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Radiochemotherapy in the Management of Gastroesophageal Junction Tumours: Basic Evidences in the Neoadjuvant Setting

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Abstract

In recent years the incidence of gastroesophageal junction (GEJ) tumors has been rapidly increasing. Many trials have investigated the role of preoperative radiochemotherapy for this specific subgroup. In past, GEJ tumors were sometimes considered either esophageal or gastric cancer, due to their anatomical location. Purpose of this paper is to elucidate the benefit of radiotherapy in combination with concurrent chemotherapy in neoadjuvant setting, reviewing the literature by the point of view of the recent classification provided for GEJ tumors.

Keywords: Radiochemotherapy; GEJ tumors; Gastric cancer

Introduction

Gastroesophageal cancers (including oesophageal, gastric and gastroesophageal junction lesions) are worldwide a leading cause of death being relatively rare but highly aggressive [1]. Frequency of the distal stomach cancer decreased, while the incidence of cancer of the cardia and gastroesophageal junction (GEJ) has been rapidly rising [2,3]. The GEJ anatomically separates the lower oesophagus from the proximal part of the stomach, in the area where the squamous epithelium of oesophagus changes into the columnar epithelium of gastric cardia [4]. In developed countries, the incidence of gastric cancer originating from the cardia follows the distribution of oesophageal cancer [5,6], suggesting similar behaviours.

Adenocarcinomas of the GEJ represent around 90% of all the GEJ cancers [7]. In general adenocarcinomas are considered at lower level of radiosensitivity than squamous cell carcinomas, but there are still no clear evidences on this issue for the specific subset of GEJ tumours.

In general, caucasian, male and over 40 years old patients (pts) are the most affected subgroup. The predominant risk factors are: gastroesophageal reflux disease (GERD), Barrett's oesophagus and obesity, followed by tobacco and alcohol abuse [7,8].

Even though the modern surgical techniques gained better results over last decades, outcomes after resection are still poor, ranging by 20-30% of survival at 5 years [9]. The integration of pre- or peri-operative multimodal approaches, as radiotherapy (RT) and chemotherapy (CT) (eventually combined), seems promising to further improve clinical outcome for such presentations.

Purpose of this review is to discuss the basic evidences of neoadjuvant treatment involving radio chemotherapy (RTCT), from the new point of view of the recent classification of GEJ tumours to evaluate the efficacy of such treatment in the frame of multimodal integrated therapies.

Classification and Staging of GEJ

One of the main issues about GEJ is the classification: in past, GEJ was alternatively considered a gastric or oesophageal cancer due to their anatomical location at the boundary of these two primary sites [10]. A fundamental classification was proposed by Siewert and colleagues: three types of lesions were defined according to the localization of the lesion's epicentre and detailed on the base of the range of distance from the GEJ [11]. The actual 3 Siewert types of GEJ tumours are summarized in Table 1.

Recently the American Joint Committee on Cancer (AJCC) changed the staging system for GEJ to harmonize some staging aspects for oesophageal and gastric cancer [12]. The same changes were adopted by the International Union Against Cancer (UICC) TNM Classification [13]. In the 7th classification, GEJ tumours (i.e. the Siewert type I-II-III) are grouped as a subsite of oesophageal cancer, which epicenter is in the GEJ, or in the distal oesophagus, or as well within the proximal 5 cm of the stomach (cardia) if extending into the GEJ (and distal oesophagus). On the base of the new classification, the three Siewert types together belong to oesophagus. In particular, the Siewert type III lesion in not considered a subsite of gastric cancer any more (unless primary originating within the first 5 cm of stomach but not infiltrating the gastroesophageal junction and oesophagus).

While the three Siewert types are almost equally distributed in Western countries, in the Eastern ones a much lower proportion of type I respect to the others [14].

For what concern the nodal staging, that is now defined by the number of pathologically positive nodes rather than the location of the involved stations since it better correlates with the prognosis [12]. The actual classification has some shortcomings in terms of clarity of interpretation and is still object of debate [1].

