Review Article

Interim position emission tomography-computed tomography during multimodality treatment of locally advanced esophageal cancer: a scoping review

Hongcheng Zhu[1,2,3,4#], Shengnan Hao[1,2,3,4#], Ihsuan Tseng[1,2,3,4#], Jingyi Shen[1,2,3,4], Eleonor Rivin del Campo[5], Amy Davies[6], Eva Segelov[7], Qiufang Liu[2,8], Yun Chen[1,2,3,4], Shaoli Song[2,8], Kuaile Zhao[1,2,3,4]

[1]Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; [3]Shanghai Clinical Research Center for Radiation Oncology, Shanghai, China; [4]Shanghai Key Laboratory of Radiation Oncology, Shanghai, China; [5]Department of Radiation Oncology, Tenon University Hospital, Sorbonne University, Paris, France; [6]Department of Oncology, Monash Health and Monash University, Melbourne, VIC, Australia; [7]Department of Clinical Research, University of Bern, Bern, Switzerland; [8]Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai, China

Contributions: (I) Conception and design: S Song, K Zhao; (II) Administrative support: Q Liu, Y Chen; (III) Provision of study materials or patients: H Zhu, S Hao, I Tseng, J Shen, E Rivin del Campo, A Davies, E Segelov, Q Liu, Y Chen; (IV) Collection and assembly of data: H Zhu, S Hao, I Tseng; (V) Data analysis and interpretation: H Zhu, S Hao, I Tseng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Kuaile Zhao, MD. Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Shanghai Clinical Research Center for Radiation Oncology, Shanghai, China; Shanghai Key Laboratory of Radiation Oncology, 270 Dong'an Road, Shanghai 200032, China. Email: kuaile_z@sina.com; Shaoli Song, MD. Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Shanghai Key Laboratory of Radiation Oncology, 270 Dong'an Road, Shanghai 200032, China. Email: shaoli-song@163.com.

Background: Among cancers, esophageal cancer (EC) has one of the highest incidences and mortality in Asia. As recognized in many national guidelines, functional imaging performed with position emission tomography is recommended for patients with locally advanced disease. This review evaluated evidence for the use of fluorodeoxyglucose (FDG) interim positron emission tomography (PETint) in bimodality (chemoradiation) and trimodality (chemoradiation followed by surgery) management of locally advanced esophageal cancer (LAEC), with a focus on its prognostic and predictive value.

Methods: The MEDLINE database was searched from January 1, 2001, to January 1, 2022, as part of a scoping review. References of selected articles were manually checked to identify other articles meeting the inclusion criteria; only original articles were included, and reviews, guidelines, letters, editorials, and case reports were excluded.

Results: A total of 63 articles were included in this review. PET-computed tomography (PET-CT) is recognized as having a significant role in the assessment of treatment response. Studies on the predictive PETint suggest that it has a certain value, particularly for early response. Identification of poor responders or nonresponders soon after commencement of multimodality treatment allows for treatment modification.

Conclusions: The scoping review indicated variable utility for the prognostic value of PETint. There is a need to improve its accuracy, which can likely be achieved through greater standardization of measurements and reporting and testing as well as combination with other promising measures of response to residual disease.

Keywords: Esophageal cancer (EC); PET-CT; FDG; interim; prognostic value

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Introduction

Esophageal cancer (EC) has one of the highest incidences and mortality among cancers in Asia and other regions, with a total of 346,633 new cases and 323,600 deaths estimated to occur China in 2022, along with 19,042 new cases and 16,916 deaths estimated in the United States (1). An analysis of the CONCORD database, which comprises 290 registries across 60 countries with 730,000 patients, indicated a 5-year survival rate for patients with EC of 10–30% (2). In order to improve this low survival rate, advances in the accuracy of screening, diagnostic imaging, staging, impact of multimodality treatment, and individualized tailoring of therapies are needed.

Functional imaging performed with position emission tomography-computed tomography (PET-CT) is the gold-standard modality for patients with locally advanced disease as recognized by numerous guidelines (3,4). Fluorodeoxyglucose (FDG) PET-CT in addition to CT and endoscopic ultrasound (EUS) yields a more precise estimation of tumor volume (5). FDG PET-CT can also be used to identify the biological target volume (BTV) within the radiotherapy target volume delineation. Moreover, FDG PET-CT has been identified as a promising approach for imaging-based biomarkers in a few studies; however, there is other research that contradicts this conclusion (6).

Neoadjuvant chemoradiotherapy plus surgery has been established as the standard of care for locally advanced EC (LAEC), while neoadjuvant chemotherapy plus surgery is also popular in some regions (7). Definitive chemoradiotherapy has been globally accepted as the standard nonsurgical approach, although there are still uncertainties in the specificities of radiation dose and choice of chemotherapy regimen. Immunotherapy and targeted therapies have also added new insights to the multimodality treatment of LAEC (8).

