PALLIATIVE HDR BRACHYTHERAPY IN TREATMENT OF ADVANCED ESOPHAGEAL CANCER

Janusz Skowronek[1], Krystyna Adamska[1], Magdalena Suwalska[2], Grzegorz Zwierzchowski[3].

[1]First Department of Radiotherapy, [2]Department of Radiology, [3]Department of Medical Physics, Greatpoland Cancer Centre Garbary 15 Street, 61-866 Poznań, Poland.

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SUMMARY

Introduction: Patients not qualified for surgery due to the location and clinically advanced stage of oesophageal cancer constitute a group with poor prognosis. Only few of them qualify for radical teletherapy, most of them are being treated symptomatically. The paper presents preliminary results of HDR brachytherapy applied in patients with inoperable oesophageal cancer.
Material and Methods: Between May 1999 and February 2000, 37 patients with inoperable oesophageal cancer were treated by HDR brachytherapy. The patients' age ranged between 42 and 81 years, mean: 53.1 yr. In HDR brachytherapy the most commonly employed dose was that of 21.5 Gy (in three fractions) at the tumour site. In four cases the mediastinum was additionally irradiated with a dose of 20 Gy in five fractions, and in nine patients treated radically, teletherapy with a dose of 50-60 Gy at the vicinity of the oesophagus was used following brachytherapy. The effect of the treatment in the form of local remission and regression of dysphagia was assessed in the 1st, 3rd and 6th month of follow-up after the completion of the treatment.
Results: The mean follow-up was 6 months. Total remission, partial remission and no remission, as assessed in the 1st month after the treatment, was found in 7 (18.9%), 18 (48.6%), and 12 (32.4%) patients, respectively. After the 3- and 6-month follow-up remission was re-affirmed in two-thirds of the patients under observation. In the group of patients treated with the combination method total remission was found in two (20%) patients, whereas partial remission was ascertained in 6 (60%) patients. In four (10.8%) patients oesophageal fistula was detected during the follow-up period.
Conclusions: HDR brachytherapy was found to lead to regression of dysfagia in a significant number of patients with inoperable oesophageal cancer. In some patients total remission was achieved lasting more than six months. Tolerance for the treatment was good, and the number of complications did not differ from that reported by other authors.
Key words: advanced oesophageal cancer, HDR brachytherapy.

INTRODUCTION

As few as 10-20% of patients with esophageal cancer are treated surgically. Those not qualified for surgery due to cancer location, as well as those with an advanced clinical stage of cancer constitute a group with poor prognosis. In the remaining 80% of patients the tumour infiltrates the outer wall of the esophagus, whereas the probability of metastasis to regional lymphatic nodes is proportional to the size of the tumour: it is higher than 50-60% for the tumour size exceeding 5 cm [1,2,3,4,5].

Radiotherapy and/or chemotherapy remain the standard treatment in these patients. When employing teletherapy alone only 1% and 8% of all patients had been found to demonstrate the 5-year survival rate. At the same time, a large majority of patients die due to the lack of success in treating the primary lesion and/or the infiltration of the neighbouring organs by the cancer. Frequently, aspiration of food or fistulae causing aspiration pneumonia lead to death. The above considerations have resulted in attempts to apply higher dose of radiation to the tumour.

Endoesophageal brachytherapy makes it possible to use high doses of radiation to the tumour itself with concurrent protection of the adjoining healthy tissues due to the rapid fall in the dose with

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the square of the distance from the centre of the dose. The above treatment also leads to a smaller proportion of late radiation complications [6,7,8,9,10]. The aim of palliative brachytherapy is to reduce dysphagia, diminish pain and bleeding, as well as improve the patient's well-being.

However, there have been only few reports to confirm that the number of local remissions and long-term survival rates have been increased in patients treated with teletherapy combined with brachytherapy. Doses used in teletherapy were as high as 35-60 Gy, whereas those in HDR brachytherapy ranged between 10 and 25 Gy administered in 2-4 fractions. The combined treatment can be radical or palliative [11,12,13,14].

