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High dose rate brachytherapy (HDR-BT) in locally advanced oesophageal cancer. Clinic response and survival related to biological equivalent dose (BED)

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Abstract *Introduction:* Ninety percent of oesophageal cancers are locally advanced at diagnosis, and treatment yields discouraging results. High dose rate brachytherapy (HDR-BT) permits an increment of local doses without a significant increment of toxicity. The goal of our study is to compare different HDR-BT fractions and assess global survival (GS) and cause-specific survival (CSS). *Material and methods:* Twenty-six patients were treated for locally advanced oesophageal cancer with chemotherapy concomitant with conformal three-dimensional radiotherapy (C3DR) from January 1994 to December 2000. Of this group, 96.2% were males, mean age 63.08 years; the most frequent location was medium third, for 50% of cases. Eighty-four percent of cases were G2-3 epidermoid carcinomas. The administration consisted of 44.2 Gy with C3DR and 5 applications of HDR-BT of 500 cGy each. *Results:* Actuarial GS and CSS at 5 years is 10.18% and 12.96%, a mean survival of 25.68 and 29.14 months respectively. The following factors (C3DR total dose, fraction dose and total dose of HDR-BT, number of applications, active length of application, total dose of C3DR plus HDR-BT, and BED of HDR-BT) are evaluated to find if they have an influence on treatment response, GS and actuarial CSS.The only result that yields statistical significance, in univariant analysis, is the active length in HDR-BT, thus for a greater active length of application, a minor response is obtained and GS diminishes (p=0.05). We grouped BT fractions on biological equivalent dose (BED) into: <28, 28–33 and >33 Gy; mean survival and GS at 5 years increases with BED≥28 Gy (p=0.016). *Conclusion:* Tumour response increases (complete and partial) when BED on HDR-BT is increased, regardless of the fraction employed. A BED higher than 28 Gy yields a significant increase of mean survival and GS at 5 years (p=0.016).

Key words Oesophageal cancer • HDR brachytherapy • Radio-chemotherapy

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Introduction

Oesophageal cancer is not a common tumour, but it is highly virulent. It represents the seventh cause of death for cancer, and more than 90% of diagnosed patients die from this condition, as 50% of them show distant metastasis at diagnosis and the rest show advanced locoregional disease [1].

A series of epidemiological changes have been seen in western countries in the last 30 years. In 1975 nearly 75% of diagnosed cancers were epidermoid carcinomas and the rest were adenocarcinomas; at present, the proportion is 56% and 44%, respectively [2]. Causes for the increase in incidence seem to be related to Barrett's oesophagus secondary to chronic [3] oesophageal reflux and a fall in *Helicobacter pylori* infections [4].

Oesophageal carcinoma is a treatable disease that rarely heals. Numerous retrospective studies show a 5-year survival of 6% of patients treated with radical irradiation and 11–12% with surgery only [5, 6]. Better surgical techniques and pre-operative tumour dryability in 50% of cases; on the other hand, peri-operative mortali-

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ty has dropped to 15% [7]. Despite all this, survival at 5 years in complete resection cases is 20% [8]. The same goes for patients treated with exclusive irradiation, where survival at 5 years is 12% [9], despite the fact that total doses have been increased thanks to modern imaging technologies and better delimitations of treatment volumes.

With regard to chemotherapy as a pre-op treatment, response length is short and survival at 5 years remains unaltered [10, 11], despite the fact that tumour responses have been reported in 20–60% of cases, depending on the chemotherapy agents employed.

In view of these discouraging results, studies employing pre-op [12], post-operative [13] radio-chemotherapy or exclusive treatment [14] have been conducted. Results show that exclusive radio-chemotherapy is the best option. Surgery does not provide any benefits but has a significant morbidity/mortality.

Local control is related to total dose received [15], so altered fractions have been used to reach high doses without increasing the side effects for organs at risk. High dose rate brachytherapy (HDR-BT) fills this objective: it allows the administration of high doses at local tumour level, preserving peri-tumour tissues and minimising acute late toxicity [16].

