Treatment Outcome of Definitive Endoesophageal Brachytherapy for Epithelial or Intramucosal Esophageal Cancer

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食道粘膜上皮・粘膜内癌に対する高線量率食道腔内照射の治療方法と成績

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【目的】食道粘膜上皮・粘膜内癌に対する高線量率食道腔内照射の治療方法と成績について報告した．
【対象と方法】1999年4月から1998年3月までに広島大学放射線科において，高線量率食道腔内照射を施行した食道癌患者116例のうち，腔内照射単独で治療した20例を対象とした．組織型は全例扁平上皮癌であった．深達度の診断は，内視鏡・超音波内視鏡・病理組織診で行い，11例は粘膜上皮癌に，9例は粘膜内癌に分類された．高線量率食道腔内照射は，高線量率イリジウム照射装置に，二重バルーンアプリケータを装着して施行した．腔内照射の線量評価点は，バルーン表面から5mmの多数点を設定し，最適化計算法を用いて算出した．腔内照射の総線量は25Gy/5回/2.5週から36Gy/18回/3.5週であった．
【結果】生存者の中央観察期間は24カ月である．15例は無病生存中であり，5例は再発の徴候無く他病死した．照射野内に局所再発した症例，およびリンパ節再発した症例は認めていない．3例は照射野外の食道に再発を認めたが，いずれの症例も局所治療で救済された．1例に食道潰瘍を認めたが，入院加療により治癒した．5年原病生存率・局所制御率・潰瘍発生率は，それぞれ，100%，100%，5%であった．
【結論】食道の粘膜上皮癌・粘膜内癌に対する高線量率食道腔内照射の治療成績は，極めて良好であった．上記の深達度が証明されている患者に対して，内視鏡的粘膜切除術が困難な症例，あるいは非耐術症例には，高線量率食道腔内照射は有効かつ安全な治療方法であると考えられた．

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Introduction

Recent advances in endoscopic procedures have permitted identification of many esophageal cancer patients at an earlier stage.[1] Surgically resected specimens have revealed the very low risk of lymph node metastasis and the excellent prognosis of epithelial and intramucosal cancer of the esophagus, and new criteria for 'early' carcinoma of the esophagus have been proposed.[2),3)] Unfortunately, these criteria have not been internationally accepted. To support their adoption, Nabeya and Nakata calculated that the 5-year survival rate after endoscopic mucosal resection was 98-100% for mucosal cancer in Japan.[4)] On the other hand, an increasing number of early stage esophageal cancer patients have also been treated by high-dose-rate (HDR) endoesophageal brachytherapy (EBT).[5),6)] However, there has been no literature describing the long-term treatment outcome for epithelial or intramucosal esophageal cancer treated with HDR EBT. Therefore, we examined the treatment procedure and outcome for epithelial or intramucosal cancer of the esophagus treated with HDR EBT.

Materials and Methods

Patients

The study population consisted of 20 consecutive patients who received EBT out of 116 EBT patients between April 1992 and March 1998 at Hiroshima University Medical Center, which employs a micro-Selectron HDR (10 Ci) from Nucletron, Holland. According to the pathological subclassification of invasion that was recently developed for early esophageal cancer, superficial esophageal cancer is divided into 2 categories: mucosal cancer and submucosal cancer; and mucosal cancer is subdivided into 3 categories: epithelial cancer, intramucosal cancer, mucosal cancer invasive to the muscularis mucosa.[1)] The subclassification of invasion was diagnosed to be epithelial or intramucosal esophageal cancer by barium study, endoscopy, endoscopic ultrasonography, CT scan and histological

Table 1 Profile of patients

Number of patients	20
Treatment period	1992. 4 - 1998.3
Median age (range)	68 y. o. (52 - 89)
Sex (male/female)	(18/2)
Epithelial/ intramucosal	(11/9)
Lymph node metastasis (N0/N1)	(20/0)
Reason for radiotherapy	
Second malignancy	7
Aged (>= 75 years)	3
Refusal of surgery	10
Reason for EBT	
Too wide lesion	10
Postive EMR margin	4
Failed EMR	3
Multicentric cancers	3

Table 2 Summary of treatment factors

Number of patients	20
Median number of EBT fractions (fx, range)	14 (5-18 fx)
Median EBT dose (Gy, range)	35 (25-36)
Median total mucosal dose (Gy, range)	59.5 (42.5-61.2)
Total treatment duration (days, range)	23 (15-59)

EBT: endoesphageal brachytherapy

study. According to this subclassification, 11 patients were categorized as having epithelial cancer and nine intramucosal cancer. No patient had regional lymph node metastasis (Table 1).

