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The role of interventional radiotherapy (brachytherapy) in stage I esophageal cancer: an AIRO (Italian Association of Radiotherapy and Clinical Oncology) systematic review

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Abstract. – OBJECTIVE: This review aimed at examining efficacy of interventional radiotherapy (brachytherapy-IRT) alone or combined with external beam radiotherapy (EBRT) in stage I esophageal cancer as exclusive treatment.

MATERIALS AND METHODS: A systematic research using PubMed, Scopus, and Cochrane library was performed. ClinicalTrials.gov was searched for ongoing or recently completed trials, and PROSPERO was searched for ongoing or recently completed systematic reviews. We analyzed only clinical study as full-text publication, reporting on patients with stage I esophageal cancer treated with IRT alone or in combination with other treatments (e.g., EBRT). Conference paper, survey, letter, editorial, book chapter, and review were excluded. Patients who underwent previous surgery were excluded. Time restriction (1990-2018) was applied for years of the publication.

RESULTS: Twelve studies have been selected. The number of evaluated patients was 514; the median age was 69 years. In the IRT group, the median: local control (LC) was 77% (range 63%-100%), disease-free survival (DFS) was 68.4% (range 49%-86.3%), the overall survival (OS) was 60% (range 31%-84%), the cancer specific survival (CSS) was 80% (range 55-100%), and grade 3-4 toxicity range was 0%-26%.

CONCLUSIONS: IRT alone or combined to EBRT is an effective and safe treatment option for patients with stage I esophageal cancer. Definitive radiation therapy could be an alternative to surgery in patients with superficial cancer.

Key Words:
Interventional radiotherapy, Brachytherapy, Esophageal cancer.

Introduction

Advances in endoscopic techniques have led to an increase in early diagnoses of esophageal cancer: it is nowadays possible to observe tumors located within the mucosa or submucosa only[1-3]. The distinction among the aforementioned layers is relevant as it modifies the indication of surgery. There is a different risk of lymph nodes metastases (0-6%) in the presence of mucosal involvement or

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in case the submucosa is also involved (38-53%)[4-9]. Usually, endoscopic resection is reserved for patients with involvement of the lamina propria mucosa, while esophagectomy, with lymph nodes sampling, is indicated for patients with tumors invading the muscolaris mucosa[4-9]. Despite the improvements of surgical techniques (e.g.: robotic esophagectomy), some complications are still observed[10-12]. Eligibility for surgery depends, not only on the disease's stage, but also on patient's performance status, age, comorbidities and possibility to preserve the quality of life. Hence, radiotherapy (RT) could replace surgery as a curative treatment for patients with stage I disease since its efficacy is comparable with surgery[13-15]. Moreover, interventional radiotherapy (IRT) also indicated as brachytherapy (BT) may play an important role in this scenario because of its ability to provide an excellent dose distribution, short treatment time and organ at risk preservation.

According to international guidelines, good candidates for IRT include patients with tumors <10 cm in length and confined to the esophagus wall, those with thoracic locations, and patients without regional node involvement[16].

However, there is still no standardization among the different centers in terms of IRT technique used and prescribed dose. Thus, the role of IRT on local control (LC) and overall survival (OS) in patients with early esophagus cancer is still controversial[17-22].

The aim of this review is to examine the efficacy of IRT after external beam radiotherapy (EBRT) in stage I esophagus cancer in terms of LC, disease-free survival (DFS), cancer-specific survival (CSS), OS and safety.

The project was conceived and developed within the frame of the Brachytherapy study group, Interventional Radiotherapy, and intra-operative radiotherapy (IORT) of the Italian Association of Radiotherapy and Clinical Oncology (AIRO).