At our centre, the radical radiotherapy treatment of oesophageal cancer is conducted through conformal three-dimensional radiotherapy (C3DR) and HDR-BT boost.

Our objective is to compare different brachytherapy fractions and assess response to treatment, global survival (GS) and specific survival on the basis of the biological equivalent dose (BED).

Material and methods

From January 1994 to December 2004, we treated 26 locally advanced (stages II and IV) and inoperable oesophageal cancer patients with C3DR concomitant with chemotherapy and HDR-BT boost. In this group, 96.2% (25 cases) were male, mean age 63.08 years (range 26–85). Mean follow-up was 58.7 months (range 5–120 months) until tumour progression and death, or the time of conclusion of this study.

Tumour location on the oesophagus was: 30.8% for superior third, 50% for medium third and 19.2% for distal third.

For diagnosis reasons, all patients underwent an endoscopy and biopsy punch. Histological results yielded epidermoid carcinoma in 84.6% and adenocarcinoma in 15.4% of cases. Histological differentiation grades are divided into the following categories: well differentiated (G1) in 15.4% of patients, moderately differentiated (G2) in 50% of cases and undifferentiated (G3) in the remaining 24.6%.

Informed consent was obtained from the patients.

Twenty-three patients (88.5%) were given•C3DR, mean dose 44.2 Gy (26–64 Gy in standard fractioning): 16 received 50.4 Gy, one patient received 64 Gy and C3DR was suspended at 26 Gy in a single case; the rest, five patients, received 44–46 Gy. CAT simulation was carried out with oral contrast and cuts every 0.5 or 1 cm, and 3D volumetric reconstruction employing PLATO RTS v 2.6.3 planning (Nucletron). Target volume includes tumour with 5 cm of cranium-caudal margin and 2 cm lateral margin. Treatment on patients was carried out in supine position, by anterior–posterior and oblique fields from 40 Gy to avoid spinal cord, employing 6–18 MV photons from a lineal accelerator.

Three patients (11.5%) received only HDR-BT treatment, as they had received external radiotherapy previously for thorax tumours/ORL.

All patients received HDR-BT by placing, under endoscopic control, a catheter 6–10 mm in external diameter into the oesophageal lumen, depending on oesophageal permeability. An HDR-BT simulation consists in producing orthogonal radiographies with the help of a fictitious probe inside the catheter. Planning is conducted through a PLATO Brachytherapy System, version 14.2.6 (Nucletron). Target volume includes tumour with 2 cm of cranium-caudal margin; dose is specified at 0.7 cm from the applicator (range, 0.5–1 cm). The treatment is administered through a high dose rate Iridium 192 source by an afterloading system, microSelectron-HDR model; it is conducted weekly. The mean number of applications is 5 (range, 1–17 fractions), mean dose per fraction is 500 cGy (range, 250–1000), total mean dose is 21 Gy (range, 10–51 Gy) and active mean length is 8.15 cm (range, 4–14 cm). In view of the variability of fractions employed, we have tried to standardise them by calculating the BED to conventional fractioning. A mean BED of 30.89 Gy is obtained (range 15–61 Gy) (Fig. 1).

Chemotherapy treatment comprises 2 cycles of different cisplatin and 5-fluoruracil-based regimes concomitant to C3DR. Later on, patients resumed their chemotherapy treatments with diverse schemes, so it is difficult to analyse its impact in the evolution of the condition.

SPPS, version 12.0, was employed for the statistical analysis. Once it was verified that the sample did not follow a normal distribution pattern (Kolmogorov–Smirnov test), non-parametric tests were employed, and used to determine the significance level of á=0.05 (confidence interval, 95%). The Kaplan–Meier method is employed for the survival analysis.

Results

The treatment employed yields an objective response in 19 patients (73%), 6 complete responses (23%), 13 partial/stabilisation responses (50%) and progression in 7 patients (27%). At the conclusion of the study, 4 patients (15%) were alive and disease-free, 2 patients (8%) had died from other causes (oesophageal varices), 3 patients had (12%) died from local tumour and distant metastasis and 17 (65%) had died from local tumour progression.

