ELSEVIER

Brachytherapy 3 (2004) 87–94

BRACHYTHERAPY

Palliative treatment by high–dose-rate intraluminal brachytherapy in patients with advanced esophageal cancer

Janusz Skowronek[1,*], Tomasz Piotrowski[2], Grzegorz Zwierzchowski[2]

[1]*Department of Brachytherapy, Great Poland Cancer Centre, Poznań, Poland*
[2]*Department of Medical Physics, Great Poland Cancer Centre, Poznań, Poland*

ABSTRACT

PURPOSE: The aim of this work was to analyze the results of palliative HDR brachytherapy in patients with advanced esophageal cancer.

METHODS AND MATERIALS: Ninety-one patients with unresectable, advanced esophageal cancer were treated palliatively by HDR brachytherapy. All patients received a total dose of 22.5 Gy in three fractions per week. Remissions of dysphagia and other clinical and radiological factors were assessed in the first month posttreatment, and then in the third, sixth, and twelfth months. The survival rate was compared with some chosen clinical factors using a log-rank test and the Kaplan–Meier method.

RESULTS: The median survival time among all patients was 8.2 months. The median survival time according to the obtained remission was 14.6, 7.2, and 3.8 months (log-rank $p = 00001$, F Cox $p = 0.00001$) for complete remission (CR), partial remission (PR), and lack of remission (NR), respectively. A longer median survival time was observed when tumor size was less then 5 cm (12.1 months), than between 5 and 10 cm (7.8 months), or longer than 10 cm (6.4 months) (log-rank $p = 0.002$). Longer median survival times were observed in clinical stage II (14.1 months), compared with clinical stage III (7.7 months) and IV (7.2 months) (log-rank $p = 0.01$). Significant correlations were found between survival and the Karnofsky Performance Status, grade of dysphagia, and age.

CONCLUSIONS: HDR brachytherapy for advanced esophageal cancer allowed for improvement of dysphagia in most patients. The complete or partial remission, the older age of patients, and the lower grade of dysphagia observed in first month posttreatment were the most important prognostic factors allowing for prolonged survival (confirmed by a multivariate analysis). In the univariate analysis, important prognostic factors for prolonged survival were: a higher Karnofsky Performance Status, a lower clinical stage and a small tumor size.

Keywords: Esophageal cancer; HDR brachytherapy; Radiotherapy; Palliative treatment

Introduction

As few as 10–20% of esophageal cancer patients qualify for surgical treatment. Those who do not qualify for surgery due to tumor 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 tumor infiltrates the outer wall of the esophagus. The probability of metastasis to the regional lymphatic nodes is proportional to the size of the tumor; it is higher than 50–60% for a tumor exceeding 5 cm (1–5).

Various methods of palliation have been used in an attempt to improve patients' quality of life and to provide near normal, if not normal, swallowing until death occurs because of progressive systemic disease. These methods include surgical bypass, laser treatment, chemotherapy, intubation, and external beam radiotherapy (EBRT) of 10–40 Gy, or a combination of the above. The prognosis continues to be dismal, with a median survival of 2.5–5 months from any of these techniques alone or a marginal improvement with a combination (6–8). At the same time, a large majority of patients die due to a lack of success in treating the

Received 17 March 2004; received in revised form 25 May 2004; accepted 28 May 2004.

* Corresponding author. Department of Brachytherapy, Great Poland Cancer Centre, Ulica Garbary 15 61-866, Poznań, Poland. Tel.: +48-61-854-0654, +48-60-261-8538; fax: +48-61-852-1948.

E-mail address: janusko@priv6.onet.pl (J. Skowronek).

1538-4721/04/$ – see front matter
doi:10.1016/j.brachy.2004.05.003

primary lesion and/or the infiltration of neighboring organs by cancer. Frequently, aspiration of food or fistulae, causing aspiration pneumonia leads to death. The above considerations have resulted in attempts to apply higher doses of radiation to the tumor.

Endoesophageal brachytherapy makes it possible to use high doses of radiation to the tumor itself with concurrent protection of adjoining healthy tissues due to the rapid fall in the dose with the square of the distance from the center of the dose. The above treatment also leads to a smaller proportion of late radiation complications (9–13). The aim of palliative brachytherapy is to reduce dysphagia, diminish pain and bleeding, and to improve the patient's well-being (6, 10, 14).

Due to a high mucosal dose and intratumoral necrosis, esophagobronchial fistulas are frequent complications. Recently, the risk of late complications has been shown to be strongly affected by an esophageal mucosal dose, a large fraction dose, a smaller applicator, and combined therapy (15).