Material and Methods

A systematic research using PubMed, Scopus, and Cochrane library was performed to identify full articles evaluating the efficacy of IRT in patients with stage I esophagus cancer. ClinicalTrials.gov was searched for ongoing or recently completed trials, and PROSPERO was searched for ongoing or recently completed systematic reviews. The studies were identified using the following medical subject headings (MeSH) and keywords including: "esophageal neoplasms", "brachytherapy", "intraluminal radiotherapy". The search was restricted to the English language. The Medline search strategy was: ("Brachytherapy" [Mesh] OR "Brachytherapy" [All fields]) AND ("Esophageal Neoplasms" [Mesh] OR "Esophageal Cancer" [All fields]). To avoid missing relevant studies we chose this strategy with high sensitivity but low specificity.

We analyzed only clinical study as full-text publication, reporting on patients with stage I esophagus cancer treated with IRT alone or in combination with other treatments (e.g., external beam radiation therapy). Conference papers, surveys, letters, editorials, book chapters, and reviews were excluded. Patients who underwent previous treatment were excluded. Regarding the years of publication, time restriction (1990-2018) was considered.

Three independent authors expert in esophagus cancer with respect to IRT (VL – Rome, BF – Rome) and EBRT (FC – Rome) screened citations in titles and abstracts to identify appropriate papers. In addition, two radiation oncologists of another institution performed an independent check of the data (FF – Brescia, DT – Brescia). Eligible citations were retrieved for full-text review. Uncertainties about their inclusion in the review were considered by a multicenter expert team from 4 different institutions and involved in the AIRO Interventional Radiotherapy study group (VDS – Rome, VF – Rionero in Vulture, CV – Trieste, AV – Milan). Finally, a committee composed by the Chair of the "Brachytherapy, Interventional Radiotherapy and IORT Study Group" (LT), a member of AIRO committee expert in Gastroenteric cancer (MAG), two members of the scientific commission of AIRO expert in Gastroenteric cancer (DG, PF), Chair of the scientific commission of AIRO (RC) performed a definitive check and the approval of the review.

The primary outcome was the LC after IRT while the secondary outcomes included: DFS, CSS, OS and the rate of adverse events rate.

A summary table was created, including sample size, median age, LC, DFS, CSS, OS and Toxicity.

Results

The literature search allowed us to retrieve 429 articles. After exclusion of papers (based on abstracts) and after exclusion of conference pa-

pers, surveys, letters, editorials, book chapters, reviews, and papers not using the English language, 17 papers were included. Among these, 5 articles were excluded because of insufficient data, leaving 12 studies assessing the clinical efficacy of IRT in DFS and LC, as reported in Figure 1.

All studies were retrospective and monocentric[15,22-32]. In accordance with the selection criteria, only data from the IRT and EBRT treatment arms were extracted and considered for the analyses. The global number of evaluated patients was 514, and the median age was 69 years. The median LC was 77% (range 63-100%), DFS was 68.4% (range 49-86.3%), the OS was 60% (range 31-84%), the CSS was 80% (range 55-100%), and the grade 3-4 toxicity range was 0%-26%.

Table I lists the characteristics of the included studies.

Discussion

The present systematic review of 12 studies showed that IRT, in combination with EBRT in early esophagus cancer patients, is comparable in terms of outcome to surgery. Although radiotherapy has shown favourable outcomes for

