Management of esophageal superficial tumors : non take away approaches

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Abstract

Development of screening programs in patients with high risk of developing esophageal cancer, as well as recent advances in diagnostic endoscopic techniques, have allowed clinicians to improve early detection of esophageal malignant tumors. Surgical resection, although currently considered as the standard of care for patients with early stage esophageal cancer, is sometimes contra-indicated. In this subset of patients, endoscopic resection techniques including endoscopic mucosal resections (EMR), thermal or non-thermal laser, or cryoablation are amongst the well-recognized modalities safely and efficiently used by gastroenterologists. However, in some patients, these options are contra-indicated or incomplete, necessitating medical treatments such as chemotherapy and/or radiation therapy. A systematic search of all the English literature regarding non-take away approaches has therefore been performed, based on a MEDLINE search (Pubmed) carried out between January 1990 and March 2011. Future radiation therapy developments will also be pointed out. (Acta gastroenterol. belg., **2012**, 75, **5-8**).

Key words : esophageal neoplasm, endoscopic mucosal resection, radiation therapy, brachytherapy, proton therapie.

Although the overall survival rate has been improved during the last years, the outcome of esophageal tumors is generally poor, except for patients who are identified and treated at an early clinical stage (1). Remarkable progresses have therefore been made during the last decades in development of new endoscopic techniques, allowing physicians to detect esophageal tumors early and to better characterize tumor depth inside the esophageal wall, a well-recognized prognostic factor of regional lymph node involvement and metastases (2). Surgery, although complex and associated with non negligible mortality and morbidity, remains to date the reference treatment for superficial esophageal tumors (3-5). However, for some patients, surgery is not appropriate since co-morbidities or age could render this option hazardous. Several other approaches have therefore been developed in order to offer alternative treatment for patients not eligible for surgery. Amongst them, endoscopic mucosal resection (EMR) is considered as a reasonable option and has proven to be effective in very small tumors located in the mucosa (6). Non take away approaches such as exclusive external beam radiotherapy (EBRT) (7), brachytherapy alone or combined with EBRT (8), concomitant radio-chemotherapy (9), proton therapy, and photodynamic therapy (10), are potential options in patients either incompletely resected by EMR or for whom surgery or EMR are not indicated.

External beam radiotherapy has been used for years in the treatment of esophageal tumors, regardless of the disease stage (11,12). It has been considered by many authors as the cornerstone of non take away approaches for mucosal and sub-mucosal esophageal tumors, and thereforehave extensively been studied either as exclusive treatment, alone or in combination with brachytherapy (BT) or chemotherapy (CT), or as a salvage therapy after EMR.

Results of sequential combination of EBRT and BT for stage I esophageal cancers seem interesting. Pasquier *et al*., using EBRT followed by high dose rate (HDR) BT (HDRBT) with a 192Ir source showed a 3-years OS of 54%, with manageable toxicity (Table 1) (13). Ishikawa and co-authors treated 68 patients with either EBRT alone (32) or EBRT plus BT (36) (14). Among patients treated with the combined treatment, 19 received HDRBT, whereas the others were treated with low dose rate (LDR) BT. The 5-years OS in the combination groups was better compared to the EBRT group, but statistically not significant ($p = 0.123$). The results in terms of local control were however statistically significant when tumor length (< 5 cm) was taken into account (Table 1). Furthermore, LDRBT was more frequently associated with ulcers than HDRBT.

Two Japanese prospective studies demonstrated better results with the sequential combination of EBRT and BT compared to EBRT alone (Table 1). Nishimura *et al*., using HDRBT in all patients, showed a significantly better local control rate and 3-years OS in patients treated by the sequential treatment ($p < 0.05$ for both) (Table 1). Okawa *et al*. treated 97 patients with EBRT followed by a randomization where patients were assigned to either receive a boost external irradiation of 10 Gray (Gy) or 10 Gy of HDR/LDR BT. There was a trend to a better OS in the combination group but it was not significant. However, in a subgroup analysis, patients with a 5 cm or less tumor length, the 5-years OS was significantly better in the EBRT/BT group (64%vs39.4%, $p = 0.025$) (15,16).

All 4 studies demonstrated a very high local control rate with the association of EBRT and BT. Favorable toxicity was observed, with late esophageal stenosis and strictures as main toxicities in less than 5% of patients.

