Evaluation of the Effectiveness of Radiation Treatment Methods for Treatment of Early-Stage Esophageal Cancer

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Abstract

Purpose: We reviewed the treatment outcome of 41 early-stage esophageal cancer (34 mucosa layer cases, 7 sub mucosa stage cases) for three treatment methods focusing on the effectiveness of brachytherapy for cases treated from January 1991 to December 2005.

Materials and Methods: The age of the patients ranged from 38 to 84 years old (median age 68 years) with 37 male patients and 4 female patients. The treatment methods reviewed were (1) External beam radiation therapy (EBRT) group: 5 cases, 60 〜 66 Gy (one case radiotherapy only, 3 cases with chemotherapy and 1 case with endoscopic therapy). (2) High dose rate remote after load system (RALS) endoesophageal brachytherapy group (BT) group: 9 cases (3 cases radiotherapy only, none case with chemotherapy, 6 cases with endoscopic therapy). Irradiation was 6 〜 20 Gy in 2 to 3 fractions. (3) Combined external beam radiation therapy and brachytherapy (EBRT + BT) group: 27 cases, after external beam radiation of 30 〜 66 Gy, patients were treated with 12 〜 18 Gy in 2 or 3 fractions by brachytherapy (17 cases radiotherapy only, 8 cases with chemotherapy, 2 cases with endoscopic therapy).

Results: There was not a significant difference in the cumulative survival rate between the BT and EBRT + BT groups. Sixteen cases of local recurrence or lymph node metastasis were observed for the 41 cases (39.0%) with a median time of 95 months (3 〜 186 months). Complications occurred for 12 of 41 cases (29.2%) with a median time of 20 months (3 〜 62 months) after the end of treatment. (Complication symptoms included mucosal ulceration, severe esophagitis, esophageal perforation, stenosis, fibrosis of mediastinal space and esophago-bronchial fistula.

Conclusions: For early stage esophageal cancer, external beam radiotherapy of about 60 Gy followed by brachytherapy appears to reduce both recurrence rate and complication rate.

Key words: Early-stage esophageal cancer, Brachytherapy (BT), External beam radiation therapy (EBRT), Complications, Recurrence
cases using IVH cases as well as for malignancies including pharyngeal cancer. There are often cases where chemotherapy is not appropriate as the primary treatment for the same reasons.

When radiotherapy is the primary treatment, there are often cases when oral feeding becomes inadequate or difficult during the course of treatment due to damage to the upper alimentary tract and completion of treatment is difficult. Particularly with elderly patients, this situation may result in worsening of the overall physical condition with prolonged treatment. Taking reduction of the damage of the treatment into account, in addition to external beam radiation therapy (EBRT), our hospital has been using treatments combining external beam radiation therapy with brachytherapy (EBRT + BT). This retrospective study reviews the results of treatment and treatment methods for early-stage esophageal cancer focusing on the effectiveness of brachytherapy (BT).

Materials and Methods

Forty-one cases of early-stage esophageal cancer treated with radiotherapy from January 1991 to December 2005 at the Kyorin University Hospital were reviewed. The median age of the patients was 61 years (38 ~ 84 years), 37 patients were male and 4 patients were female. There were 34 mucosa stage cases and 7 sub mucosa layer cases. There cases were diagnosed and stage assessed using esophagograpy, endoscopy with Lugol dye staining. All of these methods were not performed for all cases. Cases involving metastasis to the lymph nodes with tumors greater than 5 mm detected by CT are not included in this review.

Before determining radiation treatment approach, we confirmed whether there had been any pre and/or combined therapy. For cases where pre-endoscopic therapy had been conducted, ERBT doses selected were low dose. For cases involving elderly patients and patients in generally poor condition due to heavy pre treatment and cases involving chemotherapy, ERBT doses selected were low dose.

