databases (1990 to November 2011) were searched to identify relevant published trials. PRO was rarely used for evaluation of oesophageal cancer treatment before 1990 [8]. A combination of subject headings and text words relating to chemotherapy and radiotherapy for oesophageal cancer with non-curative intent was used (Supplementary Appendix 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2012.731521). There were no restrictions related to language or study design. In addition, reference lists of identified PRO articles and reviews were manually searched for additional studies. Studies published in languages other than English, French, German, and the Scandinavian languages were identified, but not included due to lack of translation resources. Duplicates, abstracts and studies of less than 20 patients were excluded.

Data collection

All identified titles were reviewed by the first author (CDA), and titles definitely failing inclusion criteria were removed. Thereafter, titles and abstracts of articles were reviewed by pairs of three of the authors (CDA, ABJ, KB) using an eligibility assessment form. Discrepancies were resolved through discussion within the pairs and review by the third author if needed. Reasons for inclusion/non-inclusion were documented. If needed, the full text was reviewed before the final decision on inclusion was made. Data on the included studies were formally extracted by the first author and thereafter reviewed by one of the three others (ABJ, MGG or KB). The search details were presented according to the PRISMA 2009 flow diagram [9].

Assessment of treatment effect, quality of PRO and risk of bias

For each study, the effect of treatment was described. The heterogeneity of the study population, treatment modalities and outcome measures did not allow a meta-analysis to be performed.

The PRO methodology must hold sufficient quality in order to be a valid treatment outcome. The current review was based on the PRO assessment checklist of the Cochrane collaboration and the criteria provided by Efficace for assessment of HRQL outcomes [4]. The following criteria were evaluated: use of a PRO measurement instrument validated for use in cancer patients in general, preferably for the patient group and clinical situation in question, and report of baseline compliance, timing of PRO assessment and missing data. Studies that did not fulfil these criteria were considered as of insufficient standard. We also addressed their ability to give the reader an understandable presentation of the PRO and whether clinical significance was discussed.

The Cochrane collaboration's tool was used to assess the risk of bias in the RCTs [10], including: concealment of allocation, sequence generation,

blinding of outcome assessors, completeness of outcome data, and selective outcome reporting. For non-randomised trials, the completeness of the dataset, whether the primary outcome measure(s) were reliable and the quality of follow-up (frequency and length) were evaluated.

Results

Search results

The search conducted in January 2011 resulted in 2338 records after removal of duplicates, of which 1077 records were not relevant (Figure 1). The search was updated until November 2011 yielding 339 additional records. Of the 1600 abstracts reviewed, 1250 did not meet the inclusion criteria and 31 were excluded due to lack of relevant linguistic knowledge. The full text of 319 articles was reviewed, and 191 of these fulfilled the study inclusion criteria. Thirty publications included PROs in addition to toxicity and another two studies were retrieved from reference lists of identified articles; these are reviewed in the current paper.

Overview of the included studies

The 32 publications originating from 28 studies were classified according to the type of PRO (Table I)