FDG PET-CT can be used to predict outcome and prognosis in the pretreatment setting and has been used increasingly in assessing treatment response (9). FDG PET-CT provides various prognostic metabolic parameters, including the standardized uptake value (SUV), which is semiquantitatively assessed by glucose uptake; metabolic tumor volume (MTV), which is defined as the volume of tumor tissue with increased FDG uptake; and tumor lesion glycolysis (TLG), which is the product of MTV multiplied by the SUV (10). The SUV is a widely used semiquantitative metric for assessing tissue accumulation of tracers, and it can be normalized to body mass, lean body mass (SUL), or body surface area. The change in SUVmax is the most frequently used parameter for evaluating tumor metabolic change during treatment and obtaining prognostic information.

There has been increasing interest in the prognostic and predictive benefit of FDG PET-CT acquired at a time point during bimodality (chemoradiation) or trimodality (chemoradiaiton followed by surgery) treatment, defined as interim FDG PET (PETint) (11). Early identification of progressive disease may expedite resection or may alternatively lead to the abandonment of a curative surgical approach; additionally, systemic therapy and/or radiation schedules can be modified (12). A scoping review was conducted to evaluate the current evidence in neoadjuvant chemoradiotherapy, definitive chemoradiotherapy, and adaptive radiotherapy concerning the value of FDG PETint in the bimodality or trimodality management of LAEC, with a focus on its prognostic and predictive capability. We present this article in accordance with the PRISMA-ScR reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1306/rc).

Methods

A systematic scoping search of the MEDLINE database from January 1, 2001, to January 1, 2022, was conducted with the following search terms: (esophageal carcinoma OR esophageal cancer OR oesophageal carcinoma OR oesophageal cancer) AND (chemoradiotherapy or chemoradiation or therapy) AND (FDG OR 18F FDG) AND (PET OR PET-CT) AND (predictive OR prediction OR response assessment OR response OR assessment). A medical subject heading (MeSH) search was also performed as follows: (esophageal neoplasms [MeSH]) AND (positron