Clinical Management

Surgery is a major component of treatment for resectable disease. Radical surgery is the most effective treatment modality, with the aim of

Siewert Type	Epicenter of the lesion
I	Within 1 to 5 cm above the anatomic GEJ
II	Within 1 cm above and 2 cm below the GEJ (i.e. true carcinoma of the cardia)
III	Between 2 to 5 cm below the GEJ, infiltrating GEJ and oesophagus from below (subcardial carcinoma)

Table 1: Siewert's classification for adenocarcinomas of GEJ.

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the en-bloc removal of primary tumour and lymphatic nodes, obtaining microscopically negative resection margins (R0) [15]. In large historical surgical series, survival was strongly affected by the accomplishment of R0 resection: among 1602 pts, Siewert reported a 5 years survival rate of 43.2% vs. 11.1% for R0 and positive margins, respectively (p<0.0001) [16]. Surgery alone is nowadays mostly confined to the treatment of early localized presentations [1]. The efficacy of neoadjuvant integrated treatments has been widely investigated over last decades. A recently published meta-analysis from 17 randomized trials including neoadjuvant radiotherapy (RT), chemotherapy (CT) and surgery for oesophageal carcinoma, strongly supported the adoption of integrated modality [17]. Selected trials included both neoadjuvant chemotherapy and radiotherapy; the latter, in the selected trial has been administered either concurrently with chemosensibilization (i.e. radiochemotherapy –RTCT-) or subsequently to CT (in the older studies included). Results addressed a clear benefit from both RTCT (p<0.0001) and CT (p=0.005) over surgery alone, and a slightly non-significant trend favouring RTCT respect to CT (p=0.07). These results were similar but more evident for the subgroup of adenocarcinomas, when separately analysed.

International Guidelines currently still don't completely agree on the standard treatment approach even if provide similar suggestion for the preferable management options for adenocarcinoma of the oesophagus (that nowadays the GEJ tumours belong to). The National Comprehensive Cancer Network (NCCN) recommend surgery alone for the very early presentations (i.e. Tis, T1a,T1bN0), and preoperative RTCT for all the others [1]. The National Cancer Institute (NCI) in its Physician Data Query (PDQ) suggests preoperative RTCT for presentation from Stage I to IV (non-metastatic) [18]. The European Society for Medical Oncology (ESMO) indicates surgery for early presentations, perioperative chemotherapy for the localized disease, or alternatively preoperative RTCT. Preoperative RTCT and perioperative CT are recommended for locally advanced disease [19].

Randomized trials of Radiochemotherapy versus Surgery

The landmark study in the literature of eosophageal cancer published by Walsh et al. in 1996, analysed a population affected by gastric cardiac lesion (i.e. Siewert II-III), or sited in the middle and lower third of oesophagus (the latter is considerable at least in part as a Siewert I, depending on the distance from the junction, data not reported in detail by authors) [20]. Between 1990 and 1995, 113 pts were enrolled: all affected by adenocarcinoma. The rate of pts affected by lesions of the middle third of the oesophagus was 14.1%, the remaining 85.9% of enrolled pts are mostly considerable GEJ in the modern classification. Pts in the experimental arm received 2 courses of CT (with 5-Fu and CDDP) in weeks 1 and 6 concurrently to a dose of 40 Gy (with 2.7 Gy per fraction in 15 fractions over 3 weeks), starting which delivery with CT administration. Of the 52 pts who underwent surgery from the chemoradiation arm, 13 (25%) had pathological complete response (pCR). Median survival of pts assigned to multimodal therapy was 16 months, and 11 month for pts of the surgery-only arm (p=0.01). The one, two and three year survival rates were 52%, 37%, 32% in the RTCT arm, and 44%, 26% and 6% in the surgery-only one, respectively (p=0.01).