Actuarial GS at 5 years was 10.18% and mean survival was 25.68 months. The actuarial cause-specific survival (CSS) at 5 years was 12.96% and a mean cause-specific survival (mCSS) was 29.14 months.

The following factors are evaluated to find if they have an influence on treatment response, GS and actuar-

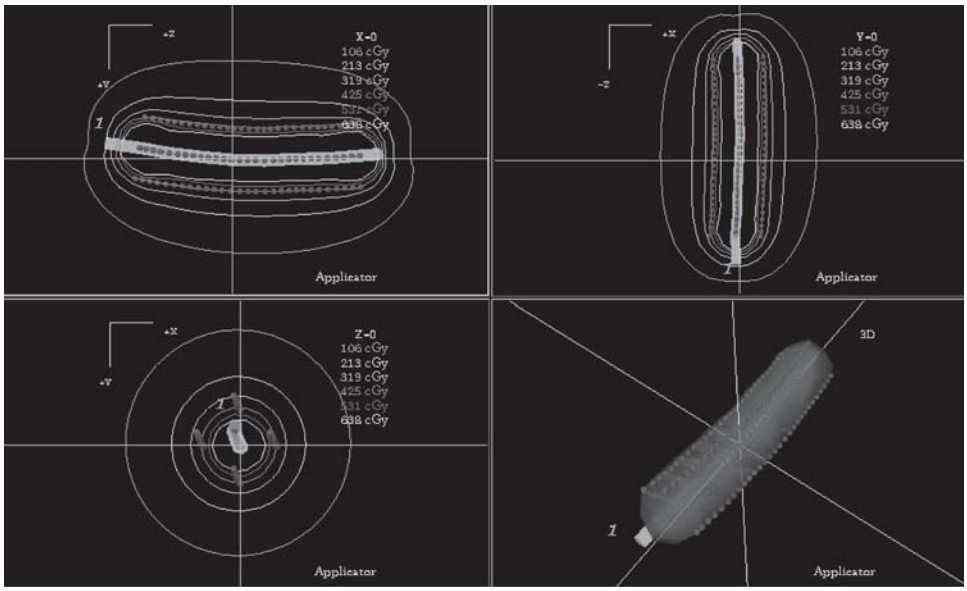

Fig. 1 *Isodoses in the brachytherapy treatment planning*. Illustrative example of the planning of a HDR-BT application on oesophageal cancer

ial CSS through a univariant analysis (Table 1): C3DR total dose, fraction dose and total dose of HDR-BT, number of applications, active length of application, total dose of C3DR plus HDR-BT, and BED of HDR-BT. The only result that yields statistical significance is the active length in HDR-BT, thus for a greater active length of application, a minor response is obtained and GS diminishes (p=0.05).

Patients are divided into three groups depending on the BED of HDR-BT: those receiving a BED inferior to 28 Gy, between 28 and 33 Gy and those receiving more than 33 Gy. No significant differences are observed in the descriptive characteristics of inter-group patients. BED influence, GS and actuarial specific survival rates are analysed in the treatment response through a univariant analysis (Table 2). The following results stand out: (1) the percentage of tumour response increases when BED is increased, and it reaches 88.8% of response from patients receiving a BED superior to 33 Gy, against 55.5% of response from patients treated with BED lower than 28 Gy; however this difference is not significant (p=0.278); (Fig. 2) (2) mean survival rises from 10.86 months, for those patients receiving a BED lower than 28 Gy, to 31.24 months for those patients receiving a BED superior to 33 Gy (p=0.016); GS at 5 years is 16.67% for a BED superior to 33 Gy against 0% for a BED inferior to 28 Gy (p=0.016) (Fig. 3).

Acute toxicity is the usual in these patients; there is no evidence that HDR-BT addition to C3DR increases toxicity. We have not seen grade 3–4 toxicity from the radiation therapy oncology group (RTOG). As for late sequels, we have not seen toxicity greater than or equal to grade 2 in any group.