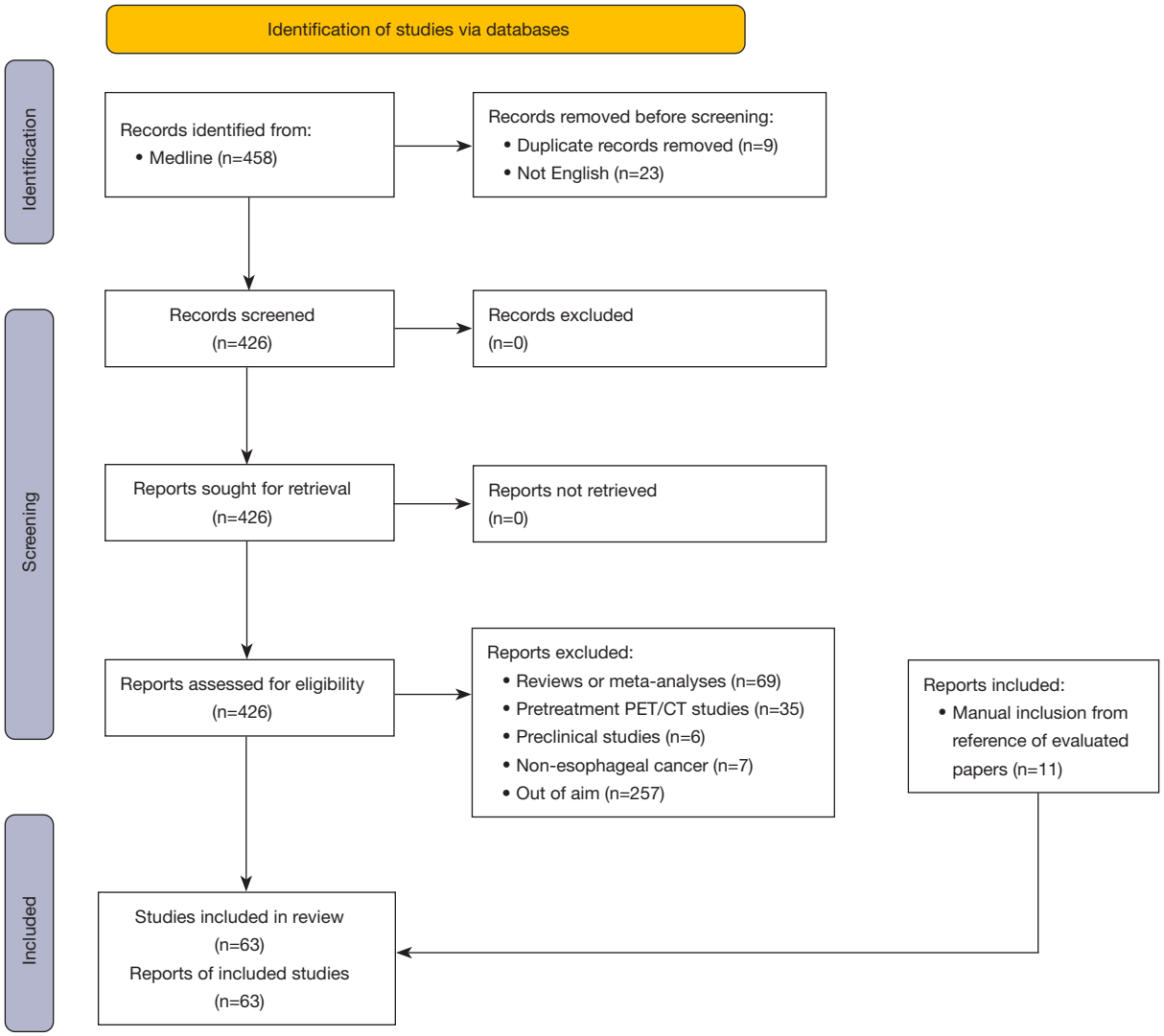

Figure 1 Flow diagram for literature screening. PET-CT, position emission tomography-computed tomography.

emission tomography [MeSH]) AND (18F FDG [MeSH]) AND (chemoradiotherapy [MeSH]) AND predictive value of tests [MeSH]). In addition, the references of selected articles were manually checked to identify other articles meeting the inclusion criteria. The search date was January 1, 2022.

Screening was conducted by 2 independent assessors (HZ and SH). Literature was selected for full-text review if the abstract reported on tumor response assessment after neoadjuvant chemo(radio) therapy or definitive chemoradiotherapy in EC. The full English text of relevant studies was retrieved for further selection. A flow diagram of the literature screening is shown in *Figure 1*. Only original articles were included. The full exclusion criteria were as follows: reviews, guidelines, letters, editorials, case reports; publications not in English; use of a PET only (rather than PET-CT); radiopharmaceuticals other than FDG; publications based on diagnosis, staging, or restaging for recurrent cancer; and nonhuman studies. The following information was extracted: author, year, region, nature of study, number of patients, treatment regimen, PET timing, metabolic parameters and cutoff, and correlation of PET with clinical response, survival, and histopathology (for neoadjuvant studies).

Results

After screening, 63 articles were included in this review: 27 prospective and 36 retrospective studies. *Table 1* summarizes the 57 articles focusing on detecting residual disease during or after completion of neoadjuvant treatment prior to surgery in trimodality management, including 18 from the United States (15,17,20,23,24,27,28,31,32,35,39,43,45,49,52,54,57,63), 6 from Germany (13,19,26,30,33,38), 6 from Korea (21,25,44,51,53,64), 5 from Japan (16,59,60,61,62), 4 from Ireland (22,34,47,56), 4 from The Netherlands (37,48,55,68), 3 from France (41,42,67), 3 from China (40,50,66), 1 from Belgium (14), 1 from Australia (29), 1 from Czechia (36), 1 from Canada (46), 1 from

Table 1 Studies on early PET-CT response in nCRT

Author, year, region (reference)	Nature of study	No. of patients	Treatment regime	PET timing	Metabolic parameters and cutoff	Correlation of PET with		
						Clinical response	Histopathology	Survival
Brücher, 2001, Germany (13)	Retrospective	27 SCC	RT: 30 Gy; Chemo: 5-FU	3 wk post-CRT	ΔSUVmean: 52%	Yes	Yes	Yes
Flamen, 2002, Belgium (14)	Retrospective	36 (27 SCC)	RT: 30 Gy; Chemo: DDP/5-FU	4–5 wk post-CRT	ΔTUR (tumor to liver uptake ratios)	Yes	Yes	Yes
Arslan, 2002, USA (15)	Retrospective	24 (2 SCC)	RT: 40–50.4 Gy; Chemo: DDP/5-FU or PTX/DDP or CBP/5-FU	4 wk post-CRT	ΔVol (tumor volume)	Yes	No	N/A
Kato, 2002, Japan (16)	Retrospective	10 SCC	RT: 40 Gy; Chemo: nedaplatin/5-FU	2 wk post-CRT	SUV	Yes	Yes	N/A
Downey, 2003, USA (17)	Prospective	39	RT: 50.4 Gy; Chemo: PTX/DDP	–	ΔSUV: 60%	N/A	Yes	Yes
Wieder, 2004, Germany (18)	Prospective	38 SCC	RT: 40 Gy; Chemo: 5-FU	2 wk after start of CRT	SUV	N/A	Yes	Yes
Brink, 2004, Germany (19)	Retrospective	20	RT: 36 Gy; Chemo: DDP/5-FU	2.7 wk post-CRT	SUV	N/A	No	NA
Swisher, 2004, USA (20)	Retrospective	103 (13 SCC)	RT: 50.4 Gy; Chemo: DDP/5-FU or CBP/PTX or CPT-11/DOC/5-FU	4–6 wk post-CRT	SUVmax ≥4	N/A	No	Yes
Song, 2005, Korea (21)	Prospective	32 SCC	RT: 45.6–56 Gy; Chemo: DDP/5-FU or DDP/Capecitabine	2.7 wk post-CRT	Post-CRT SUVmax≥4.0	N/A	Yes	N/A
Gillham, 2006, Ireland (22)	Prospective	32 (5 SCC)	RT: 44 Gy; Chemo: DDP/5-FU	After the first week of CRT	ΔSUVmax: 20%, ΔMTV: 20%	No	No	N/A
Levine, 2006, USA (23)	Prospective	64 (12 SCC)	RT: 50.4 Gy; Chemo: DDP/5-FU	4–6 wk post-CRT	ΔSUVmax: Quintile	N/A	Yes	N/A
Bruzzi, 2007, USA (24)	Retrospective	88 (13 SCC)	RT: 50.4 Gy; Chemo: various	post-CRT	SUVmax	N/A	No	N/A
Kim, 2007, Korea (25)	Prospective	62 SCC	RT: 45.6–46 Gy; Chemo: DDP, 5-FU	–	ΔSUVmax: 80%	N/A	Yes	Yes