Urba et al. published in 2001a randomised trial on preoperative RTCT versus surgery only [21] on 100 pts with oesophageal tumour from 1989 to 1994. The 92% of pts enrolled in both arms had middle or lower third lesion. The 75% of all pts had adenocarcinoma (only 24% of squamous cell cacinoma). Pts in the RTCT arm received a total dose of 45 Gy (1.5 Gy per fraction, two fraction per day, over 21 days), concurrently with a CT schema including 5-FU, CDDP and vimblastine. In the surgery-only arm 50/50 pts underwent surgery, and 45/50 (90%) had a gross total resection; in the RTCT arm 45/47 (95.7%) had a gross total resection. In the experimental arm 28% had a pCR. At median follow-up of 8.2 years there wasn't a significant survival benefit in the RTCT arm: the median survival and 3year survival for surgery and RTCT arms were 17.6 vs. 16.9 mth, and 16% vs. 30% (p=0.15), respectively. Analysing survival by pathological response, a clear significant benefit was found: the reported median survival and 3 years survival rate for the pCR group versus the non-pCR were 49.7 vs. 12 mth, and 64% vs. 19% respectively.

Later, a meta-analysis from Fiorica et al. in 2004, included 6 important trials of RTCT versus surgery alone [22]. This meta-analysis showed a significant survival benefit of neoadjuvant RTCT over surgery alone, but also highlighted a significant risk for postoperative mortality. The reported survival benefit was still not very strong in itself, since it was lost for the exclusion from the statistical evaluation of either the study from Walsh, of the one from Urba (mentioned above). Also the suspect for the toxic profile of neoadjuvant RTCT was mainly due to contribution of a trial from Bosset et al., that trial adopted a non-conventional RT dose and fractionation, questioned also from its Authors when published, and no longer used in the following experiences [23].

In 2005 Burmeister et al. published a paper on 256 pts affected by oesophageal tumour randomized (between 1994 and 2000) to either RTCT delivering a dose of 35 Gy (in 15 fraction of 2.4 Gy over 3 weeks) with concurrent 5-FU and CDDP, or surgery alone [24]. Pts had lesions sited in the proximal or middle oesophagus for 23% in the RTCT arm and for 19% in the surgery alone one. Distal oesophageal lesions accounted for 77% in the RTCT arm and for 81% in the surgery alone one. Adenocarcinomas were approximately 60% in both arms. There was no significant benefit for progression free and overall survival in the RTCT arm respect to the control one, even though a small trend favouring RTCT was reported. Interestingly, in the experimental arm a significantly higher R0 resection rate was reported (80% vs. 59%; p=0.0002), and lower rate of pathologically positive lymph-nodes (43% vs. 67%; p=0.003). Pts in the RTCT arm reported 16% rate of pCR.

Tepper et al. published a trial with the similar basic approach in 2008 [25]. Between 1997 and 2000 they enrolled pts with oesophageal or GEJ tumour (including both squamous and adenocarcinomas) Lesions of the thoracic oesophagus, and/or with less than 2 cm distal spread into the cardia were included. The 75% of the 56 enrolled pts had adenocarcinoma (thus orienting for a major presence of GEJ lesions). The study was prematurely closed for poor accrual (respect to the 475 planned pts). The experimental arm (30 pts) received RTCT with a total dose of 50.4 Gy (conventional fractions over 5.5 weeks; 45 Gy in extended field+5.4 Gy as boost) plus concomitant 5-FU and CDDP. Pathological data were available only for 25/30 pts in the RTCT arm: pCR was reported for 10/25 (40%). But this data should be interpreted with caution for the mentioned reasons. At a median fup of 6 yearsthere was a significant survival benefit for RTCT over surgery alone. Median survival was 4.48 vs. 1.79 mth and 5 years survival was 39% vs. 16% for RTCT and surgery alone (p=0.002), respectively.