The radiation methods reviewed in this study were as follows:

1. External beam radiation therapy (EBRT) group: Treatment was initiated with 2-field anterior-posterior opposed photon about 46 ~ 50 Gy followed by rotating radiation for a total of 60 ~ 66 Gy total dose. This group had 5 cases with median patient median age 73 years (63 ~ 82 years). Three cases used only radiotherapy, one case combined use of chemotherapy (CDDP, 5 FU treatment) and one case used endoscopic treatment such as endoscopic mucosal resection (EMR) prior to radiotherapy. (2) High dose rate endoesophageal brachytherapy (BT) using remote after loading system (RALS) group: Total of 9 cases with median age of 61 years (38 ~ 84 years). Three cases were radiotherapy only, no cases combining chemotherapy and 6 cases with endoscopic treatment with EMR or argon laser cauterization (APC) therapy prior to radiotherapy. For all cases of endoscopic therapy, surgical margins had been found to be negative by pathology.

Two brachytherapy methods were used. Five cases using ^{60}Co and 4 cases using ^{192}Ir. In both cases, the dose rate reference point was set 5 mm sub mucosa with 6 ~ 12 Gy radiation/1 ~ 3 fractions over 1 to 4 weeks. A plastic applicator containing either a ^{60}Co or ^{192}Ir radiation source is inserted through a 10 mm diameter rubber gastric tube by the unit during the treatment.

(3) Combined external beam radiotherapy and brachytherapy (EBRT + BT) group: 30 ~ 66 Gy external radiation was followed by brachytherapy of 12 ~ 18 Gy/2 ~ 3 fractions over 2 ~ 3 weeks. The median age was 69.5 years (55 ~ 84 years). Seventeen cases were radiotherapy only, 2 cases combining APC or EMR endoscopic treatment and 8 cases combining chemotherapy. Eight cases used ^{60}Co and 19 cases used ^{192}Ir for high dose rate brachytherapy (Table 1).

Results

1. Cumulative Survival Rate (Fig. 1)

There was a significant difference between the EBRT group and other groups. However, a statistically significant difference between the BT group and the EBRT + BT group was not observed using one-way layout analysis of variance. The standard variation was used with a Kaplan-Meier method (P = 0.024).

2. Recurrence (Table 2)

Sixteen cases of local recurrence or lymph node metastasis were observed for the 41 cases (39.9%). 11 cases were local recurrences and 5 cases involved lymph node metastases cases. The median time of recurrence was 95 months (3 ~ 186 months).

(1) EBRT group: 1 case of recurrence in the 5 cases
studied (20.0%) after 186 months. There was one recurrence case for the three cases with radiotherapy only. Recurrence was not observed for the 1 case with chemotherapy and the 1 case with endoscopic treatment.

(2) BT group: Recurrence was observed in 5 of the 9 cases (55.6%) with median time to recurrence of 18 months (12 〜 34 months). For radiation only recurrence was observed for 3 of the 3 cases studied (100%) with a median time of 23 months (12 〜 34 months). Recurrence was observed in 2 of the six cases (33.3%) of the cases with endoscopic treatment with a median time of 19 months (13 〜 34 months).

(3) EBRT + BT group: Recurrence was observed in 10 of the 27 cases (37.0%) studied. For radiation treat-
ment only, recurrence was observed in 8 of the 17 cases (47.1%) with a median time of 13 months (3 ～ 13 months). Recurrence was observed in 2 of the 8 cases with chemotherapy (25.0%) with a median time of 10 months (8 ～ 12 months). No recurrence was observed in the 2 cases with endoscopic treatment.

To consider the effects of the dose level of external beam radiation therapy preceding brachytherapy on recurrence, the EBRT + BT group was divided into 2 groups based on external radiation dose.

(A) Low dose group (external radiation less than 40 Gy): Recurrence was observed in 7 cases of 20 (35.0%) with a median time of 8 months (3 ～ 20 months). For radiation only, recurrence was observed in 5 of 12 cases (41.6%) with a median time of 8 months (3 ～ 13 months). For radiation combined with chemotherapy, recurrence was observed in 2 of 6 cases (33.3%) with a median time of 10 months (8 ～ 12 months). Recurrence was not observed in the 2 cases combining radiation with endoscopic treatment.