Table 1 (*continued*)

Table 1 (*continued*)

Author, year, region (reference)	Nature of study	No. of patients	Treatment regime	PET timing	Metabolic parameters and cutoff	Correlation of PET with		
						Clinical response	Histopathology	Survival
Lordick, 2007, Germany (26)	Prospective/ MUNICON	119 AC	RT: no; Chemo: DDP/ folinic acid/5-FU/ PTX/L-OHP	2 wk after start of CRT	ΔSUV: 35%	No	No	Yes
Mamede, 2007, USA (27)	Retrospective	25 (3 SCC)	RT: 50.4 Gy; Chemo: various	3 wk post-CRT	SUVmax: 4.35, ΔSUVaverage: 32.3%	N/A	Yes	Yes
McLoughlin, 2008, USA (28)	Prospective	81 (24 SCC)	RT: 50.4 Gy; Chemo: various	–	ΔSUVmax: 50%	N/A	No	N/A
Smithers, 2008, Australia (29)	Retrospective	45 AC	RT: 45.6–46 Gy; Chemo: DDP/5-FU	3–6 wk post-CRT	ΔSUV, ΔTLR	N/A	No	No
Vallböhmer, 2009, Germany (30)	Prospective	119 (66 SCC)	RT: 36 Gy; Chemo: DDP/5-FU	2–3 wk post-CRT	SUVmax	N/A	No	No
Javeri, 2009, USA (31)	Retrospective	151 AC	RT: 45 or 50.4 Gy; Chemo: 5-FU	post-CRT	ΔSUVmax >52%	N/A	No	Yes
Roedl, 2008, USA (32)	Retrospective	51 AC	RT: 50.4 Gy; Chemo: DDP/5-FU	16.9 d post-CRT	ΔTLG >78%	N/A	Yes	Yes
Schmidt, 2009, Germany (33)	Prospective	55 (24 SCC)	RT: 36 Gy; Chemo: DDP/5-FU	3–4 wk post-CRT	ΔSUVmax, ΔSUVmean	N/A	No	No
Malik, 2010, Ireland (34)	Prospective	37 AC	RT: 40 Gy; Chemo: DDP/5-FU	2 wk after start of CRT	ΔSUVmax: 26.4%, 35.0%	N/A	No	No
Monjazeb, 2010, USA (35)	Retrospective	163 (122 AC, 41 SCC)	RT: 3D-CRT; Chemo: DDP/5-FU or others	post-CRT	SUV ≤3	No	N/A	Yes
Myslivecek, 2012, Czechia (36)	Retrospective	73 (49 SCC)	RT: 50 Gy; Chemo: DDP/5-FU	6 wk post-CRT	ΔSUVmax: 50%	No	No	No
van Heijl, 2011, The Netherlands (37)	Prospective	100 (26 SCC)	RT: 41.4 Gy; Chemo: CBP/PTX	14 d after start of CRT	ΔSUVmax: 0%, 10%, 20%, and 30%	No	Yes	N/A
zum Büschenfelde, 2011, Germany (38)	Prospective/ MUNICON II	56 AC	RT: 32 Gy; Chemo: DDP/folinic acid/5-FU	2 wk after start of CRT	ΔSUVmax <35%	N/A	No	Yes
Jayachandran, 2012, USA (39)	Retrospective	37 (10 SCC)	RT: 45–59.4 Gy; Chemo: various	32 d post-CRT	TGA: 2.5, MTV: 2.5, ΔSUVmax: 50%	N/A	Yes	Yes
Yen, 2012, Taiwan (40)	Retrospective	90 SCC	RT: 40 Gy; Chemo: various	post-CRT	–	Yes	Yes	N/A
Piessen, 2013, France (41)	Prospective	60 (31 SCC)	RT: 45 Gy; Chemo: 5-FU/DDP	4–6 wk post-CRT	SUVmax	N/A	No	No