Radiotherapy

HDR EBT with a double balloon applicator was used in conjunction with the Ir-192 remote afterloading system at the reference dose of 25 Gy/5 fractions/2.5 weeks to 36 Gy/18 fractions/3.5 weeks (Table 2). The dwell positions of source were identified at barium positioning or endoscopic metallic marking. The reference dose points were set 13 mm and 15 mm respectively from the source axis when 16 mm and 20 mm diameter applicators were used. The inner balloon was used for centering the source, and the outer balloon for adhering to the esophageal mucosa (Fig. 1). Since there was a high incidence of late toxicity (1/2 = 50%) in the first year using an EBT fraction dose of 5 Gy, the EBT fraction dose was decreased to 2 or 2.5 Gy for the next 18 patients.

Focus

We focused on 5-year survival, local control and late toxicity. Local control was assessed every 3 to 6 months by endoscopy and tumor histology. The date of each recurrence or the first observation of the patient's most serious late toxicity was recorded. In this retrospective analysis, RTOG/EORTC toxicity criteria were used.[7] The Kaplan-Meier method was used to calculate survival, local control and late toxicity rates.

Results

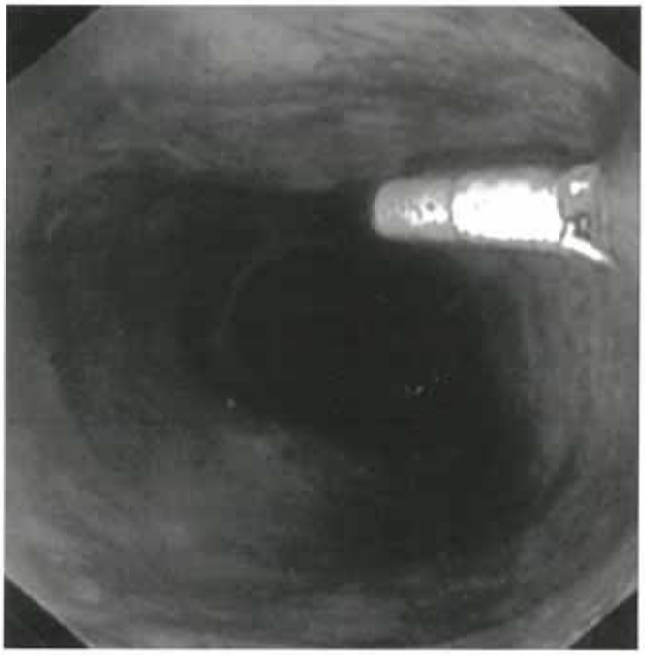
The median follow-up period of the survivors was 24 months (from 12 to 63 months). Fifteen patients have remained alive with no evidence of disease. No patient died of esophageal cancer, whereas five died of intercurrent disease. No patient showed recurrence inside the radiation field of the esophagus or regional lymph nodes. In contrast, three patients showed recurrence outside the radiation field of the esophagus, and all were salvaged by EMR, EBT or surgery. One patient who had late toxicity (esophageal ulcer Grade by RTOG/EORTC criteria = 3) had received the reference dose of 25 Gy/5 fractions/2.5 weeks. No late toxicity occurred in patients who received 2.0 to 2.5 Gy/fraction (Table 3). The 5-year overall, cause-specific, disease-free survival, local control and late toxicity rates were 62%, 100%, 53%, 100% and 5%, respectively (Fig. 2).