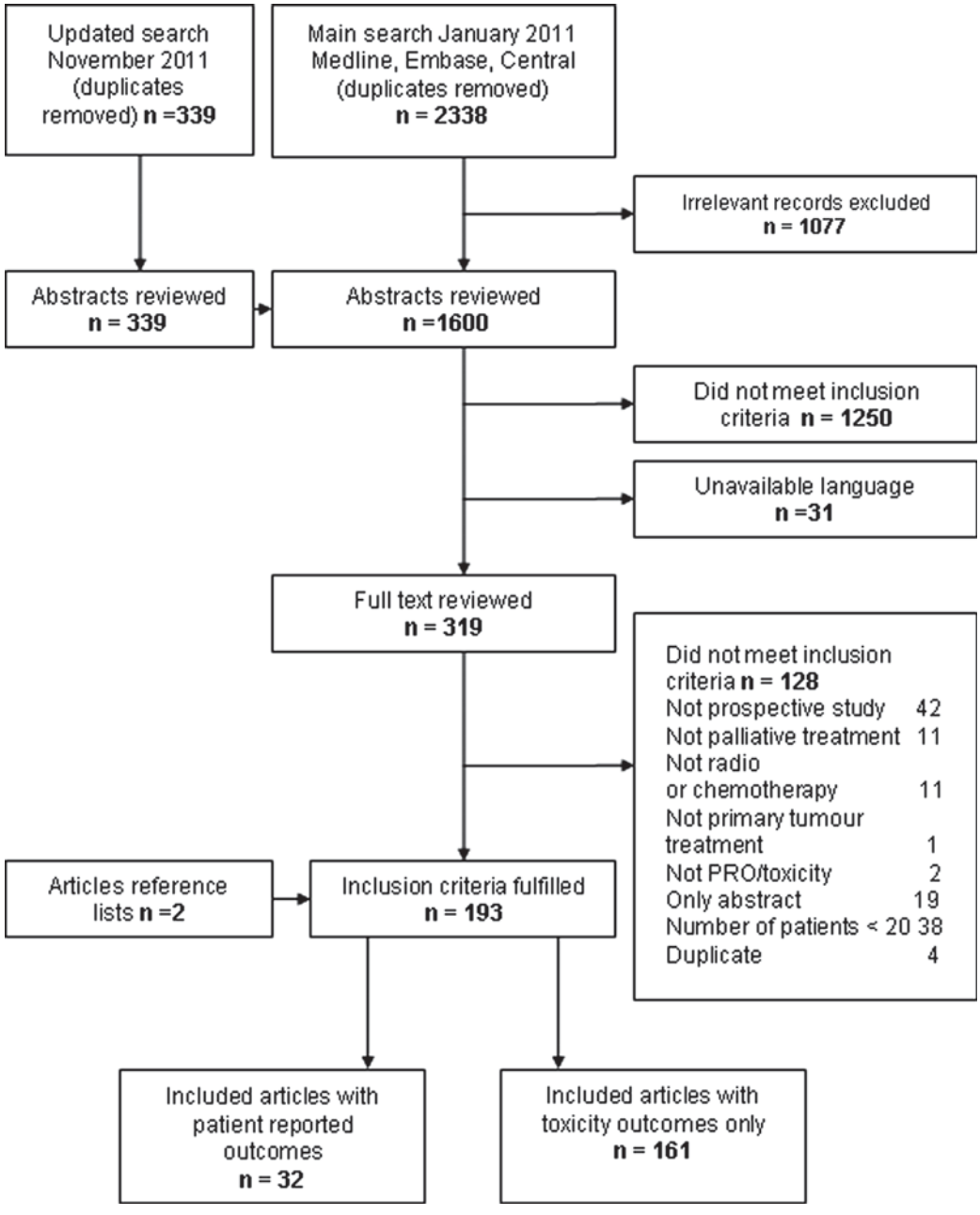

Figure 1. PRISMA search flow diagram.

Table I. Characteristics of patient-reported outcome (PRO) studies (n = 28).

			Type of study		Treatment			Quality assessment of PRO				
Patient reported outcome[a]	Total number of studies	References	Randomised controlled trial	Phase II or observational study	Chemo-therapy	Radio-therapy	Chemo-radio-therapy	Validated questionnaire	Baseline compliance reported	Time of assessment reported	Missing data reported	Sufficient standard
HRQL	21	[11–15,17–19,21, 25,27,29–32,34, 35,38,40–42]	11	10	14	6	1	19	16	21	15	14
Dysphagia only	7	[16,22–24,28, 33,37]	1	6	2	4	1	4	4	6	5	4

HRQL, health related quality of life; Sufficient standard: validated questionnaire used, baseline compliance, time of assessment and missing data reported.
[a]In addition, toxicity was reported in all studies.

[11–42]. Patient-reported dysphagia was part of HRQL assessments in 11 studies [14,15,26,27, 29–31,34,35,40,42] in addition to the seven publications reporting dysphagia only (Table I). Only five studies were published before the year 2000 [13,21,27,41,42]. The quality of the PRO reports was regarded to be of sufficient standard in 18 studies; the HRQL studies are listed in Tables II and III (n = 14) [12–15,17–19,26,30–32,40–42], and studies on patient-reported dysphagia only are listed in Tables IV and V (n = 4) [16,24,28,37].

Description of the HRQL studies

The majority of the HRQL studies evaluated palliative chemotherapy (n = 9) involving a wide range of regimens, with cisplatin and fluorouracil (CF) the most frequently used drugs (Table II). Palliative radiotherapy was evaluated in five studies; stent vs. brachytherapy in two, external radiotherapy in two, and external radiotherapy with concomitant chemotherapy in a single study.