Discussion

Despite the advances seen in the treatment of oesophageal cancer, the prognosis for these patients is dreadful, with an expected survival of 10–15% at 5 years; this coincides with our result of 10.8%. The low

Table 1 Description of the characteristics of irradiation

	Mean	Minimum	Maximal	p
C3DR doses (Gy)	44.2	26	64	n.s.
HDR-BT physical dose (Gy)	21	10	51	
BED HDR-BT (Gy)	30.89	15	61	
No. of applications (1/week)	4.96	1	17	
Dose/fraction HDR-BT (cGy)	500	250	1000	
Active length (cm)	8.15	4	14	=0.05
Dose specification (cm)	0.8	0.5	1	n.s.
C3DR+HDR-BT total dose (Gy)	73.5	45	100	

Table 2 Results of univariant analysis of BED

BED	<28 Gy	28–33 Gy	>33 Gy	*p*
No. of patients	9	8	9	0.278
% responses	55.5	75	88.8	
% progression	44.5	25	11.2	
Mean survival (months)	10.86	31.08	31.24	0.016
Global survival (5 years) (%)	0	15.63	16.67	

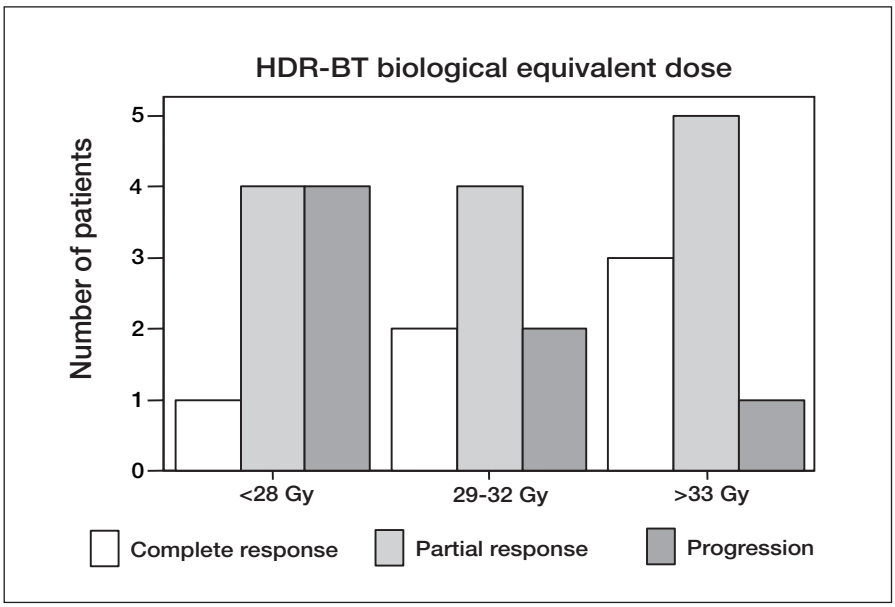

Fig. 2 Response rate on the basis of the BED

survival obtained with local treatments reflects the early dissemination these tumours produce, both loco-regional and at a distance. Traditionally, the treatment of choice varies from radical surgery, potentially curative and possible in 20% of patients (without metastasis at a distance, a good general condition and localised tumour), to palliative treatment in the remaining 80% of patients [17].

From 1980, both pre-op and post-operative radiochemotherapies have been employed in an attempt to improve surgery results and as exclusive treatments in patients who are not candidates for oesophagectomy.