The present article assesses the effect of palliative HDR brachytherapy on survival in comparison with some chosen prognostic factors.

Methods and materials

Ninety-one patients with unresectable, advanced esophageal cancer were treated by HDR brachytherapy alone at the Great Poland Cancer Center between May 1999 and June 2001. They were not qualified for surgical treatment or radical external beam radiotherapy on the grounds of advanced general condition, clinical stage, and tumor location. Palliative HDR brachytherapy was chosen as the sole treatment method due to the limited possibilities of using external beam therapy and in most of cases the patient's advanced clinical stage. We expected a quick improvement of dysphagia after brachytherapy was performed on an outpatient basis.

In all patients, gastroscopy, X-ray films, and CT were performed for a histological diagnosis and to evaluate the extent of the tumor.

The group consisted of 75 (82.4%) men and 16 (17.6%) women aged 38–81 years (mean, 59.4 years). Most patients qualified for palliative brachytherapy were in an advanced clinical stage, 40 (43.9%) at stage III and 40 (43.9%) at stage IV. Their main complaint was dysphagia, which was grade III in 53 (58.2%) cases and grade IV in 22 (24.2%) cases. Grades were qualified as follows: 0, no dysphagia; 1, dysphagia for solids; 2, dysphagia for semisolids; 3, dysphagia for liquids; and 4, total dysphagia. Pathologically, the most frequent type of cancer was squamous cell carcinoma (71, [78.0%]) and adenocarcinoma (9, [9.9%]). Clinical data on all patients are summarized in Table 1. Fifteen patients had gastrostomy performed at the onset of brachytherapy, 8 patients had metastasis to the liver, and 4 to the lung at the time of diagnosis.

Treatment

Following premedication, one radiologically verified endoesophageal catheter was placed in the esophagus. Standard esophageal applicators (2.8 and 3.2 mm in diameter) were used. They were chosen for brachytherapy because of the small lumen diameter (extensive obturation of the esophagus visualized radiologically and during gastroscopy) in most cases in this group of patients.

During treatment, 10 Ci of ^{192}Ir (nominal activity) was delivered using an HDR-GammaMed 12i unit (Mick Radio-Nuclear Instruments, Inc., Mt. Vernon, NY). Dose distribution was calculated using the ABACUS software.

All patients received a total dose of 22.5 Gy given in three weekly fractions of 7.5 Gy. The dose was prescribed

Table 1
Clinical characteristics of patients

Clinical data	Number of patients
Age (years)	Median: 59.4 years
<52	21 (23.1%)
52–57	26 (28.5%)
58–69	23 (25.3%)
>69	21 (23.1%)
Sex	
Male	75 (82.4%)
Female	16 (17.6%)
Karnofsky score	
50	9 (9.9%)
60	39 (42.9%)
70	36 (29.5%)
80	7 (7.7%)
Histology	
Squamous cell carcinoma	71 (78.0%)
Adenocarcinoma	9 (9.9%)
Carcinoma solidum	4 (4.4%)
Carcinoma anaplasticum	2 (2.2%)
Unclassified	5 (5.5%)
Location	
Cervical	6 (6.6%)
Thoracalis upper	10 (11.0%)
Thoracalis median	46 (50.5%)
Thoracalis lower	25 (27.5%)
Abdominalis	4 (4.4%)
Clinical stage	
2	11 (12.2%)
3	40 (43.9%)
4	40 (43.9%)
Length of infiltration	
<5 cm	14 (15.4%)
5–10 cm	56 (61.5%)
>10 cm	21 (23.1%)
Grade of dysphagia	
2	16 (17.6%)
3	53 (58.2%)
4	22 (24.2%)

at a 10 mm distance to the surface of the source. The target volume included the radiologically visualized residual tumor, which had been assessed previously during gastroscopy, plus 2 cm safety margins in the cranial and caudal direction. After placement of the catheter with a special marker inside, an X-ray was taken. It was used later for definition of tumor volume and in the preparation of the treatment plan. In all treatment plans optimization procedures were performed which was necessary for full coverage of the ends of the defined volume.

Methods

Remissions of dysphagia and other clinical and radiological factors were assessed in the first month posttreatment, and then at 3, 6, and 12 months. To evaluate the obtained results, clinical examination, X-rays, CT scans, and in some cases, gastroscopy (not always possible due to acute mucositis) were performed.

The patients' survival was compared with selected clinical factors such as: grade of remission assessed (radiologically and during gastroscopy) in the first month posttreatment, age, sex and histopathology, the Karnofsky Performance Status, clinical stage, location and size of tumor, and grade of dysphagia.