Table 1 (*continued*)

Table 1 (*continued*)

Author, year, region (reference)	Nature of study	No. of patients	Treatment regime	PET timing	Metabolic parameters and cutoff	Correlation of PET with		
						Clinical response	Histopathology	Survival
Cuenca, 2013, France (42)	Prospective	72 (41 SCC)	RT: 40–66 Gy; Chemo: DDP/5-FU	4 wk after start of CRT	ΔSUVmax: 50%	Yes	N/A	Yes
Cheedella, 2013, USA (43)	Retrospective	284 (20 SCC)	RT: 45 or 50.4 Gy; Chemo: PTX/5-FU or DDP/5-FU	post-CRT	SUVmax	Yes	No	No
Park, 2013, Korea (44)	Retrospective	25 SCC	RT: 40 Gy; Chemo: DDP/5-FU	post-CRT	ΔSUVmax: 72.1%	N/A	Yes	No
Stiles, 2013, USA (45)	Retrospective	120 (38 SCC)	RT: 25–70 Gy; Chemo: DDP based or PTX based	post-CRT	ΔSUVmax: Quartile	N/A	Yes	Yes
Metser, 2014, Canada (46)	Retrospective	45	N/A	–	ΔSUL: 30%	N/A	No	Yes
Elliott, 2014, Ireland (47)	Retrospective	100 AC	RT: 40 Gy; Chemo: DDP/5-FU	2–4 wk post-CRT	ΔSUVmax	No	No	No
Stiekema, 2014, The Netherlands (48)	Retrospective	76 (14 SCC)	RT: 50 or 50.4 or 41.4 Gy; Chemo: DDP/5-FU or CBP/PTX	post-CRT	ΔSUVmax: 60%	N/A	No	N/A
Elimova, 2015, USA (49)	Prospective	31 (2 SCC)	RT: various; Chemo: L-OHP/5-FU or PTX/5-FU	12 d after the start of CRT and post-CRT	ΔSUVmax: 33%, ΔTLG: 51.6%	N/A	No	Yes
Yuan, 2016, Hong Kong (50)	Retrospective	52 SCC	RT: 40 Gy; Chemo: DDP/5-FU	post-CRT	SUVmax	No	Yes	No
Kim, 2015, Korea (51)	Retrospective	93 SCC	RT: 40 Gy; Chemo: DDP/5-FU	5–6 wk post-CRT	SUVmax: 4.95	N/A	No	N/A
Kukar, 2015, USA (52)	Retrospective	77 AC	RT: 50.4 Gy; Chemo: DDP/CPT-11 or Cap/L-OHP or PTX/CBP	post-CRT	ΔSUVmax: 45%	N/A	Yes	N/A
Kim, 2016, Korea (53)	Retrospective	53 AC	RT: 46 Gy; Chemo: 5-FU/DDP	4 wk after the start of CRT	ΔSUVmax >23.5%, ΔMTV >25.5%, ΔTLG >44.8%	N/A	Yes	Yes
Chang, 2016, USA (54)	Prospective	61 SCC	RT: 46 Gy; Chemo: 5-FU/DDP	After the start of CRT	ΔSUV max: 29.2%, ΔSUV mean: 26.1%, ΔMTV: 22.9%, ΔTLG: 48%	N/A	N/A	Yes
Hagen, 2017, The Netherlands (55)	Prospective	106 (19 SCC)	RT: 41.4 Gy; Chemo: CBP/PTX	2 wk after start of CRT	ΔSUVmax: 30%	N/A	N/A	No
Heneghan, 2016, Ireland (56)	Prospective	138 (35 SCC)	RT: 40 to 44 Gy; Chemo: CBP/PTX or 5-FU/DDP	4–6 wk post nCRT	SUVmax <4	N/A	No	N/A

Table 1 (*continued*)

Table 1 (*continued*)