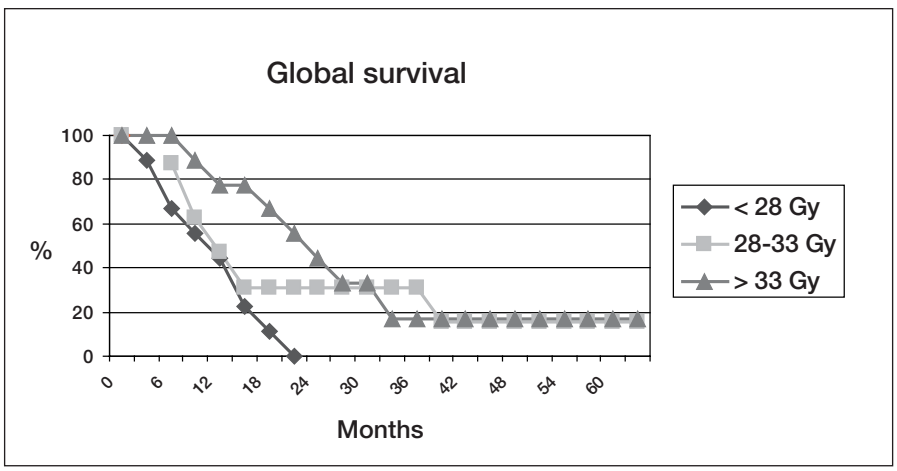

Fig. 3 Global survival on the basis of BED

Several randomised studies compare exclusive radiotherapy with chemotherapy (cisplatin and 5-FU), simultaneous to radiotherapy on inoperable oesophageal cancer patients; the latter shows better results than exclusive radiotherapy and an acceptable toxicity. The RTOG, in a phase III study (RTOG85-01), randomised 129 patients affected by epidermoid carcinoma to receive exclusive radiotherapy (64 Gy) or chemotherapy (two cisplatin and 5-FU cycles) concomitant to 50 Gy of radiotherapy (30 Gy on the whole oesophagus and 20 Gy on the tumour, 5 cm of proximal and distal margin). Mean survival was 8.9 months for patients treated with exclusive irradiation, and 12.5 months for the group receiving combined treatment; survival, at 5 years, was 0% and 26%, respectively. In the radiotherapy group, 40% of the patients showed tumour persistence at the end of treatment against 27% in the combined treatment group ($p<0.01$). The most local control was associated with a minor relapse percentage at a distance (22% *vs*. 38%, $p<0.005$) [14]. Acute toxicity was greater in the combined treatment group, but the difference was not significant and late toxicity values were similar in both treatment groups. In view of these results, radiotherapy treatment has been established as a standard in oesophageal cancer patients who are not candidates for surgery; it has been, from the moment it was published, the therapeutic protocol.

To define the optimum target volume in oesophageal cancer patients is controversial [18]; to delimit the target volume after oesophagectomy is difficult due to anatomical and functional changes produced. Besides, there is little information with regard to including [19] or not including surgical anastomosis in the irradiation field [20, 21]. Despite the best improvements obtained through radiotherapy, local relapse is very high, so new strategies are under study for improving local control by increasing radiotherapy dosage. In a phase III study (INT 0123) [22], patients were randomised to received a radiotherapy combined treatment (tumour showing 5 cm of proximal and distal margin) of 50.4 Gy doses *vs*. 64.8 Gy and equal chemotherapy (cisplatin and 5-FU) for both groups. The study was concluded before the scheduled time as it did not demonstrate improvement in survival at 2 years (31% *vs.* 40%) or on loco-regional relapse, and inter-recurrent deaths increased in the branch of dosage escalation (11 *vs*. 2). This study confirms that the model defined by RTOG85-01 is efficient and 50.4-Gy doses are the standard line in concomitant treatment. With regard to our study, 69.5% of patients received 50 Gy of C3DR on conventional fractioning.