(B) High dose group (external radiation greater than 60 Gy): Recurrence was not observed in 7 cases including radiation

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<th>Radiotherapy alone</th>
<th>Radiotherapy with chemotherapy</th>
<th>Radiotherapy with endoscopic treatment</th>
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<td>EBRT group (n = 0)</td>
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<tr>
<td>BT group (n = 2)</td>
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<tr>
<td>EBRT + BT group (n = 10)</td>
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<td>3 (3.0) *</td>
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<tr>
<td>Total</td>
<td>8</td>
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Complication case (n = 12)
*: (Low dose BT, High dose BT)

3. Complications (Table 3)

Complications were observed in 12 cases of the 41 (29.2%) with a median time from the end of radiotherapy of 33 months (3 ～ 62 months). The complications first appear in the form of ulceration of the mucosa 9 cases and reported disorders include severe esophagitis 2 cases, hematemesis 1 case and esophageal perforation 1 case. Other symptoms included pain during swallowing due to poor esophageal dilation due to esophageal stenosis, fibrosis of mediastinal spaces and formation of esophago-bronchial fistula that corresponded to previous reports. Five cases of passage disorders due to stenosis treated by bougie dilation techniques were reported.

Complication reported by treatment method:

(1) EBRT group: complications were not reported for the 5 cases regardless of therapy combination.

(2) BT group: 2 complication cases were reported for the 9 cases (22.2%). One complication case was reported for the 3 radiotherapy cases (33.3%) and 1 disorder case was observed for the 6 cases of combined radiation and surgical treatment (16.7%). The complications were observed 10 months after treatment.

(3) EBRT + BT group: 10 complication cases were reported for the 27 cases (37.0%). Seven complication cases were reported for the 17 radiation only treatment cases (41.1%) with a median time of 7.5 months (3 ～ 12 months). Three complication cases were reported for the 8 cases treated with radiation and chemotherapy (37.5%) with a median time of 4.5 months (3 ～ 6 months). No complications were reported for the 2 cases combining radiation and endoscopic treatment.

The effects of external radiation dose level in treatments combining external beam radiation therapy with brachytherapy on the occurrence of complications were considered.

Low dose group (under 40 Gy): Complications were observed in 10 of 20 cases (50%) with a median time of 8.5 months (3 ～ 14 months). For cases where chemotherapy was also used, complications were observed in 3 of 6 cases (50%) with a median time of 10 months (7-14 months). For treatments with radiation alone, complications were observed in 7 of 12 cases (58.3%) with a median time of 7 months (3 ～ 12 months). Complications were not observed in cases where endoscopic treatment was also used.

(A) High dose group (greater than 60 Gy): Complications were not observed in 7 cases including radiation
treatment only or in combination with endoscopic treatment or chemotherapy.

**Discussion**

The results of this review showed that the EBRT group had the best consequences in terms of survival rate (100%), local control rate (recurrence rate 20%) and complication incidence (0%) of the groups studied. However, the cases in this group were old and there were very few cases in this group where long term follow-up to the present was possible compared to the aggregated cases. Despite the limitations of the data, the results showed that this was the best method evaluated for treating esophageal cancer. Thus, these cases should be considered as a reference in the context of this retrospective study.

In this study, we focused on whether an alternative therapy method, brachytherapy was useful or not. Especially in cases involving elderly patients cases, for various reasons the patients could not receive adequate beam radiotherapy. There was no significant difference between the BT and EBRT + BT groups for survival rate. The main reason for the lower survival rate for the BT and EBRT + BT groups compared to the EBRT group was probably the cases composing the groups. Some factors included the occurrence of other diseases among the elderly patients and general overall condition degradation such as operations on other nearby organs and esophageal varices due to liver cirrhosis. Lopez et al. have reported that for locally advanced cancer treated by HDR-BT, the results for 5 year global survival and cause specific survival were 10.18% and 12.96%, a mean survival of 25.68 and 29.14 months respectively. A 39.0% recurrence rate with an average of 25 months for recurrence was observed in the overall study group. This was similar to less than two years reported by Sai et al. There were 8 cases of local recurrence and 8 cases of metastasis to the lymph nodes. However, there was no particular pattern in the recurrence related to the treatment methods for the 16 cases.