All except one of the HRQL studies used the European Organisation of Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) [43]. In addition, the oesophagus module (EORTC QLQ-OES18 or QLQ-OES24) was used in six studies. One study used the Rotterdam symptom checklist [44]. Reports of timing of assessment and the frequency of missing questionnaires varied between the studies. Baseline compliance ranged from 31% to 100%. The compliance during follow-up was more than 90% in one study in which patients received home visits by trained research nurses. For most of the studies, the attrition due to death or dropout for other reasons increased rapidly over time.

Some publications used tables and graphs to display the HRQL results [12,14,17,19,25,30], while others gave a short summary in text only [18,32,40,41]. Clinical significance was addressed in four of the studies [14,15,17,30].

Description of the dysphagia studies

The clinical intervention in the patient-reported dysphagia studies was multi-drug chemotherapy (n = 3) or radiotherapy with concomitant chemotherapy (n = 1) (Table IV).

There were small differences in the wording, but the dysphagia questions employed in each of the studies had a categorical response scale ranging from the ability to eat all food without problem to complete dysphagia. Baseline compliance was 100% in all studies, the number of patients was limited (n = 22 to 93) and compliance ranged from 63% to 100% for the second time point.

Treatment outcome

The main outcomes of the studies with sufficient standard on HRQL and patient-reported dysphagia are displayed in Tables III and V.

As listed in Table III, a significant difference in HRQL between treatment arms were reported in five of the eight RCTs. Docetaxel added to CF (DCF) improved HRQL compared to CF and epirubicin added to CF (ECF) resulted in longer preserved HRQL than its comparators; mitomycin + CF (MCF) and fluorouracil, doxorubicin and methotrexate (FAMTX) [12,32,41]. Brachytherapy resulted in better HRQL compared to stent placement in two trials [14,25]. In the other three RCTs, no significant difference in the main HRQL outcome was reported [18,19,31], but better physical functioning and less nausea/vomiting was reported for irinotecan combined with fluororouracil (IF) vs. CF [19]. All phase II studies with HRQL as an outcome (n = 5) reported maintenance or some improvement in quality of life, and low toxicity of chemotherapy [13,17,40] and of external radiotherapy [15,30]. Most of the papers (15/18) included PRO and toxicity results in their final conclusions.

Dysphagia after chemotherapy or chemoradiotherapy (treatments listed in Table IV) was improved in three and stable in one of the four phase II studies

Table II. Health related quality of life (HRQL) studies of sufficient standard (n = 14).