The present paper also assesses the effect of HDR brachytherapy on local remission and regression of dysphagia two, three and 6 months after the termination of treatment. In some cases, the follow-up was as long as 12 months.

MATERIAL AND METHODS

Thirty-seven patients with unresectable cancer of the esophagus were treated by HDR brachytherapy at the Greatpoland Cancer Centre between May 1999 and February 2000. They were not qualified for surgical treatment on grounds of advanced general condition, clinical stage and tumour location. The patients included 30 men and 7 women, aged 42 to 81 years (mean: 53.1 yrs). Pathologically, the most frequent type of cancer were adenocarcinoma (n=5) and squamous cell cancer (n=26) (Table 1). Five patients had gastrostomy administered at the onset of brachytherapy, whereas two patients had metastasis to the liver at diagnosis.

Tab. 1. Clinical data of oesophageal cancer patients.

Age	Number of patients n= %
40 – 50	9 (24,3%)
51 – 60	15 (40,5%)
61 – 70	8 (21,6%)
71 – 80	3 (8,1%)
> 80	2 (5,4%)
Sex: men - 30, women - 7	
Histological diagnosis:	
1/ squamous cell carcinoma	17
2/ squamous cell carcinoma G1	1
3/ squamous cell carcinoma G2	6
4/ squamous cell carcinoma G3	2
5/ adenocarcinoma	4
6/ tubular adenocarcinoma	1
7/ solid carcinoma G3	2
8/ solid carcinoma partim squamous	2
9/ anaplastic carcinoma	2

Twenty-four patients were treated with palliative brachytherapy alone in two to three fractions of 7.5 Gy (at 1 cm from the catheter's axis) at weekly intervals. In one case, the patient received a second series of brachytherapy with a dose of 2 x 5 Gy due to relapse after 5 months.

Thirteen patients were treated with HDR brachytherapy combined with teletherapy. In four cases the treatment was palliative, whereas in 9 cases it was radical (Table 2). Radical treatment was given only to patients in good general condition, at an early clinical stage of the disease and with the 1st and 2nd degree dysphagia.

The palliative treatment included additional irradiation of the mediastinum with a 20 Gy dose of 6 MV or 9 MV photons in 5 or 10 fractions from two opposite fields, whereas the radical conformal treatment used doses of 40 to 60 Gy to the tumour target. Teletherapy was started 4 to 6 we-

eks after the termination of brachytherapy. In brachytherapy, the GAMMAMED 12i unit equipped with an Iridium-192 source of 10 Ci activity was used, together with an ABACUS planning system. Esophageal applicators 0.28cm and 0.32 in diameter were employed, the position of catheters being verified radiologically.

Remission was assessed radiologically and clinically during a 1-, 2-, 3- and 6-month follow-up.

Tab. 2. Methods of treatment

Methods of treatment	Number of patients
A/ Only brachytherapy:	
a/ 3 x 7,5 Gy	17
b/ 2 x 7,5 Gy	1
c/ 1 x 7,5 Gy	4
d/ 2 x 7,5 Gy (bronchial cancer with oesophageal infiltration	1
e/ two series of brachytherapy : 3 x 7,5 Gy and after recurrence (5 months) 2 x 5 Gy	1
	n = 24
B/ Brachytherapy and teletherapy:	
1Palliative treatment:	
a/ 3 x 7,5 Gy + hypofractionation (20 Gy)	3
b/ 2 x 7,5 Gy + hypofractionation (20 Gy)	1
2/ Radical treatment:	
a/ tele (40 Gy) + 3 x 7,5 Gy	2
b/ 3 x 7,5 Gy + tele (50 Gy)	3
c/ tele (60 Gy) + 3 x 6 Gy	1
d/ laser, tele (60 Gy) + 2 x 5 Gy	1
e/ tele (40 Gy), chtch + 3 x 7,5 Gy	1
f/ chtch + tele (40 Gy) + 2 x 6 Gy	1
	n = 13