Statistical evaluation

The survival time was defined as the time from the beginning of radiation therapy to the death of the patient or to the end of the twelfth month of observation. A univariate categorized analysis calculated by the Kaplan–Meier method and log-rank, F Cox tests were performed for overall survival. For non-categorized data, such as age, Cox's regression model was used.

Results

The average period of observation was 7.4 months. The median survival time among all patients was 8.2 months (Fig. 1).

Univariate and multivariate analyses revealed differences in survival according to age (Fig. 2, log-rank test $p = 0.04$, F Cox test $p = 0.02$). Age was grouped into four groups (equal to or lower than the median and two outside quartiles). Older patients had longer survival, especially those 69 or more years of age.

Survival was analyzed according to Karnofsky status. Patients with better performance status (a Karnofsky score 80 or 70) had a better survival rate than those with a lower score (Fig. 3, log-rank test $p = 0.003$). The median survival times according to this score were: for 50, 4.2 months; for 60, 7.1 months; for 70, 9.6 months; and for 80, 11.9 months.

Longer median survival times were observed for stage II (14.1 months) compared with stages III (7.7 months) and IV (7.2 months) (Fig. 4, log-rank test $p = 0.01$).

The influence of tumor location on survival was analyzed. Longer median survival times were observed when the tumor size was less then 5 cm (12.1 months), than between 5 and 10 cm (7.8 months), or larger than 10 cm (6.4 months) (Fig. 5, log-rank test $p = 0.002$).

The influence of local response assessed in the first month after brachytherapy on survival was analyzed. Complete remission (CR) rated at 4 weeks posttreatment was ascertained in 21 (23.1%) cases, partial remission (PR) in 52 (57.1%) cases, lack of remission (NR) in 17 (18.7%) cases, and progression in 1 case (1.1%). The median survival time according to the obtained remission was: for CR, 14.6 months; for PR, 7.2 months; and for NR, 3.8 months (Fig. 6, log-rank test $p = 0.00001$, F Cox test $p = 0.00001$).

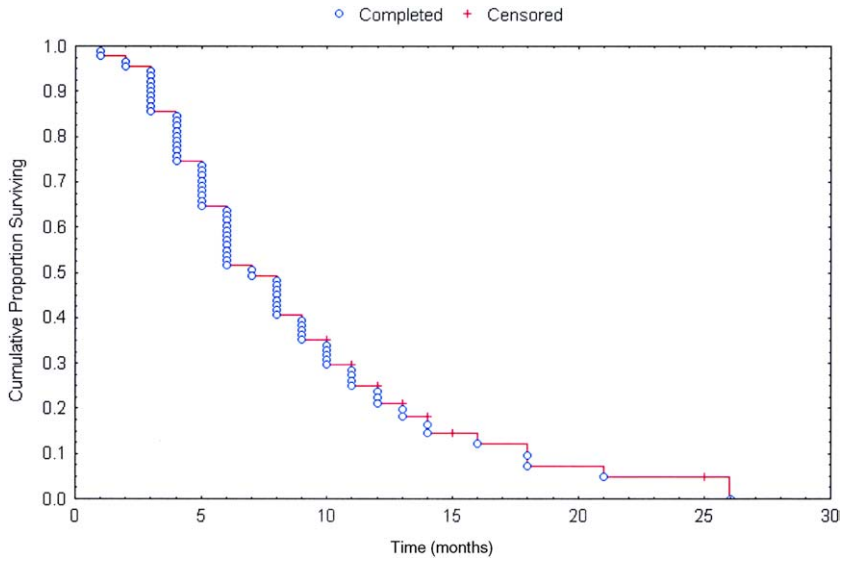

Fig. 1. Survival for all patients.