Author, year, region (reference)	Nature of study	No. of patients	Treatment regime	PET timing	Metabolic parameters and cutoff	Correlation of PET with		
						Clinical response	Histopathology	Survival
Arnett, 2017, USA (57)	Retrospective	193 (23 SCC)	RT: 50.4 Gy; Chemo: various	5 wk post nCRT	SUVmax, SUVmean, SUR-blood pool, SUR-liver	N/A	No	No
Dewan, 2017, India (58)	Prospective	70 SCC	RT: 50.4 Gy; Chemo: DDP	≥6 wk post nCRT	ΔSUVmax: 72.32%	Yes	Yes	Yes
Hamai, 2016, Japan (59)	Retrospective	111 SCC	RT: 40 Gy; Chemo: 5-FU/DDP or 5-FU/DXM	5 wk post nCRT	ΔSUVmax: 70%	Yes	Yes	Yes
Makino, 2017, Japan (60)	Retrospective	130 SCC	RT: 40–60 Gy; Chemo: 5-FU/DDP	2–3 wk post-CRT	ΔSUVmax: 60%	N/A	Yes	Yes
Sasaki, 2017, Japan (61)	Retrospective	30 SCC	RT: 40 Gy; Chemo: 5-FU/DDP	3–4 wk post-CRT	ΔSUVmax: 56.6%	N/A	No	No
Motoyama, 2017, Japan (62)	Prospective	100 SCC	RT: 40 Gy; Chemo: 5-FU/DDP	3–4 wk post-CRT	SUVmax: 2.5	N/A	Yes	N/A
Tandberg, 2018, USA (63)	Prospective	26 (3 SCC)	RT: 45–50.4 Gy; Chemo: CBP/PTX	32.4 Gy	MTV: 2.5, TLG: 2.5, MTV: 40%, TLG: 40%	N/A	Yes	N/A
Kim, 2019, Korea (64)	Retrospective	21 SCC	RT: 54–63 Gy for dCRT, 37.8–44.1 Gy for nCRT; Chemo: 5-FU/DDP	11 d after start of CRT	ΔMTV: 1.14, ΔSUVmean: 35%	Yes	N/A	Yes
Fatima, 2019, Pakistan (65)	Prospective	34 (11 SCC)	N/A	–	SUVmax	Yes	Yes	N/A
Huang, 2017, Taiwan (66)	Prospective	114 SCC	RT: 42–66 Gy; Chemo: 5-FU/DDP based	–	ΔSUVmax: 71.6%, 50%, SUVmean: 2.4, MTV: 2.2, TLG: 4.99	N/A	N/A	Yes
Hammoudi, 2019, France (67)	Retrospective	116 (81 SCC)	RT: 40–66 Gy; Chemo: 5-FU based	2 wk after start of CRT	ΔSUVmax: 30%, 50%, 70%	Yes	Yes	Yes
Valkema, 2019, The Netherlands (68)	Prospective/ preSANO trial	129 (43 SCC)	RT: 41.4 Gy/23 Fx; Chemo: CBP/PTX	4–6 wk post-CRT	Δ%SULmax: 56.31%	N/A	Yes	N/A
Sánchez-Izquierdo, 2020, Spain (69)	Prospective	40 AEG	RT: no detail; Chemo: no detail	2 wk post-CRT	ΔSUVmax ≤45%	N/A	Yes	Yes

PET-CT, position emission tomography-computed tomography; nCRT, neoadjuvant chemoradiotherapy; SCC, squamous cell carcinoma; RT, radiation therapy; Chemo, chemotherapy; 5-FU, 5-fluorouracil; wk, week; CRT, chemoradiotherapy; SUV, standardized uptake value; DDP, cisplatin; TUR, tumor to liver uptake ratios; PTX, paclitaxel; CBP, carboplatin; N/A, not applicable; CPT-11, irinotecan; DOC, docetaxel; MTV, metabolic tumor volume; AC, adenocarcinoma; TLR, tumor/liver ratios; TLG, tumor lesion glycolysis; TGA, total glycolytic activity; SUL, SUV normalized by lean body mass; Cap, capecitabine; L-OHP, oxaliplatin; dCRT, definitive chemoradiotherapy; SUR, standard uptake ratio; AEG, adenocarcinoma of the esophagogastric junction.

Table 2 Studies on long-term predictive/prognostic value of survival in esophageal cancer dCRT

Author, year, region (reference)	Nature of study	No. of patients	Chemoradiotherapy regimen	PET timing	Metabolic parameters and cutoff	Correlations of PET with		
						LC	PFS	OS
Yang, 2011, China (70)	Retrospective	61 SCC	RT: 56–64 Gy; Chemo: 5-FU/DDP	4–5 wk after start of CRT	ΔSUVmean: 51%	N/A	Yes	Yes
Palie/Vera, 2013/2014, France (71,72)	Prospective/ RTEP3	57 SCC	RT: 50 Gy; Chemo: 5-FU/DDP	21 d after start of CRT	SUVmax, SUVmean, MTV, TLG	Yes	N/A	N/A
Li, 2015, China (73)	Retrospective	160 SCC	RT: 60 Gy; Chemo: DDP or 5-FU/DDP	PET1: prior to RT; PET2: 50 Gy; PET3: end of RT; PET4: 1 mo after RT	SUVmax, MTV, TLG	N/A	N/A	Yes
Chen, 2015, China (74)	Retrospective	34 SCC	RT: 60 Gy; Chemo: DDP or 5-FU/DDP or PTX/DDP	4 wk after start of CRT	ΔSUVmax: 60%, 75%	Yes	Yes	N/A