Gy – Grey
Hypofractionation – 5 fractions each day with 4 Gy (mediastinum)
Tele – teletherapy – 20 to 30 fractions each day with 2 Gy, conformal treatment planning
Laser – excision of endoesophageal tumor using laser
Chtch – chemotherapy, usually Cisplatin and 5-Fluorouracyl

RESULTS

In a whole group of 37 patients, complete remission (CR), partial remission (PR), and lack of remission were found in 7 (18.9%), 18 (48.6%) and 12 (32.4%) cases, respectively. CR was achieved in 7 patients with the tumour located in the thoracic part of the esophagus. In two cases with the tumour in the abdominal and cervical part of the esophagus, no remission was observed. The size of the tumour infiltration did not have any effect on remission (Table 3). After the 2-, 3- and 6-month follow-up, subjective improvement (regression of dysphagia) and radiological improvement was found in 25 out (67%), 19 (51.4%) and 12 (32.4%) out of 37 cases (Tables 4 and 5).

One-year survival was observed in three patients, however, this group can become larger with a longer follow-up. Nine patients (24.3%) died within a 6-month follow-up.

In five patients with gastrostomy applied prior to radiotherapy, one patient survived 11 months with the gastrostomy removed after 4 months, in one patient a broncho-mediastinal fistula was detected after 5 months, whereas five patients survived more than three months. In the 6-month follow-up after treatment the most serious complication was fistula, which was found in 6 patients, including three patients who had fistula observed within one month after termination of treatment.

A/ patients treated only with brachytherapy

Out of 24 patients who had HDR brachytherapy applied only palliatively, three (12.5%) showed CR, 13 patients (54.2%) had PR, and 8 patients (33.3%) showed no remission as assessed 4 weeks after termination of treatment. After the 2-, 3- and 6-month follow-up, subjective and radiological improvement continued in 16 (66.7%), 12 (50.0%) and 7 (29.2%) cases, respectively. In the above period of time, five patients died (Tables 4 and 5). No improvement was found in four patients who had been treated with a single fraction of 7.5 Gy.

B/ patients treated with brachytherapy and teletherapy

Complete remission assessed after the four-month follow-up was observed in four patients treated radically, partial remission was found in 5 cases, whereas four patients showed no remission (including two treated radically). Out of 13 patients, after 3-month and 6-month follow-up clinical improvement (in swallowing) and radiological improvement was observed in 7 (53.9%) and 5 patients, respectively, including one patient treated palliatively. Due to cachexia resulting from the progression of the disease, four patients died during the 2-, 3, 4- and 5-month follow-up, respectively (Tables 3,4 and 5)

Tab. 3. Clinical and radiological assessment 4 weeks after the end of treatment in comparison with chosen clinical data

Clinical data	CR	PR	Nr
***1/ Age*:**			
40 – 50	**3**	**3**	**3**
51 – 60	**1**	**8**	**6**
61 – 70	**2**	**4**	**2**
71 – 80	**1**	**1**	**1**
> 80	**-**	**2**	**-**
***2/ Localization*:**			
a/ cervical part	-	-	1
b/ thoracic part:	-	1	
- upper part	1	6	7
- median part	6	9	3
- lower part	-	2	-
c/ abdominal part	-	-	1
***3/ Length of infiltration*:**			
a/ till 5 cm	2	5	5
b/ 5 – 10 cm	5	11	6
c/ more then 10 cm	-	2	1
Summary	**7 (18,9%)**	**18 (48,6%)**	**12 (32,4%)**

CR – complete remission
PR – partial remission
NR – no remission

Tab.4. Clinical and radiological assessment 4 weeks after the end of treatment in comparison with methods of treatment

Methods of treatment	CR	PR	NR
A/ Only brachytherapy:			
a/ 3 x 7,5 Gy	2	12	3
b/ 2 x 7,5 Gy	-	1	-
c/ 1 x 7,5 Gy	-	-	4
d/ 2 x 7,5 Gy (bronchial cancer with oesophageal infiltration	-	-	1
e/ two series of brachytherapy : 3 x 7,5 Gy and after recurrence (5 months) 2 x 5 Gy	1	- -	-