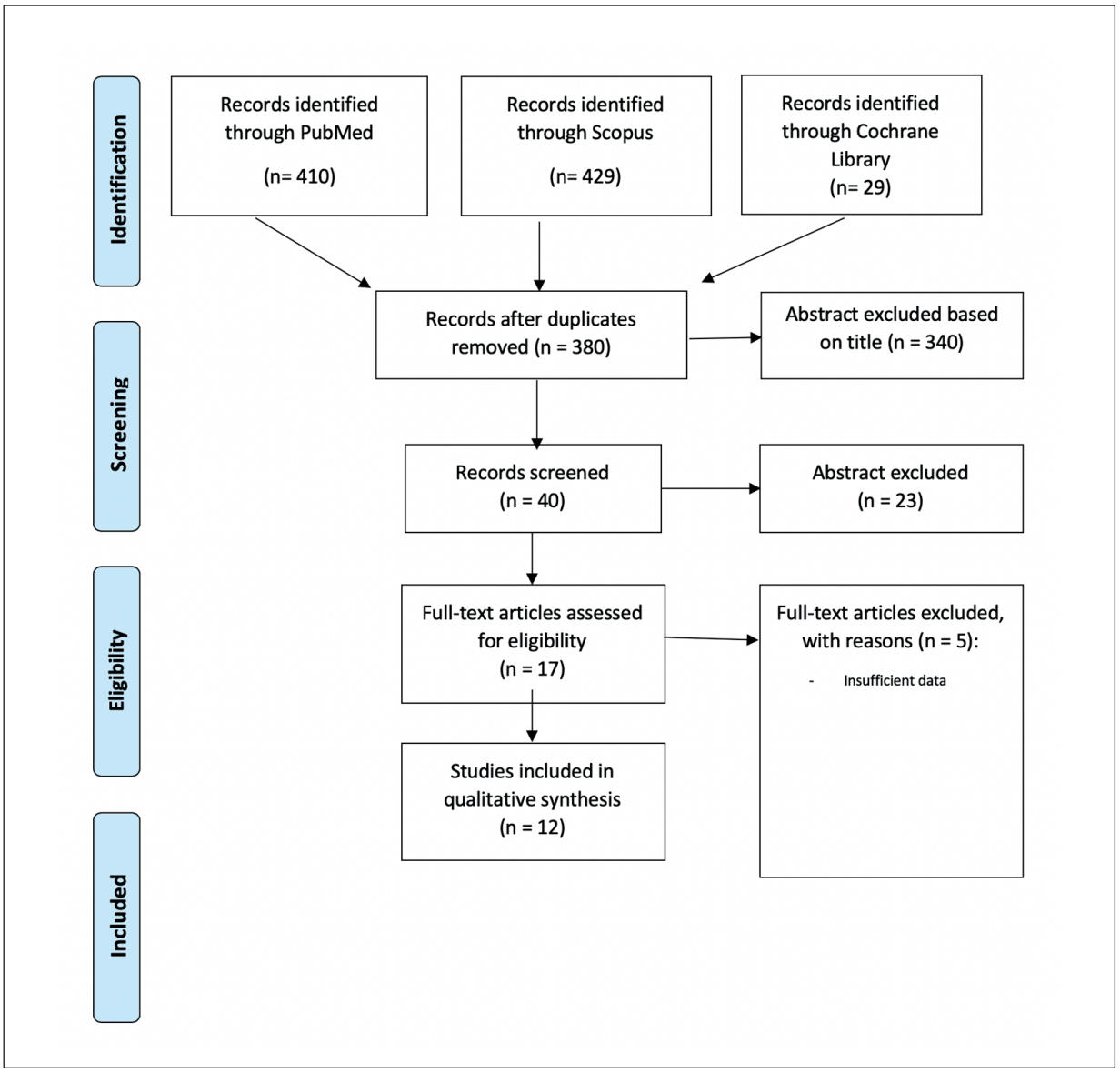

Figure 1. PRISMA Flow-chart for outcomes and toxicity.

Table I. Characteristics of the included studies.