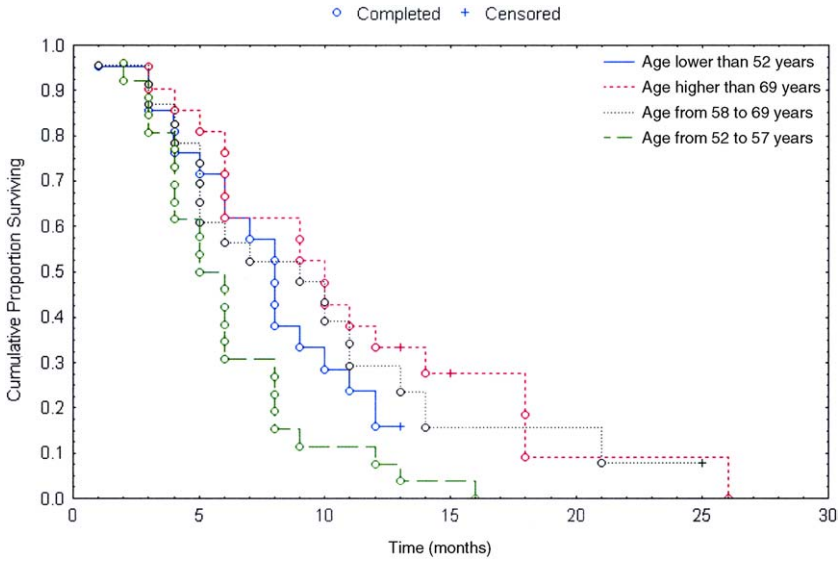

Fig. 2. Survival according to age (log-rank test, p = 0.04, F Cox test p = 0.02).

Nineteen (20.9%) patients had a 1-year survival rate, however, this group may increase with longer follow-up. Thirteen patients (14.3%) died within the first 3 months of follow-up.

The influence of the dysphagia grade on survival was studied. Patients with grade II dysphagia survived significantly longer than the patients with grade III and IV (Fig. 7, log-rank test $p = 0.0002$, F Cox test $p = 0.003$).

In the univariate analysis we did not observe any correlations between survival time and sex (log-rank test $p = 0.5$), location of the tumor (log-rank test $p = 0.4$), or the histology of the tumor (log-rank test $p = 0.5$).

In 15 patients with gastrostomy performed prior to radiotherapy, 1 patient survived 11 months with the gastrostomy tube removed after 4 months, in 3 patients an esophagobronchial fistula was detected after 5 months, whereas 11 patients survived more than 3 months. The median survival time for patients with metastasis to the liver or lungs was 5.5 months.

Complications

At the 6-month follow-up the most serious complication was the presence of an esophagobronchial fistula, in 9 cases (9.9%) during supervisory investigations. In the next 6 months fistula occurred in another 2 patients. The presence of fistula was correlated with tumor size (clinical stage) and a lower Karnofsky score. A fistula occurred in 7 cases at stage IV and in 4 cases at stage III. It seems that fistulas

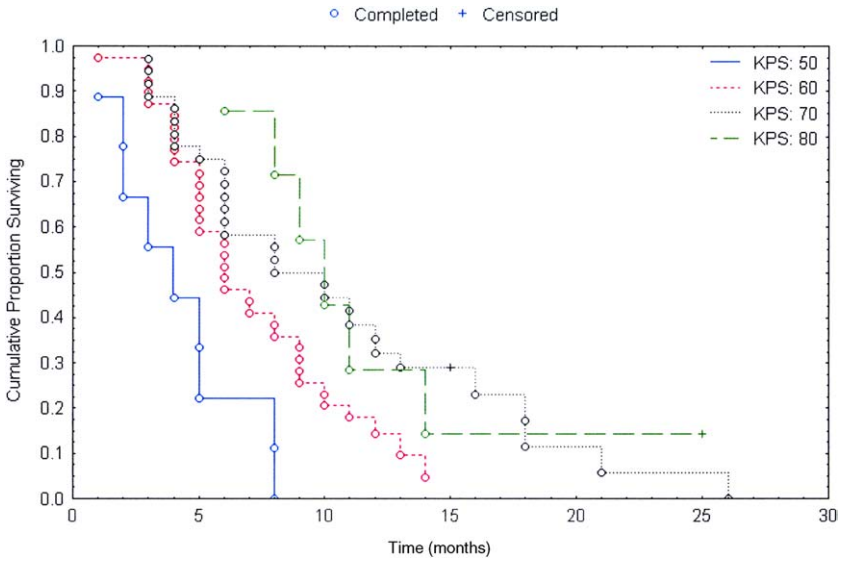

Fig. 3. Survival according to Karnofsky score (log-rank test, p = 0.003).