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Ulcers were more frequently observed when LDRBT was used. Eventually, tumor length seems of interest as prognostic a factor of better OS and local control rate.

Three other studies assessed EBRT in combination with HDRBT. Complete response rates ranged between 48 and 100%, with a 5-year local control rate between 17 and 43%. Late complications, such as ulcerations and strictures were frequent and occurred in approximately 15% of all treated patients (17-19). Maingon and colleagues used HDRBT in 25 patients suffering from superficial esophageal tumors (23 squamous cell carcinomas), amongst them 11 were classified as in situ neoplasms. Brachytherapy was used in combination with external-beam radiotherapy (EBRT) in 8 patients, with EBRT plus chemotherapy in 4 patients and alone in 13 patients. Three months after irradiation, 75% of the patients had a CR, 21% a PR, with a mean overall survival of 21 months and a 3-year OS of 14%. In patients treated with BT alone, the overall survival was 43%. Treatment failure was similar between the three groups as well as the treatment's tolerance (20).

External beam radiotherapy (EBRT) has also been studied as a salvage therapy after EMR. Nemoto *et al*. treated 30 patients suffering from squamous cell esophageal cancers (SCEC) limited to the submucosal layer for whom surgery was contra-indicated. The total dose of EBRT was between 60 and 70 Gy, with chemotherapy used in 9 patients. Five-years OS and local control rate were 51% and 73%, respectively. Patients with mucosal tumors had a better prognosis, although not significant, than patients with submucosal involvement (21).

Since the esophagus is surrounded by highly radiation-sensitive organs (e.g. lungs, heart), new radiation techniques have been developed to circumvent toxicities to the surrounding tissues. Intensity modulated radiotherapy (IMRT) and intensity modulated arc therapy (IMAT) are emerging irradiation techniques consisting of modulating the beam intensity distribution within a field. The main advantage of IMRT is to lower the risks of late adverse effects of radiotherapy and to improve local control of the tumor, due to the possibility of safe dose escalation. Dosimetric studies in esophageal cancers demonstrated an advantage of IMRT compared to conventional EBRT in tumors of all parts of the esophagus. IMRT shortens treatment time and allows a higher radiation dose on the tumor bed. Clinical results of IMRT for esophageal cancer are however still limited to a few small studies (22-25), but deserve further evaluation.

Proton beam irradiation has also been developed to allow high dose radiation delivery on the tumor bed, without significant irradiation to the adjacent organs. Protons have a distinct physical advantage over photons used in conventional irradiation therapies since the beams produce little side scatter and stop abruptly at any prescribed depth. Proton beams can be shaped to deliver homogeneous radiation doses to irregular three-dimensional volumes such as those required for esophageal carcinoma. This makes it possible to deliver high doses of irradiation to the target volume while simultaneously reducing the amount of protons reaching normal esophageal or adjacent normal tissues (26). Three trials have been published so far using proton-beam therapy (27,28). Koyama *et al*. treated 13 patients with superficial esophageal neoplasms, amongst which 11 previously treated by EBRT. Complete response was obtained in all patients, with a median overall survival of 30 months and a 100% 5-year disease-specific survival. Esophageal ulcers and strictures were observed in almost 70% and 25% of the patients, respectively (27). Sugahara *et al*. reported the clinical results of proton beam therapy in 46 patients with squamous cell carcinomas. Forty patients were treated by a combination of photons and protons as a boost to a median total dose of 76.0 Gy (median fraction dose 3.0 Gy), six patients were irradiated only by protons to a median total dose of 82.0 Gy (median fraction dose 3.1 Gy). The local control rate at 5 years was 57% (83% with stage T1 and 29% with stage T2-T4). Postradiation esophageal ulcers were observed in 48% of patients (29). More recently, Mizumoto and colleagues published a series of 51 patients treated either with proton beam therapy alone (18) or in combination with EBRT (23). The overall 5-year actuarial survival rate and the median survival time for the 51 patients was 21.1% and 20.5 months (95% confidence interval 10.9-30.2), respectively. Furthermore, complete response was observed in only 78% of the patients. The 5-year local control rate for all 51 patients was 38.0% and the median local control time was 25.5 months (95% confidence interval 14.6-36.3) (28). Although encouraging, one should keep in mind that proton therapy is not yet available in most of western countries.