Discussion

Endoscopic mucosal resection (EMR) can be considered the first-line treatment for selected cases of early-stage esophageal cancer, because the treatment outcome of EMR for these cancers is excellent.[8),9)] Surgically resected specimens have

Table 3 Summary of results

	Epithelial	Intramucosal
Patient number	11	9
Follow-up (months) (range)	26 (12-63)	24 (19-57)
In-field local recurrence (percent)	0 (0%)	0 (0%)
Out-of-field local recurrence (percent)	1 (9%)	2 (22%)
Nodal recurrence (percent)	0 (0%)	0 (0%)
Complications (Grade 2/Grade 3/Grade 4)	1 (0/1/0)	0 (0/0/0)
Death (Died of ca. /intercurrent dis.)	4 (0/4)	1 (0/1)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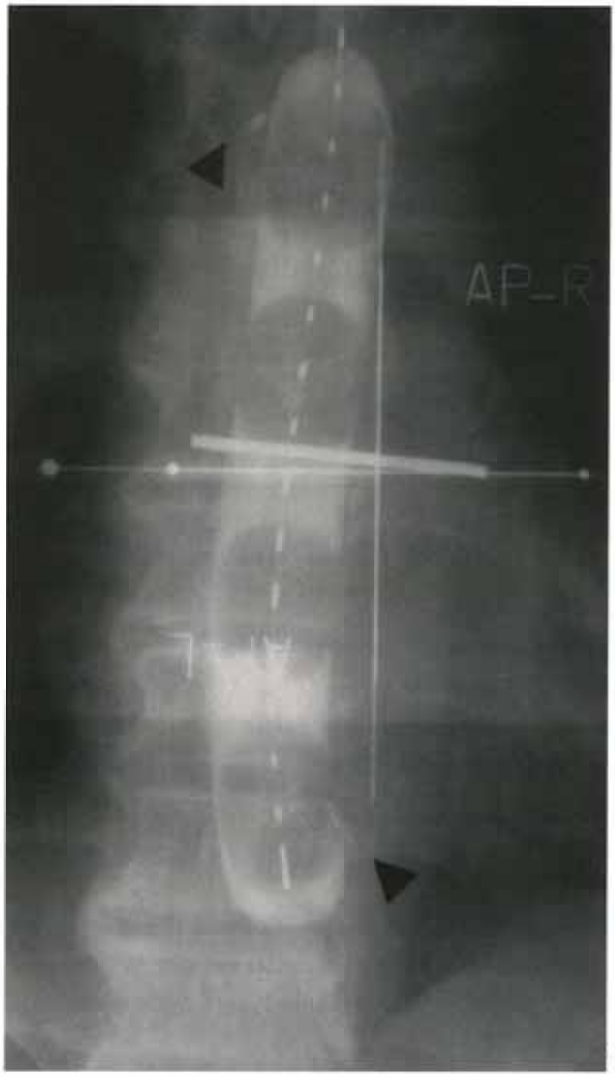

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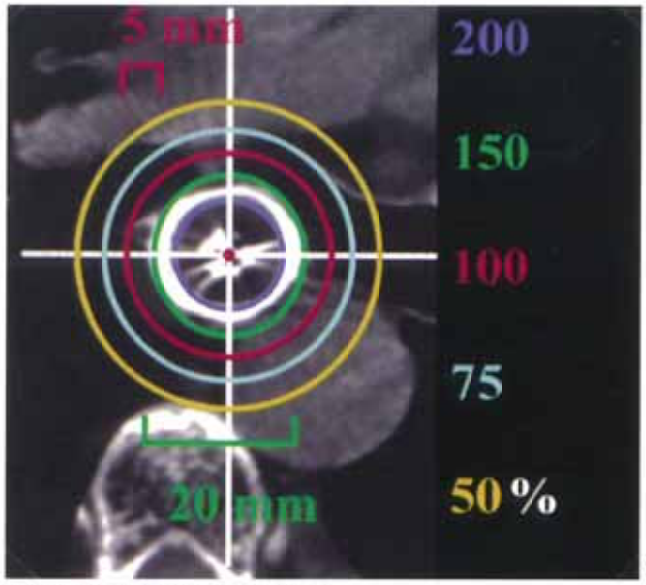

(C)