Intraluminal brachytherapy may be able to increase the dosage in the oesophagus with minimal exposure of critical adjacent organs, as the dose decays at the distance of the radioactive source. HDR-BT has been widely used in oesophageal cancer as a palliative treatment ever since it was discovered, as a boost procedure in intentional healing treatments and as a stand-alone therapy in superficial tumours. The Japanese Society for Therapeutic Radiology and Oncology (JASTRO) [23] conducted a multi-institutional and prospective study aimed at establishing the optimum irradiation method on oesophageal cancer patients who are candidates for radical radiotherapy. This study randomised patients to receive external radiotherapy or both radiotherapy and brachytherapy, and ulterior etoposide chemotherapy (3 cycles). Once 60 Gy were administered with external radiotherapy, a 10-Gy boost was carried out with external radiotherapy, or LDR or HDR brachytherapy, two 5 Gy fractions separated by a week. GS was 20.3% and CSS at 5 years was 31.8%. The percentage of complete response was 49% for the external radiotherapy group and 55.8% for radiotherapy and brachytherapy treatment. In our study, we have achieved an objective response index of 73% with only 23% of complete responses. These results are inferior to those published by Okawa et al.; this is justified because of the use of a lower total irradiation dose in our protocol. CSS is 27% in patients treated with external radiotherapy and 38% in the radiotherapy and brachytherapy group, but the difference is not significant.

In our study, CSS is 12.96%. It is worth noting that our sample only includes locally advanced oesophageal cancer patients, while the JASTRO study included all stages. A high percentage of II and III stages is seen, thus better results are expected on local control and survival.

In a retrospective study, Yorozu et al. [24] compared external radiotherapy and brachytherapy against external radiotherapy, chemotherapy and brachytherapy on localised oesophageal cancer patients. Mean dose of external radiotherapy was 50 Gy (41–60 Gy) on classical fractioning. HDR-BT was conducted one or two weeks later after external radiotherapy with a 7-mm diameter catheter. It included tumour pretreatment with a 2-cm cranium-caudal margin and the administration of a 16-Gy mean dose (8–24) in 2–4-week applications. Chemotherapy was administered concomitantly with external radiotherapy (first and last week) and was comprised of 5-FU and cisplatin. In the three-mode treatment, 60% obtained better local control against 42% ($p=0.029$) and a better mean survival at 2 years in stages II and III ($p=0.046$). Acute and late toxicity was higher in the three-mode treatment group ($p=0.010$). It concluded that treatments comprising external radiotherapy, chemotherapy and HDR brachytherapy obtain a better local control and survival in selected patients. It recommended not going beyond 10–12 Gy in two or three fractions with HDR-BT in order to diminish side effects. There was great variability in the number of HDR-BT fractions and doses, due to the fact there was no recommendation about this when we began HDR-BT treatment on oesophageal cancer in January 1994. As for the last phase of treatment, it was homogenous; our protocol comprises 45–50 Gy on C3DR concomitant to chemotherapy (two cycles of cisplatin and 5-fluo-

rouracil) and a later boost of 20 Gy of HDR-BT in 5 applications, 400 cGy each, once a week. Thus our HDR-BT dosage is higher than that recommended by Yorozu et al., however we have not seen any acute or late toxicity of relevance. Other authors [25] think brachytherapy, as a boost technique, is more efficient than external radiotherapy only in stage I.

The risk of late sequels is related to total dose and fraction dose [26] of HDR-BT boost; it is recommended to not go beyond a total 10–12 Gy dose on radio-chemotherapy treatments and HDR-BT boost [27]. In patients affected by advanced oesophageal cancer and non-candidates for radical radio-chemotherapy treatment, Hujala et al. conducted a palliative treatment with external radiotherapy (40 Gy in 20 fractions) and HDR-BT boost technique (10 Gy in 4 fractions) [28]. Symptoms improved immediately in 40% of cases and no complications superior to grade 3 were found. Patients yielded a mean survival of 30% and 17.5% at 1 and 2 years, respectively. It concluded that brachytherapy is, as a palliative treatment, a safe and efficient method to obtain a normal deglutition, and survival is prolonged over 24 months in some patients. Patients in our study are similar to those in this work; we, however, suggest conducting a radical treatment to obtain 10.18% GS at 5 years on a mean survival of 25.68 months, a 12.96% CSS at 5 years and a mCSS of 29.14 months. Therefore, we think it is worth trying a radical radio-chemotherapy treatment on locally advanced, inoperable oesophagus cancer patients.

Sur et al. [29] confirm these results in patients who are candidates for palliative treatment; they conclude that 18-Gy HDR-BT doses in 3 fractions or 16 Gy in 2 fractions are similar for dysphagia control, GS and side effects.