Photodynamic therapy (PDT) uses a photosensitizing chemical agent, activated by light to selectively destroy the neoplastic cells via the formation of singlet oxygen molecules, which mediate tumor cell necrosis. In a study performed by the Mayo Clinic, 102 patients were treated for either Barrett's high grade dysplasia (69) or mucosal adenocarcinoma (33). Focusing on the latter, complete response after one course of PDT was observed in 76% of the patients, 15% developing a local stricture (30). More recently, Lecleire et al treated 40 patients suffering from superficial esophageal carcinoma, 25 as a primary intent and 15 as a salvage therapy after chemotherapy combined with radiation therapy (CRT) (31). Complete response was observed in 76 and 53% of the patients, respectively. Perforation and strictures were more frequently observed when PDT followed CRT. Therefore, PDT should be used with extreme caution as a salvage therapy.

Conclusions

Based on the available literature, one could say that non-take away approaches used either as exclusive ther-

Table 1. — **Results of external beam radiotherapy, either alone or in combination with chemotherapy or brachytherapy**

	N	BT doses (Gy)	EBRT doses (Gy)	3-Y PFS (%)	5-Y PFS (%)	3-Y OS (%)	5-Y OS (%)	Combined therapy (%)	
								CT	BT
Kodaira *et al*. (7)	97	10	CT-/+:60/66	55.8	48.1	81.5	63	63	27
Pasquier *et al*. (13)	66	7	60	55.2	44.6	53.7	41	/	100
Ishikawa *et al*. (14)	68	10-18	BT-/+:65/56-60	/	/	/	BT-/+:57.8/81	/	53
Nishimura *et al*. (15)	21	10-12	BT-/+:55/66	BT-/+:45/85	/	BT-/+:50/85	/	/	62
Okawa *et al*. (16)	94	10	BT-/+:70/60				BT-/+:38/27		
Sasaki *et al*. (34)	34	/	60	80	/	90	/	88	3
Yamashita *et al*. (9)	18	/	50.4	/	/	CT-/+:40/75	/	72	–
Nemoto *et al*. (8)	147	10 (34*)	BT-/+:65/56	/	/		/	3	53
Nemoto *et al*. (21)	78	/	65.5	66	/	45 (5-y OS)	/	/	/
Yamada *et al*. (35)	63	10-12	55-59.4	63.7	/	66.4	/	100	100

PFS, Progression Free Survival ; OS, Overall survival ; CT, Chemotherapy ; BT, Brachytherapy ; EBRT, External Beam Radiotherapy ; Gy, Gray ; *, BT alone.

apy or salvage therapy after EMR could offer prolonged local control rate and survival for patients suffering from mucosal or sub-mucosal tumors and non-eligible for surgery. However, local complications such as ulcers and strictures are not rare, especially when high dose photon therapy is used, as well as for proton therapy and phototherapy.

It should be stressed that major differences exist inside and between studies, rendering the analysis of results rather thorny. These differences include heterogeneity in treatment schedules and radiation doses, inclusion of different histological (squamous cell carcinomas and adenocarcinomas) and locally advanced tumors (mucosal and sub-mucosal lesions), administration of different treatment modalities in different settings (post-mucosectomy, exclusive medical treatment). Better trial design should therefore render results more reliable in the future. Secondly, most of trials using new radiation techniques such as IMRT or proton therapy included very few patients. Results, although encouraging, must be repeated in larger clinical studies in order to validate these techniques in the future. It is also of interest to point out that new techniques such as carbon-ion radiotherapy or proton therapy are not yet available in many countries all around the world. They are also associated with high rate of local complications and, therefore must be ameliorated to become widely used in the future.

Prospects for future research

Clinicians should focus on minimizing post-treatment complications without modifying efficacy. Reduction of radiotherapy-related toxicity by improving either the imaging techniques (positron emission tomography/CT based radiation or 4D-computer tomography and respiratory control techniques) or the radiation treatment (IMRT, IMAT proton beam therapy as well as new radiation therapy such as Carbon Ion Radiotherapy) could improve the local control rate by better targeting the tumor bed (32,33).

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