Fig. 1 Double balloon applicator.
A: A metallic marker inserted into the edge of an area unstained with iodine.
B: Localization film. The outer balloon is positioned with the aid of contrast medium to permit adherence to the esophageal wall. The inner balloon is placed at the source in the center of the lumen. Metallic markers were easily seen at both edges of the double balloon applicator (arrowheads).
C: Dose distribution of EBT. The diameter of the double balloon applicator is 20 mm. The reference point is placed 5 mm from the surface of the applicator. The double balloon applicator enables a uniform esophageal mucosal dose to be delivered.

revealed a very low risk of lymph node metastasis for epithelial and intramucosal cancer of the esophagus.[2,3] However, it is common that indications for EMR are limited, and patients who have lesions more than 3 cm in diameter, multiple lesions (> 3) or lesions more than one-third of the circumference of the esophagus should be recommended for the operation. Recent developments in radiotherapy have enabled precise spatial irradiation of the clinical target volume. A double balloon applicator makes it possible to irradiate a uniform dose to the target by adhering to the esophageal mucosa and placing the source at the center of the lumen.[10] This study showed that the prognosis of epithelial and intramucosal cancer of the esophagus is excellent, showing the same treatment results as EMR and surgery. Because we had three patients with out-of-field local recurrence, we consider it necessary to follow up endoscopic screening closely for early discovery of new lesions. When follow-up endoscopy is not expected to be completed, we should consider the indications for surgery. Although patients have a choice of treatments, we recommend safe, effective EBT for epithelial and intramucosal esophageal

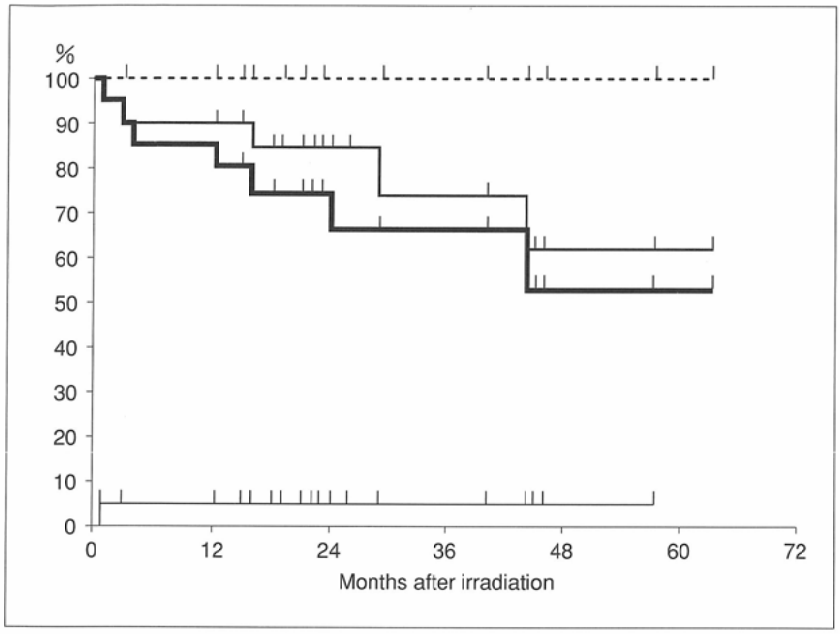

Fig. 2 Survival, late toxicity, and local control rates. Overall: straight line, Cause-specific and local control: dotted line, Disease-free: bold line, Late toxicity: thin line.

cancer patients who cannot be treated with EMR and surgery.

In 1992, we started definitive EBT with a fraction dose of 5 Gy. Although two of our patients showed complete response, there was a high incidence of late toxicity (1/2 = 50%). We decided to decrease the fraction dose and increase the fraction number in order to decrease late toxicity. We obtained the same local control rates, and there has been no patient with late toxicity who received a fraction dose of 2.0 or 2.5 Gy. Our treatment results suggest that it is necessary for safe EBT to irradiate smaller fraction doses such as 2 or 2.5 Gy at the reference dose points. Although the number of our cases is small, the results have encouraged us to continue to treat epithelial and intramucosal esophageal cancer with definitive EBT.

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