The number of fractions to administer, dosage per fraction and the point where the dose is specified at remain to be defined with regard to the use of brachytherapy as part of a multidisciplinary treatment on oesophagus cancer. Some authors [30] recommend not going beyond 20 Gy, as an increase of bleeding and stenosis will be produced from that dose on. Some other authors [31] think 12 Gy is the optimum dose to obtain the maximum response with the minimum complications.

In an effort to unify criteria, the American Brachytherapy Society (ABS) [32] and the Institute Gustave Roussy [33] have issued a series of consensus guidelines on oesophagus cancer brachytherapy; these are based on publications and on their own clinic experience. They recommend 10–15 Gy in 2–3 HDR fractions.

The main problem of brachytherapy lies in the dose gradient produced between the radioactive source and the mucous surface of the oesophagus. If we use a catheter with a diameter inferior to 8 mm, the dosage on the mucous surface is very high and it increases the risk of late toxicity, and fistulas, above all. To avoid this, we must bear in mind the *hyperdose sleeve* described by Marinello et al. [34] as the volume receiving a dose equal to or greater than twice the reference dose; he recommends the lowest possible dose.

We came across a great variety of doses and fractions in use when we tried to compare the treatment results of brachytherapy in oesophageal cancer. To unify criteria, Akagi et al. [26] employ the linear-quadratic model formula to calculate the BED for the tumour (Gy10 means alpha/beta equals 3 Gy) and for the oesophageal mucosa (Gy3 means alpha/beta equals 3 Gy) in oesophageal cancer patients receiving 50–60 Gy through external RT and 2 different schemes of HDR-BT; one group receives 2 applications of 4–5 Gy and the other group 4–5 applications of 2–2.5 Gy. The results of the linear-quadratic model correlate with late complications and show that a BED >134 Gy3 and a number of fractions less than or equal to 3 are associated with late complications superior to grade I. The BED analysis demonstrates that dosage per fraction at 2–2.5 Gy, specified at 0.5 cm from the applicator surface, must be reduced and the number of fractions must be increased up to 4–5 one per week to obtain a BED <134 Gy3.

Geh et al. conducted a study revision on neoadjuvant radio-chemotherapy in oesophageal cancer [35]. To compare results he calculates oesophageal cancer α/β (superior to 4.9 Gy), the estimated dose lost daily (0.59 Gy), the estimated equivalence in Gy of 1 g/m^2 of 5-FU (1.9 Gy) and 100 mg/m2 of cisplatin (7.2 Gy). The result is that the chance to obtain a complete pathological response is greater when there is an increment in irradiation dose (p=0.06), cisplatin (p=0.018) and 5-FU (p=0.006). When the patient's age increases (p=0.019) as well as total time of radiotherapy treatment (p=0.035), the chances of obtaining a complete pathological response are reduced. In our study, it is confirmed that incrementing BED increases mean survival and GS at 5 years. Therefore, we recommend the following scheme in case of a radical treatment on locally advanced oesophageal cancer: 50 Gy of C3DR doses on conventional fractioning together with 2 concomitant chemotherapy cycles (cisplatin and 5-FU) and HDR-BT boosting (5 applications, 400 cGy per application).

Radio-chemotherapy is still the standard treatment for locally advanced oesophageal treatment, as the role of surgery is not clear and more phase III studies are needed to define it [36]. HDR is useful for reaching high doses on the tumour without increasing toxicity for critical organs. Recent advances in the development of new drugs and the identification of molecular targets yield new opportunities for attempting to improve results for these patients.

Conclusions

Radio-chemotherapy is the standard treatment for locally advanced oesophageal cancer. HDR-BT boost consti-

tutes an effective and safe method for dose escalation. When the BED of HDR-BT is increased, so is the percentage of tumour responses (complete and partial), regardless of the fractioning employed. A significant increment of mean survival and GS at 5 years (p=0.16) is obtained with a BED superior to 28 Gy.

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