dCRT, definitive chemoradiotherapy; PET, positron emission tomography; LC, local control; PFS, progression-free survival; OS, overall survival; SCC, squamous cell carcinoma; RT, radiation therapy; Chemo, chemotherapy; 5-FU, 5 fluorouracil; DDP, cisplatin; wk, week; CRT, chemoradiotherapy; SUV, standardized uptake value; N/A, not applicable; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PTX, paclitaxel.

India (58), 1 from Pakistan (65), and 1 from Spain (69). *Table 2* summarizes the 5 articles the focused on identifying poor responders or nonresponders during definitive chemoradiation (70-74), 2 of which describe the same study (71,72). One single study describes adaptive radiotherapy based on the use of molecular PET imaging (75).

Neoadjuvant chemoradiotherapy

A total of 57 studies involving 4,823 patients assessed response to neoadjuvant chemoradiotherapy during or after planned trimodality treatment (*Table 1*). Of these, 27 reported a favorable value of FDG PET-CT in predicting pathological response. Treatment details of the studies were as follows: the radiation doses ranged from 25–59.4 Gy, with almost half of the studies (28/59) using 41.4–50.4 Gy; and chemotherapy regimens were predominantly based on cisplatin (DDP), 5-fluorouracil (5-FU), or paclitaxel (PTX), with 56% using doublet DDP/5-FU. Moreover, 48 studies evaluated quantitative PET for the primary tumor by using SUVmax, while 30 studies reported a percentage reduction of SUVmax (%SUVmax), with the median cutoff values varying from 10% to 70%, and more than one-third (11/30) of these reporting values of 50–60%. SUVmean was reported in 7 studies, and 10 studies focused on qualitative synthesis (MTV, TLG), evaluating metabolic complete response (mCR) for residual disease at the primary tumor. Finally, 2 studies investigated and validated a clinical parameter model for predicting pathologic response following EC neoadjuvant chemoradiation (38,59).

Definitive chemoradiotherapy

There were 4 studies comprising 312 patients, all describing definitive chemoradiotherapy for squamous cell carcinoma, 1 of which was prospective (70-74) and 3 of which were conducted in Asia. In this approach, radiation doses ranged from 50–66 Gy, with concurrent chemotherapy regimens being similar to the trimodality schedules described above. The timing of PETint after the start of CRT ranged from 21 days to 5 weeks. One study included 4 serial PETs (prior to radiation therapy at 50 Gy, on completion of radiation, and 1 month after) (73). PET parameters included qualitative, semiquantitative (SUVmax, SUVmean, SUVmax, ΔSUVmean), and quantitative (MTV, TLG) measures. Two of the studies reported a favorable role of PETint in predicting local control, and the other two reported favorably on its ability to predict survival. The Chinese study by Yang *et al.* suggested that a 51% decrease in FDG uptake during chemoradiation was a sensitive and accurate cutoff point for predicting progression-free survival (PFS) (70). Li *et al.* analyzed 160 patients with esophageal squamous cell carcinoma (ESCC) and concluded that sequential FDG PET-CT scanning is useful for predicting the overall survival of patients treated with chemoradiotherapy for ESCC (73). The prospective

French study of 57 patients indicated that a larger tumor volume and higher SUVmax/TLG were associated with poor outcome at 3 months, with a higher SUVmax values also predicting a poor outcome at 1 year (71,72). Chen *et al.* used fluorothymidine (FLT) and showed that early interim 3'-Deoxy-3'-[18F]-FLT PET-CT was a significant predictor of 2-year PFS and locoregional recurrence (LR) and was more correlated with early responses and late outcomes than was interim FDG PET-CT (74).

Adaptive radiotherapy

One prospective study of 10 patients reported the role of PET for adaptive radiotherapy, which incorporates changes in anatomy and/or deviations in planned delivered dose due to deviations in patient setup or variability machine delivery to estimate the actual delivered dose to a patient as the treatment progresses (76). The authors compared treatment plan simulations with combinations of 50 or 66 Gy, with the volumes defined in FDG PET-CT images prior and during radiotherapy. When the total dose was increased to the target volume, planning based on the MTV of the initial FDG PET-CT resulted in significantly lower doses to the organs at risk (OARs), including the spinal cord and the lungs.