First author (year of publication) (references)	Total number of patients (number with oesophageal cancer)	Treatment	Study design	Treatment details	HRQL instrument	Baseline compliance	Time of assessment	Toxicity assessment
Rao (2010) [31]	72 (41)	Chemo-therapy	Randomised phase II	matuzumab + ECX vs. ECX	EORTC QLQ-C30 EORTC QLQ-OES18 study-specific questions	84%	Baseline, 4th chemotherapy cycle, end of treatment	NCI-CTC version 3
Curran (2009) Dank (2008) [19,20]	333 (65)	Chemo-therapy	Randomised phase III	IF vs. CF	EORTC QLQ-C30 EQ-5D	86%	Baseline, every 8 weeks until progression, every 3 months until death	NCI-CTC
Cunningham (2008) Sumpter (2005) [18,36]	1002 (581) 204 (133)	Chemo-therapy	Randomised phase III	ECF vs. ECX vs. EOF vs. EOX	EORTC QLQ-C30	96%	Baseline, every 3 months until 12 months	NCI-CTC version 2
Ajani (2007) van Cutsem (2006) [12,39]	445 (98)	Chemo-therapy	Randomised phase III	DCF vs. CF	EORTC QLQ-C30 EQ-5D	88%	Baseline, every 8 weeks until progression, every 3 months until death	NCI-CTC version 1 Karnofsky performance status
Ross (2002) [32]	580 (218)	Chemo-therapy	Randomised phase III	ECF vs. MCF	EORTC QLQ-C30	68%	Baseline, every 3 months until 12 months	NCI-CTC version 1 Observer rated symptom response and weight change
Webb (1997) [41]	274 (111)	Chemo-therapy	Randomised phase III	ECF vs. FAMTX	EORTC QLQ-C30	73%	Baseline, week 12, week 24	NCI-CTC version 1 Observer rated symptom response and weight change
van Meerten (2007) [40]	51 (51)	Chemo-therapy	Non-randomised phase II	oxaliplatin + capecitabine	EORTC QLQ-C30 EORTC QLQ-OES18	92%	Baseline, every other chemotherapy cycle, end of treatment	NCI-CTC version 3
Conroy (2002) [17]	71 (71)	Chemo-therapy	Non-randomised phase II	vinorelbine + cisplatin	EORTC QLQ-C30	83%	Baseline, 2nd and 4th chemotherapy cycles	SWOG toxicity criteria Dysphagia
Bamias (1995) [13]	235 (119)	Chemo-therapy	Non-randomised phase II	ECF	EORTC QLQ-C30	31%	Baseline, week 14, week 26	NCI-CTC version 1 Observer rated symptom response and weight change
Kassam (2008) [30]	47 (47)	Radio-therapy	Non-randomised phase II	Accelerated fractionation 2 Gy × 20 (10d)	EORTC QLQ-C30 EORTC QLQ-OES24	100%	Baseline, week 8, time of progression	RTOG toxicity criteria
Homs (2005) Homs (2004) [25,26]	209 (209)	Radio-therapy	Randomised phase III	Stent vs. brachytherapy	EORTC QLQ-C30 EORTC QLQ-OES24 EQ-VAS and EQ-5D	100%	Baseline, 2 weeks every month until 1 year after treatment	Dysphagia Complications listed
Bergquist (2005) [14]	65 (65)	Radio-therapy	Randomised phase III	Stent vs. brachytherapy	EORTC QLQ-C30 EORTC QLQ-OES18	100%	Baseline, 1 month, every 3 months until 12 months	Dysphagia Karnofsky performance status Complications listed
Burmeister (2005) [15]	46 (46) 24[a]	Chemo-radio-therapy	Non-randomised phase II	3 Gy × 10–15 + concomitant fluorouracil	EORTC QLQ-C30 EORTC QLQ-OES18	100%	Baseline, every 3 month until 12 months, 18 months, 24 months	NCI-CTC version 2 Weight loss and dysphagia
O'Hanlon (1995) [42]	69 (69) 43[a]	Radio-therapy	Observation	No details	Rotterdam symptom checklist	88%	Baseline, week 6, week 16	Symptom score

CF, cisplatin + fluorouracil; DCF, docetaxel + cisplatin + fluorouracil; ECF, epirubicin + cisplatin + fluorouracil; ECX, epirubicin + cisplatin + capecitabine; EOF, epirubicin + oxaliplatin + fluorouracil; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30-item version; EORTC QLQ-OES24, EORTC oesophagus cancer module 24-item version; EOX, epirubicin + oxaliplatin + capecitabine; EQ-5D, EuroQoL generic questionnaire; FAMTX, fluorouracil + doxorubicin + methotrexate; IF, irinotecan + fluorouracil + folic acid; MCF, mitomycin + cisplatin + fluorouracil; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; RTOG, Radiation Therapy Oncology Group; SWOG, South West Oncology Group.
[a]Patients treated with palliative intent.

Table III. Outcome of health related quality of life (HRQL) studies of sufficient standard (n = 14).