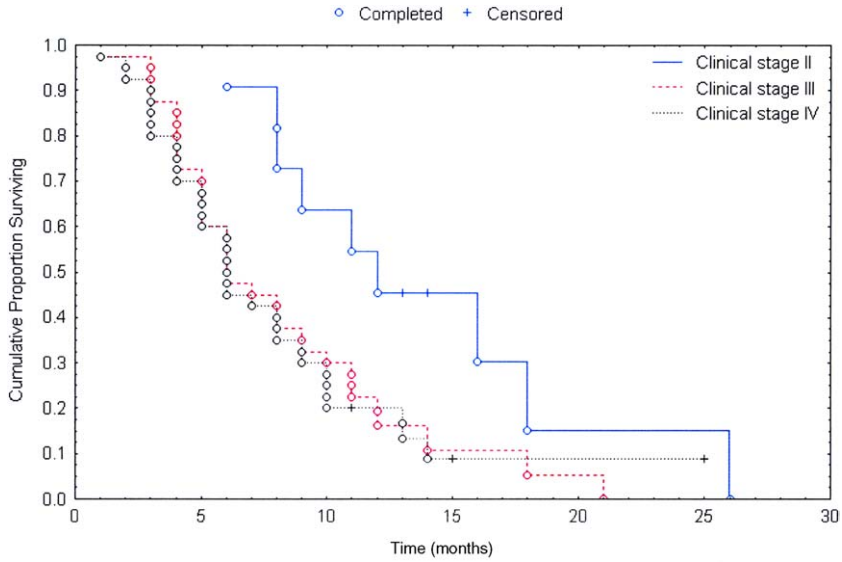

Fig. 4. Influence of clinical stage on survival (log-rank test, p = 0.01).

were tumor related rather then treatment related. In most patients (65/91, 71.4%) we observed a temporary worsening of swallowing and an increase of pain (during treatment and up to 1–3 weeks later).

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 30–40% and 10–25%, respectively, regardless of the tumor stage and treatment options (4, 9, 16–18). 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 multidisciplinary 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 usually have poor prognosis due to medical contraindications (e.g., 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 randomized 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%

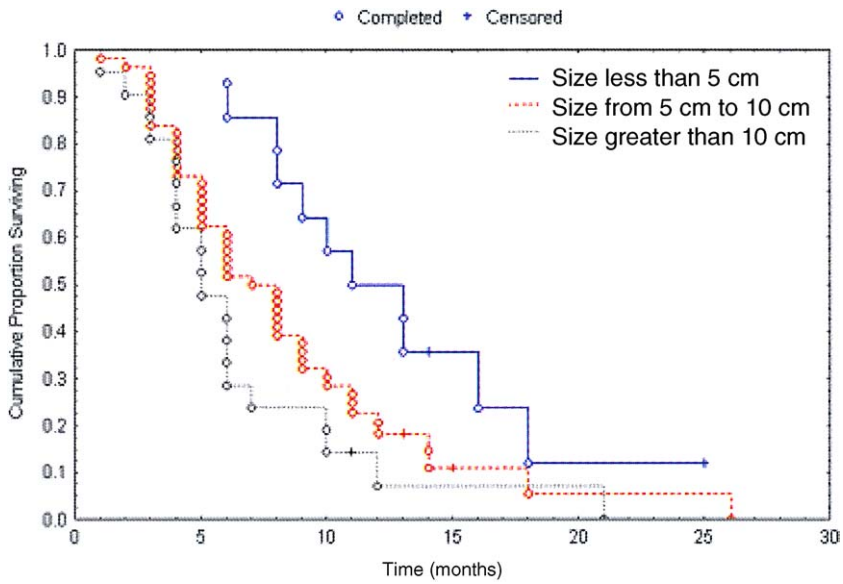

Fig. 5. Influence of infiltration length on survival (log-rank test, p = 0.002).

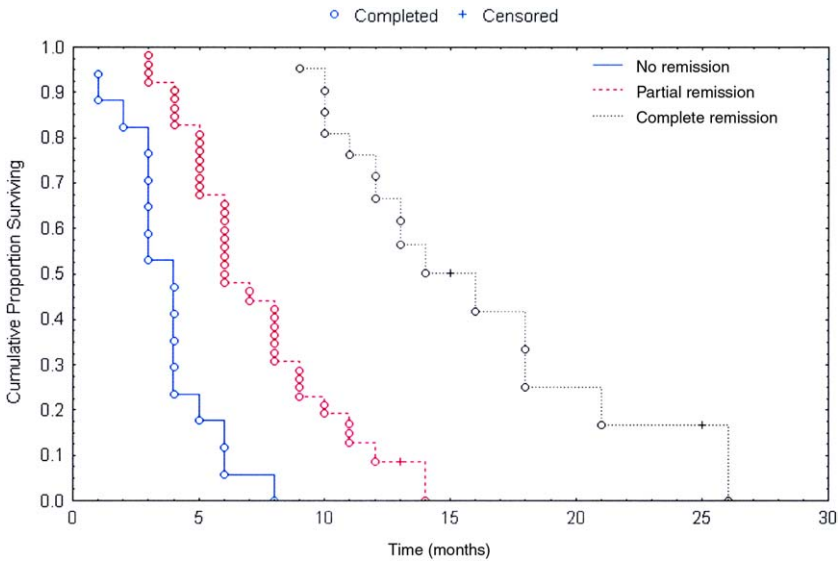

Fig. 6. Survival according to remission assessed in first month after treatment (log-rank test p = 0.00001, F Cox test p = 0.00001).