B/ Brachytherapy and teletherapy:			
1/Palliative treatment:			
a/ 3 x 7,5 Gy + hypofractionation (20 Gy)	-	2	1
b/ 2 x 7,5 Gy + hypofractionation (20 Gy)	-	-	1
2/ Radical treatment:			
a/ tele (40 Gy) + 3 x 7,5 Gy	1	1	-
b/ 3 x 7,5 Gy + tele (50 Gy)	2	1	-
c/ tele (60 Gy) + 3 x 6 Gy	1		
d/ laser, tele (60 Gy) + 2 x 5 Gy	-	1	-
e/ tele (40 Gy), chtch + 3 x 7,5 Gy	-	-	1
f/ chtch + tele (40 Gy) + 2 x 6 Gy	-	-	1

Tab. 5. Radiological and clinical improvement of dysphagia after 2, 3 and 6 months of observation

Methods of treatment	2 mth	3 mth	6 mth	Death (mth)
A/ Only brachytherapy:				
a/ 3 x 7,5 Gy	14/17	10/17	6/17	
b/ 2 x 7,5 Gy	1/1	1/1	0/1	
c/ 1 x 7,5 Gy				5
d/ 2 x 7,5 Gy (bronchial cancer with oesophageal infiltration	0/1	0/1	0/1	1,3,3,4
e/ two series of brachytherapy : 3 x 7,5 Gy and after recurrence (5 months) 2 x 5 Gy	1/1	1/1	1/1	
Rate of remission	**66,7%**	**50,0%**	**29,2%**	
B/ Brachytherapy and teletherapy:				
1Palliative treatment:				
a/ 3 x 7,5 Gy + hypofractionation (20 Gy)	2/3	2/3	1/3	2,4
b/ 2 x 7,5 Gy + hypofractionation (20 Gy)	0/1	0/1	0/1	-
2/ Radical treatment:				
a/ tele (40 Gy) + 3 x 7,5 Gy	2/2	1/2	1/2	-
b/ 3 x 7,5 Gy + tele (50 Gy)	3/3	3/3	2/3	-
c/ tele (60 Gy) + 3 x 6 Gy	1/1	1/1	1/1	-
d/ laser, tele (60 Gy) + 2 x 5 Gy	1/1	0/1	0/1	-
e/ tele (40 Gy), chtch + 3 x 7,5 Gy	0/1	0/1	-	5
f/ chtch + tele (40 Gy) + 2 x 6 Gy	0/1	0/1	-	3
Rate of remission	**69,2%**	**53,9%**	**38,5%**	
Total	**67,5%**	**51,4%**	**32,4%**	

DISCUSSION

The prognosis in patients with unresectable advanced esophageal cancer is still very poor despite the introduction of improved treatment modalities such as surgery, radiotherapy and chemotherapy. The reported 2- and 5-year survival rates range from 30% to 40% and 10% to 25%, respectively, regardless the tumour stage and treatment options [4,6,15,16,17]. Moreover, the prognosis is much worse in patients with stage IV and in those with inoperable advanced cancer.

In recent studies, several model variations of the multi-disciplinary treatment have been applied to patients, such as preoperative adjuvant or primary treatment. It must be pointed out, however, that the patients selected for those treatments

without typical surgery have usually had poor prognosis due to medical contraindications (eg. fistulae), invasion of adjacent organs and/or metastasis. The most critical aspect of this study is its retrospective investigation. However, it is difficult to carry out a randomised prospective trial comparing palliation and survival times.

Due to progression of the disease prior to diagnosis, dysphagia and weight loss are observed in more than 90% of patients. It is very important to provide an effective palliation for complaints that should be relieved with minimum morbidity.

Brachytherapy has been widely performed for the palliation of dysphagia due to esophageal cancer. Several reports have suggested that palliation of this type can be achieved with brachytherapy alone [18,19,20,21,22].