	Endpoints		Results			
First author (references)	Primary	Other	Clinical response	HRQL	Non-haematologic toxicity (> grade 2) and symptoms	Authors conclusion
Rao [31]	Tumour response	Overall survival, progression free survival, HRQL	Addition of matuzumab to ECX did not improve tumour response or median overall survival (9.4 vs. 12.2 months)	No difference in global health status (no other scales reported)	No difference in grade 3/4 Increased skin disorders (any grade) with matuzumab (66% vs. 31%)	No increase in response or survival with matuzumab, no further evaluation of this treatment is warranted
Curran Dank [19,20]	Time to progression	Overall survival, safety, time to 5% deterioration of global health status	No difference in time to progression (5.0 vs. 4.2 months) or median survival (9.0 vs. 8.7 months)	No difference in time to 5% deterioration of global health status	No difference in time to deterioration of KPS, weight or appetite Higher rate of diarrhoea with IF (22% vs. 7%), less stomatitis (2% vs. 17%) and neurological toxicity (0% vs. 4%)	IF did not provide longer time to progression or better overall survival, but had another toxicity profile and better outcome on some HRQL scales. Recommended as an alternative to CF
Cunningham Sumpter [18,36]	Non-inferiority in overall survival	Progression-free survival, response rates, safety and HRQL	No difference in overall survival (9.9 vs. 9.9 vs. 9.3 vs. 11.2 months) between treatment arms	No difference in mean scores of global health status at 12 weeks	More diarrhoea (11%/12% vs. 3%) and peripheral neuropathy (8%/4% vs. 3%) with EOF/EOX vs. ECF hand-foot syndrome increased (10% vs. 4%) with ECX *vs.* ECF	Regimens with oxaliplatin and capecitabine were as effective as ECF. Recommended non-inferior treatment option
Ajani van Cutsem [12,39]	Time to progression	Overall survival, safety, time to 5% deterioration of global health status	DCF longer time to progression (5.6 vs. 3.7 months) and overall survival (9.2 vs. 8.6 months)	Time to 5% deterioration of global health status longer for DCF.	Longer time to deterioration of KPS with DCF, diarrhoea increased (19% vs. 8%) with DCF *vs.* CF	DCF provided longer time to progression, better HRQL but more toxicity compared to CF
Ross [32]	1-year survival	Failure free survival, response, safety, HRQL	No difference in median survival (9.4 vs. 8.7 months) or median failure free survival (7 months)	Global health status and physical and emotional functioning was maintained with ECF, declined with MCF at 3 and 6 months.	No difference in symptomatic response or weight loss, more alopecia (88% vs. 39%), less plantar-palmar erythema (30% vs. 43%) with ECF vs. MCF	No difference in survival or response Better HRQL with ECF than MCF. ECF reference treatment
Webb [41]	1-year survival	Response, toxicity, HRQL	ECF improved median overall (8.9 vs. 5.7 months) and failure free survival (7.4 vs. 3.4 months)	Global health status better with ECF than FAMTX at 24 weeks	Significantly more nausea (17% vs. 5%) with ECF vs. FAMTX, no difference in symptomatic response	ECF superior to FAMTX for patients with advanced oesophagogastric cancer
van Meerten [40]		Tumour response toxicity, HRQL survival	Overall response 19/49 (39%). Median survival 8 months	Physical function declined, emotional function improved. Less pain, more dry mouth.	Low toxicity, all < 10%. (nausea/vomiting 8%, lethargy 6%)	Oxaliplatin and capecitabine outpatient treatment, preserved HRQL, probably less toxicity than cisplatin

(Continued)

Table III. (*Continued*).

First author (references)	Endpoints		Results			
	Primary	Other	Clinical response	HRQL	Non-haematologic toxicity (> grade 2) and symptoms	Authors conclusion
Conroy [17]		Tumour response toxicity, survival, HRQL	Overall response 24/71 (34%). Median survival 6.8 months	Improvement of global health status and physical function.	No improvement in dysphagia after treatment 22%, fatigue 19%, anorexia 11%, vomiting 10%, other < 10%	Vinorelbine and cisplatin shorter treatment and probably less toxic than CF. HRQL data inconclusive
Bamias [13]		Tumour response, toxicity, symptomatic response, HRQL, survival	Overall response 135/220 (61%) median survival 8.4 months	Physical and role functioning maintained, pain decreased, global health scale improved	Nausea and vomiting 13%, other < 10%	ECF is effective with low toxicity and no negative impact on HRQL
Kassam [30]		Dysphagia relief toxicity, HRQL	Dysphagia score improved in 27/39 (67%), median survival 8 months	Improvement in emotional function and global health scale	Only 1% grade 3 toxicity (anorexia and nausea) Radiation induced oesophagitis any grade 18%	Accelerated fractionation radiotherapy offers a favourable response profile with minimal toxicity and short treatment time
Homs [25,26]	**Dysphagia relief**	Complications, HRQL, treatment for persistent dysphagia, cost	Dysphagia score improved more rapidly with stent than brachytherapy. No difference at 30 days median survival 5.5 months	Brachytherapy was more beneficial over time on most of the HRQL scales	Complications more frequent after stent than brachytherapy total (33% vs. 21%), haemorrhage (13% vs. 5%), pain (11% vs. 6%)	Brachytherapy gave better long-term relief of dysphagia, better HRQL and fewer complications than stent. Recommended as treatment of choice.
Bergquist [14]	**HRQL**	Level of dysphagia control	Dysphagia improved more rapidly with stent vs. brachytherapy (1 month vs. 3 months) median survival 5.0 months vs. 5.2 months	HRQL more stable for the brachytherapy group than in the stent group	No difference in time to deterioration of KPS, weigh, dysphagia or in rate of complications	Stent initially more effective, brachytherapy offers better long-term HRQL
Burmeister[a] [15]		Toxicity, HRQL (dysphagia and physical function), survival	Complete dysphagia relief 16/24 (67%) median survival 9 months	Dysphagia scores improved and physical function maintained for 12 months	Low toxicity, oesophagitis 8%	Radiotherapy with concomitant fluorouracil gave good response with low toxicity and maintained HRQL
O'Hanlon [42]	**HRQL**	Relief of dysphagia	Dysphagia score improved significantly at 6 weeks	The HRQL parameters deteriorated for palliative group	Not stated	HRQL assessment useful for assessing patients well-being after treatment