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 (7, 19–22). 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. Generally in brachytherapy, a sufficient dose distribution in the tumor can only be achieved in tumors 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 (8, 10, 21, 23). 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 treated the involved endoscopically visible mucosa with a 1–2 cm margin. The drawback of using larger margins is that small esophageal applicators deliver

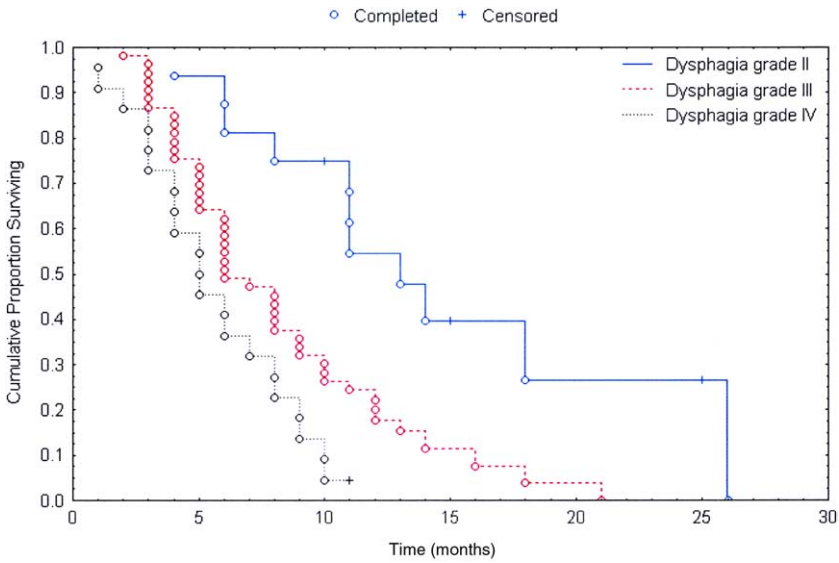

Fig. 7. Influence of dysphagia grade on survival (log-rank test p = 0.0002, F Cox test p = 0.003).

relatively larger doses of radiation to normal healthy mucosa. The problem of using appropriate margins can never be satisfactorily resolved in clinical practice.

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 (24–26). Spencer *et al.* (18) reported a randomized comparative study of 23 patients using laser treatment and a single application of 10 Gy intraluminal brachytherapy as a palliative procedure. The treatment using a Selectron (Nucleotron UK Ltd, Tattenhall, UK) unit with an iridium source lasted 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 9 of 23 patients had small cell pathology. 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 ($p < 0.05$), respectively. These data suggest that HDR brachytherapy might prolong the survival time in esophageal patients considerably when performed in combination with external irradiation (7).

Jager *et al.* reported the results of treatment of 36 patients with intraluminal brachytherapy (19). 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, pretreatment weight loss, and previous surgical intervention including laser treatment do not appear to have affected the response. The group randomized for external beam therapy alone was treated with 70 Gy in 35 fractions over 7 weeks. The group with combined treatment received 50 Gy of external beam therapy followed by brachytherapy, one application per week. The doses delivered were 19.6 Gy or 26.1 Gy for a total of three or four applications. A statistically significant difference in the 5-year survival (17% vs. 10%, $p < 0.05$) was found in the study favoring the combined treatment group. Local recurrences were found to be more frequent in the external beam group than in the combined treatment group: 61.3% vs. 43%. Perforation or hemorrhage occurred in 12.6% of each group treated.

Another randomized trial included 50 patients, 25 of whom received 55 Gy of external beam therapy alone, and 25 patients who were administered 35 Gy of external beam therapy, supplemented with 12 Gy of HDR brachytherapy in two HDR treatments, 1 week apart (27). The group receiving brachytherapy had better relief of dysphagia (70.6% vs. 37.5% in the external-beam-therapy-only modality), improved local control (70.6% vs. 25%), and better actuarial survival (78% vs. 47%) at 1 year. However, the incidence of strictures (8% vs. 4%) was higher for the brachytherapy modality.

One of the largest experiences in esophageal brachytherapy comes from Japan, where the histology is almost always squamous. Isawa *et al.* reported no improvement in survival, however, they found significant improvement in 2-year local control in the treatment with external beam therapy (median, 50 Gy) and HDR brachytherapy with 18 Gy in 3 fractions, compared with 50 Gy or more of external beam therapy alone (16). 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 Japanese experience, Okawa *et al.* (28) concluded that in patients with 5 cm or less tumor size, cause-specific survival was significantly greater in the intraluminal brachytherapy combined group than in the external irradiation alone group. In the patients with stage T1 and T2 disease, cause-specific survival tended to be better in the intraluminal brachytherapy combined group than in the external irradiation alone group.