In 2012 van Hagen et al. published the results of the "Chemoradiotherapy for oesophageal cancer followed by surgery study" (CROSS) group: this study has been advocated as reference for the gold standard of the modern treatment of oesophageal cancer [26]. Between 2004 and 2008, 366 pts were enrolled for this randomized

trial to receive either surgery alone or a RTCT preoperative treatment consisting of RT up to a dose of 41.2 Gy (conventional fractionation, over 5 weeks) plus weekly Carboplatin and Paclitaxel. Pts were eligible if affected by oesophageal carcinoma in general, but the vast majority of them were affected by GEJ lesions: over the 80% of the patient in both arms had the primary lesion sited in the distal third or at the GEJ, and the 75% of the enrolled pts presented an adenocarcinoma. Tolerance to RTCT was good: 91% of pts in experimental arm received the full treatment regimen; the highest Grade ≥ 3 toxicities reported were Anorexia (5%) and Leukopenia (6%). In the RTCT group, 94% of pts underwent surgery versus 99% in the control arm (p=0.01); seven pts in RTCT group had progression of disease during treatment, and one in the surgery-only group. An R0 resection was obtained for 148/161 pts (92%) versus 111/161 (69%) in the RTCT and control group respectively. No difference was found in the postoperative complications between the two groups. Two of the most interesting pathological findings should be highlighted: the first is the 29% rate of pCR (47/161 pts) in the RTCT group, higher but in line with the previously published evidences for GEJ tumours. In particular the pCR rate was 23% for the adenocarcinomas pts, and 49% for pts presenting squamous carcinoma (25% of whole group). The second is the significantly lower presence of pathological nodal involvement in the RTCT compared to the surgery only arm: 31% vs. 75% respectively (p<0.001): the impact of this aspect is enhanced by the mentioned change in the 7th edition of the TNM classification, that tend to highlight the number of involved nodes as a strong prognostic parameter for such tumours.

Table 2 summarizes the main results from the randomized trials of RTCT plus Surgery vs. Surgery alone.

Radiochemotherapy versus Chemotherapy

Stahl et al. published in 2009 a phase III trial on a population of pts affected by adenocarcinoma of the lower oesophagus and cardia (Siewert I-III) [27]. From 2000 to 2005 they randomized 126 pts to either 15 weeks of CT (with CDDP, 5-Fu, Leucovorin) or 12 weeks of the same induction CT followed by 3 weeks of RTCT (consisting in 30 Gy with conventional fractionation plus CDDP and Etoposide). The study was prematurely closed due to poor accrual. In the RTCT arm, was reported a significant improvement of the pCR rate (RTCT-15.6% vs. CT-2.0%; p=0.03). Also the tumour-free lymph-nodes rate was significantly higher in the RTCT group (RTCT-64.4% vs. CT-36.7%; p=0.01). As described by authors, preoperative RT improved the 3 years survival rate with a slightly non-statistically significant trend (RTCT-27.7% vs. CT-47.4%; p=0.07). It is important to stress as the non significance of such results should be carefully interpreted for some reasons: the study was statistically designed to detect a 10% improvement in the 3 years survival for the RTCT arm, expecting a much larger accrual in each arm; almost a 20% of improvement was

actually reported, but the total number of needed pts after the planned first stage of the protocol required 163 additional pts per each arm, then the study was closed without obtaining the required statistical power. Moreover the impact of the pathological findings reflected the subgroup survival analysis: the nodal pathologically negative pts had a significantly higher 3 years survival (64.2 vs. 38.8; p<0.001); the pCR pts were all alive at the median follow-up time of 4.1 years. These subgroup findings were independent from the treatment initially delivered to the pts obtaining the major local and nodal response (RTCT or CT). Even though significantly higher than in the CT arm, it is well lower than in the previously mentioned series. It is arguable (as suggested by the authors) that the low RT dose had an influence on that aspect. It could be also hypothesized that the choice of the RT dose was influenced by attempt to keep the overall duration of the RTCT treatment similar to the CT one (i.e. 15 weeks).