Bold text, patient-reported outcome as primary endpoint.
CF, cisplatin + fluorouracil; DCF, docetaxel + cisplatin + fluorouracil; ECF, epirubicin + cisplatin + fluorouracil; ECX, epirubicin + cisplatin + capecitabine; EOF, epirubicin +oxaliplatin + fluorouracil; EOX, epirubicin + oxaliplatin + capecitabine; FAMTX, fluorouracil + doxorubicin + methotrexate; HRQL, health related quality of life; IF, irinotecan + fluorouracil + folic acid; KPS, Karnofsky performance status; MCF, mitomycin + cisplatin + fluorouracil.
[a]Results of the palliative treatment group shown.

Table IV. Patient-reported dysphagia studies of sufficient standard.

First author (year of publication) [reference(s)]	Total number of patients (number with oesophageal cancer)	Treatment	Study design	Treatment details	Dysphagia assessment	Baseline compliance	Time of assessment	Toxicity assessment
Cho (2005) [16]	32 (32)	Chemo-therapy	Non-randomised phase II	paclitaxel + cisplatin	DeMeester symptom scores	100%	Baseline, end of treatment	NCI-CTC
Jatoi (2002) [28]	46 (46)	Chemo-therapy	Non-randomised phase II	docetaxel + irinotecan	Barr and Krasner questionnaire	100%	Baseline, before subsequent chemotherapy cycles	NCI-CTC version 2
Taieb (2002) [37]	93 (93)	Chemo-therapy	Non-randomised phase II	HLFP	Mellow and Pinkas modified score	100%	Baseline, every month	NCI-CTC
Hayter (2000) [24]	22 (22)	Chemo-radiotherapy	Non-randomised phase II	3 Gy × 10 concomitant fluorouracil + mitomycin	Medical research council symptom index	100%	Daily diary cards during treatment	Not described

HLFP, hydroxyurea + leucovorin + fluorouracil + cisplatin; NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

with patient-reported dysphagia only [16,24,28,37] (Table V).

Toxicity was usually reported by NCI-CTC, an older version of NCI-CTCAE [7]. Nausea and diarrhoea were most frequent, peripheral neuropathy was reported after oxaliplatin-containing regimens, while hand-foot syndrome was found for capecitabine. Grade 3–4 toxicity and complications were infrequently observed.

The median overall survival ranged from 4.7 months (chemoradiotherapy) to 12.7 months (multi-drug chemotherapy) [24,37]. Only two RCTs found a survival benefit (8.9 months vs. 5.7 months, ECF vs. FAMTX and 9.2 vs. 8.6, DCF vs. CF) [39,41]. Tumour response was reported in all studies of chemotherapy.

Risk of bias

Eight of the sufficient standard PRO studies were RCTs and fulfilled the criteria of sequence generation and concealment of allocation, although most of

Table V. Outcome of patient-reported dysphagia studies of sufficient standard (n = 4).