Author	Period	Size, n	Median age, years	IRT (Gy)	EBRT (Gy)	R	LC	DFS	CSS	OS	TOX
Ishikawa et al[23]	1986-2003	36	70 (50-86)	**MEC** LDR: 5Gy × 2 HDR: 3Gy × 3 **SMEC** LDR: 5Gy × 2 HDR: 3Gy × 3	**MEC** 56 (50-60) 56 (52-60) **SMEC** 60 (54–62) 60 (54-64)	CR: 88% PR: 12%	MEC: 100% SMEC: 72%	79.5%	**MEC** At 5 y 100% **SMEC** At 5 y 74.8%	At 5 y 58.7%	3%
Ishikawa et al[24]	1991-2005	36	72 (49-86)	LDR: 5Gy × 2 HDR: 3Gy × 3	60 (48-64)	CR: 88% PR:12%	EBRT: 66% IRT:81%	EBRT: 28% EBRT+ IRT:59%	**EBRT** at 5 y 62% **EBRT+IRT** at 5 y 86%	EBRT:32% EBRT+ IRT: 67%	6%
Tamaki et al[25]	1991-2007	54	70 (49-86)	LDR: 5Gy × 2 HDR: 3Gy × 3	**MEC** 56 (56-60) **SMEC** 60 (54-64)		**LDR:** 81.5 ± 19.1 **HDR:** 72.9 ± 21.3		**LDR:** 80.8 ± 19.6 **HDR:** 81.5 ± 9.2	**LDR:** 64.7 ± 22.7 **HDR:** 53.6 ± 20.1	**LDR:** 26% **HDR:** 9%
Sai et al[26]	1985-2002	27	69 (53-85)	**HDR** 7-10 Gy/2 Fr 11-12 Gy/3 Fr	50-55 56-59 60-70			At 5 y: 68.4%	At 5 y 80%	At 5 y 58.9%	2.9%
Murakami et al[27]	1992-2002	87	70 (43-89)	**HDR alone** 35 Gy/14 fr 36 Gy/18 fr 30 Gy/15 fr 25 Gy/5 fr **HDR boost** 10 Gy/ 4 fr 10 Gy/5 fr 10 Gy/2 fr 7.5 Gy/3 fr 15 Gy/3 fr	**MEC** 54 (50-58) **SMEC** 60 (54-61)	**MEC** CR: 98% PR: 2% **SMEC** CR: 98% PR: 2%		**MEC** 75% SMEC 49%	**MEC** 97% at 5 SMEC 55% at 5 y	**MEC** 84% **SMEC** 31%	7%
Ishikawa et al[28]	1987-2003	20	70 (50-85)	**LDR:** 5Gy × 2 **HDR**: 3Gy × 3	**MEC** 56 (50-60) **SMEC** 60 (54–64)	**CR**: 95% **PR:** 5%	**MEC** 100% **SMEC** 71.4%	86.3%	**MEC** 100% at 5 y **SMEC** 75.1% at 5 y	60.9%	0%
Yamada et al[29]	1992-2003	63	67 (48-83)	**HDR** 10 Gy/2 fr 12 Gy/3 fr	59.4 (55-66)		**MEC** 83% **SMEC**	**MEC** 84.4% at 5 y **SMEC**	**MEC** 85.2% at 5 y SMEC	66.4%	6.3%

Table continued

Table I *(Continued)*. Characteristics of the included studies.

Author	Period	Size, n	Median age, years	IRT (Gy)	EBRT (Gy)	R	LC	DFS	CSS	OS	TOX
Shioyama et al[30]	1992-2001	12	65 (46-81)	**LDR** 18 (12-21) **HDR** 13.5 (10-20)	60.6 (50.4-70)	**CR**: 93% **PR**: 7%	66%		77% at 5 y	62% at 5 y	6.8%
Pasquier et al[31]	1992-1999	66	60 (41-85)	7 ±3.98	60 (±4.83)	**CR:** 98% **PR:** 2%	63%	54.6%	76.9% at 5 y	35.6% at 5y	9%
Nemoto et al[32]	1987-1998	92	68 (43-89)	**LDR** 9 (3-31) **HDR** 11 (9-36) **HDR alone** 34 (25-36)	65 (54-84)		MEC 88% SMEC 77%		**MEC** 85% at 5 y **SMEC** 64% at 5 y	**MEC** 72% at 5 y **SMEC** 42% at 5 y	5.4%
Nishimura et al[15]	1985-1996	21	67 (51-85)	HDR 4/2-3 fr	60-69	CR:100%	85%		100%		9.5%
Okawa et al[33]	1981-1990	105	70 (50-88)	5-36	40-84		EBRT: 77.3% IRT: 90.2%	EBRT: 70.1 EBRT+IRT: 72%	**MEC** 100 at 5 y **SMEC** 68.5% at 5 y	38.7% at 5-y	EBRT: 6.9% EBRT+ IRT: 25.5%

Abbreviation: IRT: interventional radiotherapy; EBRT: external beam radiotherapy; Gy: gray; MEC: mucosal esophageal cancer; SMEC, submucosal esophageal cancer; DFS: disease free survival; LC: local control; OS: overall survival; CSS: cancer specific survival; TOX: toxicity; R: response to treatment; CR: complete remission; PR: partial remission; fr: fractions; y: years; HDR: high-dose rate; LDR: low-dose rate.

early esophageal cancer, the treatment has not been standardized according to the published reports[13,15,33,34].