A multicenter, prospective randomized study was conducted under the auspices of the International Atomic Energy Agency to evaluate two HDR brachytherapy regimens used in the treatment of surgically inoperable patients with squamous cell carcinoma (6). Patients were randomized to receive 18 Gy in 3 fractions on alternate days (6 Gy per fraction, Group A) or 16 Gy in 2 fractions on alternate days (8 Gy per fraction, Group B). A total of 232 patients were entered into the study (112 in Group A and 120 in Group B).The overall survival was 7.9 months for the whole group (Group A, 9.1 months; Group B, 6.9 months; $p > 0.05$). In the univariate analysis, weight, gender, race, dysphagia score, the treatment center, and tumor grade had an impact on dysphagia-free survival, whereas gender and performance score had an impact on dysphagia-free survival in multivariate analysis. Only age had an impact on the overall survival in both univariate ($p = 0.0430$) and multivariate ($p = 0.0331$) analyses. The authors concluded that fractionated HDR brachytherapy alone is an effective method of palliating advanced esophageal cancers, surpassing the results of any other modality of treatment presently available. Dose fractions of 6 Gy × 3 and 8 Gy × 2 produce similar results for dysphagia-free survival, overall survival, strictures, and fistulas and are equally effective in palliation of advanced esophageal cancer.

The aim of palliative brachytherapy in the group of patients treated at the Great Poland Cancer Centre was to diminish dysphagia, alleviate pain and bleeding, and to improve the patients' well-being. Our results suggest that a large number of patients with advanced esophageal cancer can profit from endoluminal brachytherapy. Regression of dysphagia was found in the first month posttreatment in more than 80% of our patients regardless their age, clinical stage, and tumor location. Over the 6-month follow-up period, subjective and radiological improvement was still noted in two-thirds of the patients.

The prognostic role of age, grade of dysphagia, and remission was confirmed in the multivariate analysis. We found additional correlations between the survival rate and Karnofsky score, clinical stage, and the size of the tumor in univariate analysis.

Longer survival was connected with the older age of patients, better performance status (according to the Karnofsky score), and a lower clinical advance of the tumor (clinical stage, tumor size). Better prognosis in older age was probably connected with less aggressive tumors, but this is only a hypothesis. In multivariate analysis the strongest correlation was observed between age and grade of dysphagia, meaning that older patients had a lower grade of dysphagia. Subjective and objective assessments of local remission and dysphagia also were important prognostic factors.

The location of the tumor on the esophagus failed to show any significant statistical correlation with survival. We suppose that in the case of advanced unresectable tumors the location does not play as significant a prognostic role as it does in early tumors qualified for radical treatment.

Conclusions

HDR brachytherapy for advanced esophageal cancer allows for improvement of dysphagia in most patients. The median survival time among all patients with advanced esophageal cancer treated palliatively was 8.2 months. A complete or partial remission, the older age of patients, and the lower grade of dysphagia observed in the first month after the treatment were the most important prognostic factors allowing for prolonged survival (confirmed in multivariate analysis). Important prognostic factors for prolonged survival in univariate analysis were: a higher Karnofsky Performance Status, a lower clinical stage, and a smaller tumor size. Some patients had total remission, confirmed radiologically, for more than 6 months. Tolerance for treatment was good, and the number of complications did not differ much from that obtained by other authors (6, 19, 27).

References

[1] Erickson B, Wilson JF. Clinical indications for brachytherapy. *J Surg Oncol* 1997;65:218–227.

[2] Leung JT, Kuan R. Brachytherapy in oesophageal carcinoma. *Australas Radiol* 1995;39:375–378.

[3] Makarewicz R, Czechowicz W, Kabacinska R. Effective palliation for advanced esophageal cancer using intraluminal irradiation. *Mater Med Pol* 1996;28:107–110.

[4] Reed CE. Comparison of different treatments for unresectable esophageal cancer. *World J Surg* 1995;19:828–835.

[5] Speiser BL. Brachytherapy in the treatment of thoracic tumors. Lung and esophageal. *Hematol Oncol Clin North Am* 1999;13:609–634.

[6] Sur RK, Levin VC, Donde B, *et al*. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma—An International Atomic Energy Agency study. *Int J Radiat Oncol Biol Phys* 2002;53:127–133.