The results for recurrence rate were that the EBRT + BT and EBRT groups had lower rates than the BT group. Previous studies have reported similar results. The results by group were EBRT group 20% < EBRT + BT group 37% (Low dose group 35% < High dose group 42.9%) < BT group 55.6%. These results indicate that the dosage for BT without external radiation may have been insufficient.

The method for brachytherapy used at the Kyorin University Hospital places the $^{60}$Co or $^{192}$Ir radiation source in a plastic applicator in a 10 mm diameter rubber gastric tube and the dose assessment point is a point 5 mm sub mucous. As the dosage may be insufficient, the dosage assessment point should be reviewed.

There were 13 cases using $^{60}$Co and 23 cases using $^{192}$Ir for high dose rate brachytherapy treatment. Differences between cases using these radiation sources were not considered in this study.

Also, for treatments where brachytherapy treatment is conducted after external beam radiotherapy, reduction of total brachytherapy dosage to prevent occurrence of mucosa disorders may result in insufficient dosage.

Another factor that may affect recurrence is the evaluation of the disease stage for cases. Disease stage for many of the older cases considered were evaluated using only esophagography. More recently, ultrasonic esophagography has been used in many cases in conjunction with esophagography. For early cancer, each of the evaluation methods produces slightly different results and there is the possibility that in some cases the cancer has progressed beyond mucosa-sub mucosa. Furthermore, even for surface cancers there are cases where the lesions are broadly spread and this may contribute to degrading results.

For the occurrence of complications, the results were EBRT group 0% < BT group 22.2% < EBRT + BT group 37% (High dosage group 0% < Low dose group 50%). The most common complication symptoms were cases of ulceration of mucosa and most of the complication cases for radiation only treatment remained at this level. In contrast for treatments combining surgery or chemotherapy, complication cases that progressed to severe esophagitis or esophageal perforation were observed but the frequency was low. In addition, there cases were observed where the complications progressed resulting in problems with esophagus dilation due to esophageal stenosis, sore throats due mediastinal fibrosis, and esophageal fistula. There were four cases when problems with esophagus dilation caused by stenosis required the use of bougie dilation therapy to improve passage. However, late phase complications such as radiation pneumonitis and myelitis, percarditis, and other problems were not observed.

When the BT group only is compared to external
beam radiation combined with brachytherapy EBRT + BT group, there were more recurrences for the BT group than the EBRT + BT group while the results for complications were opposite with more complications for EBRT + BT group. By dosage, the high dose group had more recurrences while there more complications for the low dose group. This relationship between recurrence and complications shows that these are two sides of the issue. Especially when brachytherapy is used in combination with external radiation, reduction of external radiation with the objective of reducing disorders results in increase in recurrence but does not contribute to reduction of complications. Yorozu have reported that esophageal ulcer, HDR intraluminal brachytherapy is safe up to a total dose of 16Gy after 50Gy external radiation7). Hirokawa have reported that HDR intraluminal brachytherapy following 60Gy external radiation has a high risk of causing fistula formation unless the dose is 20Gy or less8).

Especially for treatment of elderly patients9) and others with poor general condition, in order to reduce the occurrence of complications related to external radiation such as radiation pneumonitis related respiratory problems, esophagitis related pain and ingestion difficulty related to passage obstruction, reduction of external radiation combined with added brachytherapy and without added brachytherapy have been selected. Emphasis on reducing complications as opposed to complete cure is reflected in the results of this study.

The results of this retrospective study showed that reduction of external radiation was not appropriate even when brachytherapy is combined. As has been previously reported that after 60Gy external radiotherapy that brachytherapy of 4 fractions with 2.5Gy/fraction per week was appropriate5,11). Even with combined brachytherapy, reduction of external radiation is not appropriate and the required dosage for cure is about 60Gy that is same level for external radiation only.

Conclusions

The results of this review showed that treatment of early-stage esophageal cancer with about 60 Gy external radiation complete cure level followed by brachytherapy reduces both the recurrence and disorder rates. Review of the fundamental assessment points for brachytherapy is necessary.

References