Surgical resection is the primary treatment for stage I esophagus cancer with a 5-year OS rate of 100% for cases with mucosal involvement and 65-90% for patients with submucosal cancer[4,34,35]. The present review showed a median 5-year OS rate of 60% (range 31%-84%). The 5-year OS rate for presentation limited to mucosal involvement only is 84%[27]. Therefore, a comparison of treatment methods should be carried out separately for mucosal and submucosal cancers, because the depth of invasion is one of the most important prognostic factors for the choice of the treatment[36-40]. The discrepancy in 5-years OS between surgery and radiotherapy could be due to patient's features.

In fact, patients who underwent exclusive radiotherapy for early esophageal cancer usually presented a higher rate of comorbidities compared to those who underwent surgery, such as cardiac or pulmonary disease, which may explain the reduction of OS rates in the non-surgical group. Probably, if radiotherapy were used as an exclusive treatment in early esophagus cancer in patients without several comorbidities, the 5-years OS rate might be improved. To endorse this consideration, the present review has shown that median 5-year CSS rate was 80% (range 55-100%). These values are better than median 5-years OS and are comparable to those obtained with surgery.

A particularly controversial issue is whether the use of IRT improves outcomes of early esophagus cancer patients. IRT may be characterized by certain level of variability due to institutional-based approaches, different dose fractionation schedules and equipment availability, potentially limiting to define the effect of the IRT after EBRT. In the present review, only 5 studies reported an improvement of LC and CSS[15,23,24,28,33]. Okawa treated with EBRT alone 58 (55%) patients and both EBRT and IRT 47 patients (45%) with stage I esophagus cancer. The authors showed that LC rate in patients treated with radiation therapy was excellent, especially in the group treated with EBRT and IRT (EBRT: 77.3% *vs.* EBRT+IRT: 90.2%)[33]. Nishimura and Ishikawa demonstrated that both LC and CSS after EBRT+IRT were superior to those after EBRT alone[15,23,24,28]. On the other hand, 7 out of 12 papers showed that delivering IRT after EBRT doesn't improve LC and CSS[25-27,29-32]. The retrospective setting of the evaluated papers probably limits the strength of the evidence: new prospective trials will hopefully provide more clear data. The risk to develop high toxicity is correlated to IRT dose per fraction that should not exceed 5Gy, particularly to prevent esophageal ulcers[32-36]. The present review reported an acceptable G3-G4 late toxicity rate (range 0-26%).

Despite these positive results, IRT is not routinely considered as a treatment option in patients with early-stage esophageal cancer. Suntharalingam et al[37] reported that IRT was implemented in only 6% of cases and two recent surveys confirmed that 17.5% of the Italian centers considered it for the treatment of esophageal cancer[38,39]. Probably the lack of experience, the inadequate educational level in this field and the complexity of such treatment, that requires a multidisciplinary and multi-professional team, do not permit the widespread use of IRT in clinical routine[40]. Having regard to the rarity of this disease, discussion of clinical cases in expert multidisciplinary team may provide more homogeneous treatment approaches and improvement of clinical outcomes[41-48]. The presented results also emphasize the need to combine analysis of treatment results from different centres in order to create predictive models to define a "personalized medicine"[49-52].

Conclusions

We provided support that EBRT+IRT is an effective and safe treatment option for patients with stage I esophagus cancer. Definitive radiation therapy could be an alternative to surgery in patients with superficial cancer. Further randomized controlled studies should investigate the optimal radiation dose and number of fractions to obtain the highest outcomes rates and the lowest risk of severe adverse events.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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