[7] Sur RK, Donde B, Levin VC, *et al*. Fractionated high–dose-rate intraluminal brachytherapy in palliation of advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 1998;40:447–453.

[8] Siersema PD, Dees J, van Blankenstein M. Palliation of malignant dysphagia from oesophageal cancer. Rotterdam Oesophageal Tumor Study Group. *Scand J Gastroenterol Suppl* 1998;225:75–84.

[9] Coia LR, Minsky BD, John MJ, *et al*. The evaluation and treatment of patients receiving radiation therapy for carcinoma of the esophagus: Results of the 1992–1994 Patterns of Care Study. *Cancer* 1999;85:2499–2505.

[10] Fritz P, Wannenmacher M. Radiotherapy in the multimodal treatment of esophageal carcinoma. A review. *Strahlenther Onkol* 1997;173:295–308.

[11] Gaspar LE, Nag S, Herskovic A, *et al*. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical Research Committee, American Brachytherapy Society, Philadelphia, PA. *Int J Radiat Oncol Biol Phys* 1997;38:127–132.

[12] Swaroop VS. Re: Practice guidelines for esophageal cancer. *Am J Gastroenterol* 1999;94:2319–2320.

[13] Taal BG, Aleman BM, Koning CC, *et al*. High–dose-rate brachytherapy before external beam irradiation in inoperable oesophageal cancer. *Br J Cancer* 1996;74:1452–1457.

[14] Skowronek J, Adamska K, Suwalska M, *et al*. Palliative HDR brachytherapy in treatment of advanced esophageal cancer. *Rep Pract Radioth Oncol Radiother* 2000;5:111–119.

[15] Akagi Y, Hirokawa Y, Kagemoto M, *et al*. Optimum fractionation for high–dose-rate endoesophageal brachytherapy following external irradiation of early stage esophageal cancer. *Int J Radiat Oncol Biol Phys* 1999;43:525–530.

[16] Iwasa M, Ohmori Y, Iwasa Y, *et al*. Effect of multidisciplinary treatment with high–dose-rate intraluminal brachytherapy on survival in patients with unresectable esophageal cancer. *Dig Surg* 1998;15:227–235.

[17] Maier A, Woltsche M, Fell B, *et al*. Local and systemic treatment in small cell carcinoma of the esophagus. *Oncol Rep* 2000;7:187–192.

[18] Spencer GM, Thorpe SM, Sargeant IR, *et al*. Laser and brachytherapy in the palliation of adenocarcinoma of the esophagus and cardia. *Gut* 1996;39:726–731.

[19] Jager J, Langendijk H, Pannebakker M, *et al*. A single session of intraluminal brachytherapy in palliation of esophageal cancer. *Radiother Oncol* 1995;37:237–240.

[20] Maingon P, d'Hombres A, Truc G, *et al*. High–dose-rate brachytherapy for superficial cancer of the esophagus. *Int J Radiat Oncol Biol Phys* 2000;46:71–76.

[21] Micaily B, Miyamoto CT, Freire JE, *et al*. Intracavitary brachytherapy for carcinoma of the esophagus. *Semin Surg Oncol* 1997;13:185–189.

[22] Rovirosa A, Marsiglia H, Lartigau E, *et al*. Endoluminal high–dose-rate brachytherapy with a palliative aim in esophageal cancer: Preliminary results at the Institut Gustave Roussy. *Tumori* 1995;81:359–363.

[23] Sur RK, Levin CV, Donde B. The value of high–dose-rate microsource brachytherapy in the treatment of oesophageal carcinoma. *S Afr Med J* 1997;87:81–82.

[24] Calais G, Dorval E, Louisot P, *et al*. Radiotherapy with high–dose-rate brachytherapy boost and concomitant chemotherapy for Stages IIB and III esophageal carcinoma: Results of a pilot study. *Int J Radiat Oncol Biol Phys* 1997;38:769–775.

[25] Moni J, Nori D. The pitfalls and complications of radiation therapy for esophageal carcinoma. *Chest Surg Clin N Am* 1997;7:565–584.

[26] Schraube P, Fritz P, Wannenmacher MF. Combined endoluminal and external irradiation of inoperable oesophageal carcinoma. *Radiother Oncol* 1997;44:45–51.

[27] Gaspar LE, Qian C, Kocha WI, *et al*. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92–07): Preliminary toxicity report. *Int J Radiat Oncol Biol Phys* 1997;37:593–599.

[28] Okawa T, Dokiya T, Nishio M, *et al*. Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. *Int J Radiat Oncol Biol Phys* 1999;45:623–628.