	Endpoints		Results			
First author (year of publication) [reference(s)]	Primary	Other	Clinical response	Patient reported response	Non-haematologic toxicity (>grade 2) and symptom ratings	Authors conclusion
Cho (2005) [16]		Toxicity, response rate, relief of dysphagia and survival	Tumour response 13/32 (41%), median survival 7 months	Dysphagia relief 11/29 (38%) no change 12/29 (41%) of which 5 had no dysphagia from start	Fatigue 23%, nausea and vomiting < 10%	Effective treatment with tumour response and dysphagia relief
Jatoi (2002) [28]	Tumour response	Progression free survival, overall survival, relief of dysphagia and toxicity	Tumour response 12/46 (26%), median survival 7.3 months	Dysphagia relief 7/29, no change 21/29, deterioration 1/29. 87% had no dysphagia or grade 1 before treatment	High-dose regimen induced high toxicity, 8% grade 4 diarrhoea, nausea and dyspnoea and 15% grade 3 fatigue, dose reduction reduced toxicity	Modest tumour response and high toxicity at high-dose levels. Dysphagia not a major symptom
Taieb (2002) [37]	Tumour response	Survival, relief of dysphagia, toxicity	Tumour response 24/42 (58%), median survival 12.7 months	Dysphagia relief 26/34 (76%)	Diarrhoea 7%, nausea/ vomiting 10%, no weight gain 53%	HLFP is effective and well tolerated
Hayter (2000) [24]	Time to dysphagia relief	Toxicity, dysphagia free survival and overall survival	Median survival 20 weeks	Median time to dysphagia relief 5 weeks, dysphagia relief 15/22 (68%), and dysphagia free survival 11 weeks	Patients hospitalised for transient worsening of dysphagia (n = 1) or nausea and diarrhoea (n = 1)	Well tolerated complete relief of dysphagia in a substantial proportion of patients

HLFP, hydroxyurea + leucovorin + fluorouracil + cisplatin.

them did not describe the randomisation procedure in detail. The baseline characteristics of the groups compared were balanced, and the risk of selection bias seemed to be low. Blinding of participants or personnel was not reported, while blinding of outcome assessors for tumour response was reported in three studies [20,31,39]. Attrition is a possible source of bias, and differences in the dropout rates between the groups for PRO was either none (n = 3) [12,14,25], small (n = 1) [19] or not described (n = 4) [18,31,32,41]. Selective reporting bias was not found, and significant and non-significant differences between the intervention groups within a study were reported as required.

Discussion

In this review of treatment effects on palliative chemotherapy and radiotherapy in patients with advanced oesophageal cancer, only 32 of the records that fulfilled the inclusion criteria included PROs. This is worrying due to the lack of survival benefit for these treatments. Investigators need to question the clinical implications of a treatment when planning a study. In palliative studies, PROs are important endpoints, while tumour response may be irrelevant as long as survival is not improved.

The large heterogeneity between the studies made it difficult to draw conclusions regarding the effects of treatment on PROs. Surprisingly, more intensive chemotherapy gave better preservation of HRQL (DCF vs. CF) even though toxicity, in particular diarrhoea, was increased [12,39]. ECF resulted in better preserved global health scores than its comparator in two trials [32,41], and non-inferiority in one [18]. These PRO results provided valuable data in addition to the evaluation of clinical response, and have had an impact on the extensive use of ECF as a reference treatment for advanced gastrooesophageal cancer, in particular, in Europe.

There was no clear association between HRQL and treatment toxicity. Two RCTs of chemotherapy reported better HRQL despite more treatment toxicity in the experimental arm vs. the standard arm [12,41], while the phase II studies reported improved HRQL and low levels of toxicity after treatment. Patients may tolerate toxicity to a greater extent when they have hope of treatment effect, and information about possible side effects may improve patient coping. There may also be publication bias; only one study reported negative results [31].

It is a problem that all the RCTs on chemotherapy had mixed patient populations (gastric, oesophagogastric and oesophageal cancer). The results were reported for the whole group together, limiting the possibilities to obtain information relevant to patients with cancer of the oesophagus.

Even though radiotherapy is a commonly used palliative intervention for advanced cancer of the oesophagus [1,45], this was addressed in only nine of the 28 studies. However, the effect of palliative radiotherapy was confirmed. The effect of brachytherapy on overall HRQL was better than stent placement in two of the RCTs [14,25], and external radiotherapy provided relief from dysphagia for a substantial proportion of patients in non-randomised studies [15,24,30]. The low proportion of studies on palliative radiotherapy is worrying. This could be due to lack of interest among investigators, or caused by the lack of funding for radiotherapy studies.

Although only a few clinical studies that included PROs were identified, it was encouraging that for most of them the PRO and toxicity results were included in their final conclusions and thereby enhanced the impact of these results on clinical decision-making.