Positive results of HDR brachytherapy have been observed in patients who had not been treated surgically. In these patients, the radioisotope source is inserted through the mouth to the esophagus if the applicator can be passed through the stenotic region. In general, in brachytherapy a sufficient dose distribution in the tumour can only be achieved in tumours that are smaller than 1.5 cm in diameter, and only in patients whose esophageal lumen is kept sufficiently wide to allow passage of the applicator,

Brachytherapy treatment parameters, such as target definition, applicator diameter, dose prescription point, etc. vary widely as reported in the literature [7,20,23,24]. The length of the adjacent "normal" esophagus irradiated in brachytherapy is usually 1-2 cm proximal and distal to the primary lesion, although reports in the literature are seldom clear as to how the length of the esophagus is determined. In our recent practice we treat the involved endoscopically visible mucosa with a 1-2 cm margin. The drawback of using larger margins is that small esophageal applicators deliver relatively larger doses of radiation to normal healthy mucosa. The problem of using appropriate margins can never be satisfactorily resolved in clinical practice.

Whereas brachytherapy alone may alleviate dysphagia in patients with a life expectancy of one to three months, the addition of teletherapy may significantly prolong the duration of palliation [4,11,12,18].

The microSelectron HDR offers several advantages over the low dose rate Selectron: the high dose delivered means that treatment can be completed within approximately 15 min; the iridium source is only 1.1 mm in diameter, and the use of a 3.5 mm applicator, placed in a 14-gauge nasogastric tube, eliminates the need for a general anaesthetic. As a result, the treatment time is much shorter, and in the absence of a general anaesthetic the majority of patients can be discharged from hospital within two hours.

There have also been a number of reports concerning the use of HDR brachytherapy as a single treatment or in combination with external irradiation for esophageal cancer. Sur *et al.* [24] reported the local control and the 5-year survival rate approximately doubled when HDR brachytherapy was used, but there was no significant difference between both groups.

Siersema *et al.* [23] reported their experience with 40 patients treated palliatively with afterload casesium using a low dose rate Selectron (LDR). All patients required a general anaesthetic both to assess the size of the tumour and applicator's placement. A dose rate of 15 Gy at 1 cm off axis was administered. One patient was unable to lie flat for the required length of time due to some respiratory problems, five others experienced esophagitis, and 65% of all patients sustained good relief of dysphagia. The median duration of relief was approximately 14 weeks.

Spencer *et al.* [17] reported a randomised comparative study of 23 patients using laser treatment and a single application of 15 Gy intracavitary brachytherapy as a palliative procedure. The treatment using a Selectron unit with an iridium source lasted approximately 6 min. Both treatments were very effective: 83% of all cases improved following brachytherapy compared with 92% after laser treatment. The high response rate may be due to the fact that nine out of 23 patients had small cell pathology. Thirty percent of the laser-irradiated patients required re-treatment; laser modality was also associated with a longer hospital stay.

In another study, 10 of 39 patients (43.6%) without bypass surgery received brachytherapy, their mean survival time being significantly longer than that of the group of patients without brachytherapy: 16.5 ± 2.5 *vs.* 9.0 ± 1.3 months (p< 0,05). These data suggest that HDR brachytherapy might considerably have prolonged the survival time in esophageal patients when performed in combination with external irradiation [22].

The results of treating 36 patients palliatively with intraluminal irradiation have been reported by Jager *et al.* [18]. Thirty-two patients were available for assessment, and a good response was noted in 69% of them, with a median duration of response of 4 months. Factors that may aid patient selection such as the size of the lesion, the dysphagia score, pre-treatment weight loss and previous surgical intervention including laser treatment, do not appear to have affected the response. The group randomised for teletherapy alone were treated with 70 Gy in 35 fractions over 7 weeks. The group with combined treatment received 50 Gy of teletherapy followed by brachytherapy, one application per week. For a total of three of three or four applications the doses delivered were 19.6 Gy or 26.1 Gy. A statistically significant difference in the 5-year survival (17% *vs.* 10%, p<0.05) was found in the study favouring the group with combined treatment. Local recurrences were found to be more frequent in the external beam group than in the group with combined treatment: 61.3% *vs.* 43%. Perforation or haemorrhage occurred in 12.6% of each group treated.