Ronellenfitsch et al. published in 2013 a meta-analysis collecting 14 randomized phase III trials comparing surgery alone versus surgery proceed by a CT neoadjuvant treatment (either alone or combined with RT). All evaluated trials focused on adenocarcinoma of oesophagus GEJ or stomach; the primary outcome was time to death from the randomization, on an intention-to-treat base [9]. The analysis highlighted that administration of CT (globally evaluated as preoperative CT alone+RTCT data) was significantly associated to longer survival (HR 0.81, CI 0.73-0.89; p<0.0001) respect to surgery alone. A longer disease free survival, higher downstaging rate and R0 resection probability; conversely it wasn't associated to and higher postoperative complication likelihood. In particular, when separately analysed by anatomical subsites, the reported results were largest for the GEJ presentations, followed by oesophageal and gastric tumours. Moreover, when compared in direct subgroup analysis, RTCT showed a larger effect than CT in producing the survival benefit (HR: 0.70, CI 0.50-0.99 for RTCT vs. 0.83, CI 0.75-0.91 for CT; p=0.38) but this was not statistically significant. Authors summarize that the available evidences suggest a benefit from adding RT to CT for adenocarcinoma of GEJ and oesophagus (because all the included RTCT trial comprised pts with such diseases). Due to timing of the meta-analysis, the CROSS trial from van Hagen [26] wasn't included, and it is arguable that it could have enhanced the statistical power both for the global evaluation and for the one on subgroups.

In conclusion the current and past available evidences on the preoperative use of RTCT for the specific subset of GEJ tumours strongly suggest a high efficacy in terms of survival benefit, associated to reasonable toxicity. These findings are not always clearly separated by the presence in the series of other subside localization, but the trend favouring RTCT is evident. It is of main importance to focus the next randomized trials, opportunely customizing them through a specific

	N° Pts	Accrual	Rate AdenoCa	Dose/Fx (Gy)	Concurrent CT	% pCR (N° pts RTCT arm)	3 yy OS % [RTCT vs. Surg]	5 yy OS % [RTCT vs. Surg]	Median SVV (mth) [RTCT vs. Surg]	Median Fup (mth)
Walsh et al. 1996 [20]	113	1990-1995	100%	40/2.7	CDDP+5Fu	25% (13/52)	32 vs. 6 (p=0.01)	-	16 vs. 11	10 (0.1-59)
Urba et al. 2001 [21]	100	1989-1994	75%	45/1.5 (twice daily)	CDDP+5Fu+ Vimblastine	28% (14/50)	30 vs. 16 (p=0.15)	-	16.9 vs. 17.6	98.4 (72-118.8)
Burmeister et al. 2005 [24]	256	1994-2000	62%	35/2.4	CDDP+5Fu	16% (16/103)	42 vs. 36 (p=0.57)	21 vs. 19	22.2 vs. 19.3	65 (0.4-120)
Tepper et al. 2008 [25]	56	1997-2000	75%	50.4/1.8	CDDP+5Fu	40% (10/25)	-	39 vs. 16 (p=0.002)	53.8 vs. 21.5	72 (NR)
Van Hagen et al. 2012 [26]	366	2004-2008	75%	41.2/1.8	Carboplatin+ Paclitaxel	29% (47/161)	58 vs. 44 (p=0.003)	47 vs. 34	49.4 vs. 24	45.4 (25.5-80.9)

Table 2: Phase III Randomized Trials Comparing Radiochemotherapy plus Surgery versus Surgery Alone.
[Pts: Patients; Gy: Gray; Pcr: Pathological Complete Response; RTCT: Radiochemotherapy; Yy: Years; OS: Overall Survival; Surg: Surgery; SVV: Survival; Mth: Months; Fup: Follow-Up; CDDP: Cisplatin; 5Fu: 5fluoruracil]

selection of pts. Moreover, amelioration of the technical aspects of RT treatments, eventually including the newest drugs and the modern molecular targeted therapies in the concurrent schedules [28], could allow an improvement of the efficacy.

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