On the other hand, caution should be taken using results from clinical trials to make conclusions regarding a treatment's impact on symptom relief and HRQL in clinical practise. Patients included in trials are carefully selected and may not be representative of a broader group of patients. Only one study included unselected patients from clinical practise, but unfortunately the palliative treatment applied was not specified [42]. Further prospective observational studies of unselected patient populations receiving standard palliative treatment with PROs are warranted.

All but four studies were published in the last decade, confirming that PROs have only recently come to be recognised as valuable endpoints. Some research groups such as Cunningham's group at Royal Marsden Hospital, often include PRO [13,18,31,32,41]. Even though guidelines are provided [4,5,46], lack of motivation, resources and knowledge within research groups may be the reasons for not including PRO in most studies. On the other hand, we are pleased to acknowledge that authors such as Homs, Bergquist, O'Hanlon and Hayter have published papers using PRO as the primary endpoint [14,24,25,42]. In particular, Homs and co-workers managed both to conduct a study with a high quality of PRO methodology and to present the PRO results in a way that was easy to read [25,26].

All of the sufficient standard HRQL studies (n = 14) used questionnaires validated for cancer patients in general, but also for oesophageal cancer patients in particular. Although there is no consensus on which validated HRQL instrument to apply, the EORTC QLQ-C30 with or without diagnosis-specific modules, or the Functional Assessment of

Chronic Illness Therapy cancer instrument (FACT-G) are recommended in order to facilitate comparisons between institutions and countries [47].

In one study, one item was excluded from the chosen EORTC questionnaire because it was considered irrelevant to their patient group [25,26]. This is not recommended according to guidelines; the validity of the questionnaire may be compromised [48].

High compliance is mandatory to obtain high quality of PRO data. Baseline compliance was above 80% for 15 of the 18 selected studies (Tables II and IV). A completed patient questionnaire as an inclusion criterion in a study ensures high baseline compliance. The involvement of a research nurse is crucial to achieve high compliance both at baseline and at the follow-up evaluations [25,49]. Most of the studies had a high attrition rate, but the reasons for dropouts were seldom reported. High attrition rate and low compliance are often recognised as potential sources of bias in results. A possible bias due to different dropout rates between the treatment arms was addressed in two studies [12,19]. However, a study by Ahlner-Elmquist did not find a difference in HRQL between participants and dropouts three months before death, and concluded that data from patients close to death may be representative of a larger group [50].

To use tables and graphs to display the PRO results is an excellent way to give a concise and clear presentation of the HRQL from a number of subscales [12,25,30]. It also simplifies and explains the results for the clinicians.

Some of the studies reported the HRQL results in text only, and a few of these only reported the global health status subscale [18,31]. Publications reporting the full results of a clinical trial with HRQL as a secondary endpoint often do not have the necessary space to report quality of life results. For clinical trials with a predefined HRQL endpoint, it is recommended that this should be reported together with the clinical endpoints in the main publication [4]. However, all the subscales should be taken into account when reporting HRQL since it is well accepted that quality of life is multidimensional. A separate publication of the HRQL results was used by three studies [12,19,20,25,26,39]. This may limit the impact of the patients' HRQL on clinical decisions [51].

Only four of the studies addressed clinical significance. All of them referred to Osoba et al. who defined a difference of at least 10 points in the HRQL score after treatment, measured with EORTC QLQ-C30, as a clinically meaningful change [52]. It is worrying that the rest of the studies rely on the level of statistical significance instead of interpreting the magnitude of clinical change.

For patients in a palliative situation, it is crucial to evaluate treatment effects on their symptoms and quality of life. In this review there were few identified papers with PROs as endpoints and high quality of PRO measurement. However, in the studies with PROs and sufficient methodology, brachytherapy, external radiotherapy and combination chemotherapy improved HRQL and dysphagia. Negative results were reported in one paper only, and one may wonder whether a publication bias could be present. The results from studies with mixed patient groups or where gastric cancer patients dominate should be interpreted with caution with regard to oesophageal cancer. In palliative studies, PROs are the most important measures of treatment effect when treatment does not prolong survival, and more relevant than tumour response. In future studies, a valid evaluation regarding treatment effects on patient-reported symptoms and HRQL should include PROs as predefined endpoints and with adequate methodology to ensure high compliance. Furthermore, attrition and clinical significance must be addressed.

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Supplementary material available online

Supplementary Appendix 1.