Discussion

The role of interim PET-CT during multimodality treatment of LAEC has considerable importance, and yet, to date, most of the related studies have been small and retrospective in design. While some studies reported positive results of PETint in predicting local control or survival, there are many studies that did not reach this conclusion. Differences in PET parameters, which themselves are hard to standardize given the radiopharmaceutical nature of the test, variation in time points, and intrinsic prognostic factors, such as tumor histology and patient ethnicity, contribute to the heterogeneity of the studies and impact the interpretation of results. Other specific issues are discussed below.

Identification of microscopic residual disease

Across all cancers, the challenge of detecting microscopic disease, in this case residual foci during or following intensive treatment, remains a challenge that has yet to be overcome. Predicting complete pathological response (pCR) potentially alleviates need for inclusion of surgery, which would be a major advance for patients in terms of morbidity, mortality, and quality of life (75,77). This "organ preservation" approach is more advanced in other gastrointestinal cancers, particularly rectal cancer, and typically uses a combination of clinical and diagnostic imaging to determine to confirm a lack microscopic residual cancer. The smallest amount of residual disease should ideally be detected, although the recent demonstration of the efficacy of adjuvant therapy with checkpoint inhibitors may ultimately also facilitate this. A more nuanced understanding concerning which patients benefit from immunotherapy is anticipated. The role of PETint in combination with other assessments including serial biopsies and circulating tumor DNA (ctDNA) is a field with considerable potential (78-80).

Qualitative versus quantitative PET-CT evaluation

Different methods have been proposed to evaluate the FDG PET-CT images in EC, including visual assessment (qualitative) and semiquantitative (SUV) and quantitative analyses (81). However, the best method for balancing the accuracy, practicality, and clinical applicability in PET has not been established. PET Response Criteria in Solid Tumors (PERCIST) has been used in practice and clinical trials in EC and some other types of solid tumors (82). The standardization of acquisition and reconstruction data remain key limitations, while patient preparation and the calibration of the PET-CT scanner are also relevant. The intrinsic basal variability of SUVmax may also hamper the early treatment response prediction in patients with EC. No ΔSUVmax cutoff value has been established for defining subgroups of prognoses, and there is a need to standardize this for clinical trials as well as routine practice. Future studies are warranted to determine the ΔSUVmax cutoff values that are useful for the early identification of patients with poor treatment outcomes.

Timing

The optimal timing for FDG PET-CTint has yet to be determined for EC. For esophageal patients with favorable early treatment response, a deintensification of the therapy to maximize the therapeutic ratio may be beneficial (83). Meanwhile, for EC, patients showing no response to treatment could benefit from a timely modification of the treatment strategy or an intensification of treatment. It is

often not appreciated that radiation-induced inflammation of the peritumoral mucosal tissues can affect the interpretation of images in both the early and late phases of chemoradiation (12). The likelihood of obtaining false-positive results may increase due to radiation-induced inflammation as the radiation dose increases. A 2-week interval is one reported timing of FDG-PETint, while the consistency of a 2-week interval for the evaluation of treatment response is not supported by the literature. In this time frame, the actual delivered radiation dose may be around 20–30 Gy. However, PETint at a radiation dose >30 Gy may be more suitable for producing a decrease in FDG uptake that can be correlated with clinical outcome (83). Waiting a total of 8–16 weeks after completion of chemoradiation may be useful for assessing treatment response and providing prognostic information in EC, but in trimodality schedules, surgery is usually performed well before this (84). Designing a study to optimize the timing of PETint would be challenging but highly valued.

Biologically adaptive radiotherapy

The implementation of adaptive radiotherapy schemes presents several challenges, including devising an adequate delineation method and a means for deformable image registration, etc. Adaptive radiotherapy can generally mean 3 meanings: (I) treatment plan modification during a course of radiotherapy to account for temporal changes in anatomy, such as, internal motion, tumor shrinkage, and weight loss); (II) adjustment of radiation dose delivery based on early tumor response, such as boosting the residual imaged tumor; and (III) treatment strategy adaptation based on early tumor response, such as shifting chemotherapy regimens and adding systematic therapies or sensitizers. Molecular imaging integrated into the anatomic information is one of the most promising approaches in adaptive radiotherapy. In this method, radiosensitivity differences within the tumor can be identified, and a heterogeneous dose distribution can be achieved to allow for better local control.

Limitations

There are some limitations to this review that should be noted. First, the studies reviewed often reported conflicting findings, and thus a definitive conclusion cannot be drawn. Second, the heterogeneity of the studies may be confusing and inconclusive. Third, evidence concerning many issues of PETint, such as the time and parameters, was lacking. More well-designed clinical studies are warranted to investigate the more important clinical questions. Fourth, the current review focused on studies from the past 20 years (January 2001 to January 2022), and recent findings that could provide novel insights might have been missed.

Conclusions

This scoping review found PETint to have prognostic value in a variety of situations. However, there is a need to improve its accuracy, which will likely be achieved through a greater standardization of measurements and reporting within the testing, in addition to combination with other promising measures of response and residual disease.

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Footnote

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