Another randomised trial included 50 patients, of whom 25 received 55 Gy of teletherapy alone, and 25 patients who were administered 35 Gy of teletherapy, supplemented with 12 Gy of HDR brachytherapy in two HDR treatments, one week apart [12]. The total doses of radiation were designed with the aim of making dose-fractionation schemes biologically equivalent. The group receiving brachytherapy revealed better relief of dysphagia (70.6% *vs.* 37.5% in the teletherapy-only modality, improved local control (70.6%*vs.* 25%), and better actuarial survival (78% *vs.* 47%) at one year. However, the incidence of strictures (8% *vs.* 4%) was higher for the brachytherapy modality.

The largest experience in esophageal brachytherapy probably comes from Japan, where the histology is almost always squamous. Iwasa *et al.* [15] reported no improvement in survival, however, they found significant improvement in 2-year local control in the treatment with teletherapy (median of 50 Gy) and HDR brachytherapy with 12 Gy in fractions, compared with 50 Gy or more of teletherapy alone. The 5-year survival rate in 66 patients without distant metastasis was 18%, and the 1- and 2-year actuarial local control rates were 66% and 64%, respectively. The cause of death was attributed to local failure in 28%, distant metastasis in 29%, and an intercurrent disease in 31% of all patients.

In another Japan experience Okawa et al. [25] concluded that in patients with 5 cm or less tumor length the cause-specific survival was significantly greater in the intraluminal brachytherapy combined group then in the external irradiation alone group. In the patients with the stage T1 and T2 disease, cause-specific survival tended to be better in the intraluminal brachytherapy combined group then in the external irradiation alone group.

Our results suggest that a large number of patients with advanced esophageal cancer can profit from endoluminal brachytherapy. The aim of palliative brachytherapy in the group of patients investigated was to diminish dysphagia, alleviate pain and bleeding, and to improve the patients' well-being. Regression of dysphagia was found in more than two-thirds of our patients regardless their age, clinical stage and tumour location. Over the period of 6-month follow-up subjective and radiological improvement was noted in one-third of the patients.

The reason why we have decided to publish the results of our study despite the short period of the follow-up is that our group of patients had had a poor prognosis and their survival time was expected to be less than 6 months.

Tab. 6. Suggested schema for external beam radiation and brachytherapy* in the palliative treatment of esophageal cancer (8).

A/ Recurrent after external beam radiation or short life expectancy:
Brachytherapy:
- HDR - total dose of 10 - 14 Gy, one or two fractions
- LDR - total dose of 20 – 40 Gy, one or two fractions, 0,4 – 1,0 Gy/hr
B/ No previous external beam radiation:
External beam radiation:
- 30 - 40 Gy in 2 – 3 Gy fractions
Brachytherapy:
- HDR – 10 - 14 Gy, one or two fractions
- LDR - total dose of 20 - 25 Gy, single course, 0,4 – 1,0 Gy/hr
C/ No previous external beam radiation, life expectancy greater than 6 months:
External beam radiation:
- 45-50 Gy in 1,8–2,0-Gy fractions, five fractions per week, weeks 1-5
Brachytherapy:
- HDR - total dose of 10 Gy, 5 Gy/fraction, one fraction/ week, starting 2-3 weeks from completion of external beam
- LDR - total dose of 20 Gy, single course, 0,4 – 1,0 Gy/hr, starting 2-3 weeks from completion of external beam
* all doses specified 1 cm from midsource or mid-dwell position

CONCLUSIONS

HDR brachytherapy is an effective palliative method of treatment in advanced unrespectable esophageal cancer.
Regression of dysphagia was found in more than two-thirds of our patients, regardless their age, clinical stage and tumour location. Over the period of the 6-month follow-up subjective and radiological improvement was noted in one-third of the patients.
The most frequently encountered risk in HDR brachytherapy is that of broncho-esophageal fistula.

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