HIGH DOSE VERSUS STANDARD DOSE RADIATION THERAPY WITH CONCURRENT CHEMOTHERAPY IN ESOPHAGEAL CANCER

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HIGH DOSE VERSUS STANDARD DOSE RADIATION THERAPY WITH CONCURRENT CHEMOTHERAPY IN ESOPHAGEAL CANCER

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ABSTRACT

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Purpose: Esophageal cancer shows a poor prognosis. In operable patients, esophagectomy or neoadjuvant concurrent chemoradiation therapy (CCRT) followed by surgery is generally accepted. In other patients without distant metastasis, CCRT is the standard treatment. But the optimum radiation dose in the setting of CCRT is controversial. In this study, we investigated the efficacy of higher dose radiotherapy with concurrent chemotherapy for patients with esophageal cancer.

Methods and Materials: From January 1996 to July 2007, a total of 207 patients treated with CCRT were analyzed. Of the 207 patients, 65 had received ≤54 Gy (standard dose group) and 142 had received ≥59.4 Gy Gy (high dose group). The median doses in the standard and high dose groups were 54 Gy (range, 45 - 54 Gy) and 63 Gy (range, 59.4 – 70 Gy), respectively. A cone-down technique was used in all patients. The initial field was designed as 5 cm of longitudinal margin from the gross tumor;

the boost field was 2 cm of longitudinal margin from the gross tumor. The median dose to the initial field was 36 Gy (range, 30.6 – 41.4 Gy). There was no difference between the two groups. Cisplatin and 5-fluorouracil were administered to 85% of the patients, and the other patients received 5-fluorouracil mono-chemotherapy. Local recurrences within boost field were considered central; those within or outside the initial field were considered marginal or out-field, respectively.

Results: There were no significant differences in patients' age, sex, pathology, and histologic grade between the two groups. But Stage I-II patients were higher in the standard group (41% versus 19%). The median disease progression free survival, and overall survival in all patients were 13 months, and 24 months, and no significant differences were found between the two groups. But the 2-year local control rate is significantly higher in the high-dose group (68% vs. 38%, p=0.05). The high-dose group and the standard-dose group showed similar patterns of failure (central, 44% versus 27%; marginal, 0% versus 6%; outfield 11% versus 8%). But complete responses were higher in the high-dose group (68% versus 33%, p=0.04). No significant treatment- related late toxicities were observed.

Conclusion: Our data did not show improved survivals in the high-dose group. Despite that, advanced stage patients were higher in the high-dose group, higher dose radiotherapy showed comparable survivals and higher local control rate, and a higher complete response rate. Our results deserve further well-designed investigation into a radiation dose escalation study for esophageal cancer in the setting of CCRT.

Key words: esophageal cancer, radiotherapy, chemotherapy

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I. INTRODUCTION

Esophageal cancer shows a poor prognosis. About one half of patients presented with locally advanced stage at the time of diagnosis.[1] They have a 5-year survival rate of less than 30% after surgical resection or multimodality therapy. Esophageal cancer represents one of the few cancers for which survival has not improved substantially over the past 25 years.[2] In operable patients, esophagectomy or neoadjuvant concurrent chemo-radiation therapy (CCRT) followed by surgery is generally accepted. In the past decade, numerous single institutions and cooperative groups have investigated the use of CCRT as a definitive treatment or as a preoperative therapy for patients with localized esophageal cancer. A significant body of information suggests that chemotherapeutic agents such as 5-Fu, cisplatin, mitomycin C, gemcitabine, and taxol have a greater than additive effect when used in combination with radiation therapy. Many trials show that CCRT has improved the response and

survival rather than radiation therapy alone.[3-5] For inoperable patients or those avoiding esophagectomy related complications, CCRT is accepted for standard treatment. But in the CCRT setting, the optimum radiation dose is controversial. In the intergroup 0123 study, patients were randomized to receive combined modality therapy consisting of four monthly cycles of 5-FU (1000 mg/m^2/24 h for 4 days), and cisplatin (75 mg/m^2 bolus on day 1) with concurrent radiation to 64.8 Gy, or they were kept to the same chemotherapy schedule but with the radiation dose limited to 50.4 Gy. The trial was stopped after an interim analysis. For the 218 eligible patients, there was no significant difference in median survival (13.0 versus 18.1 months), 2-year survival (31% versus 40%), or locoregional failure (56% versus 52%) between the high-dose and standard-dose treatment arms, respectively. However, 7 of the 11 patients in the high-dose arm died before they had received 50.4 Gy, and no statistically significant difference was found in patient outcomes measured by LRC or survival between the high-dose and standard-dose arms.[6] Zhang et al. reported that radiation doses more than 51 Gy improve loco-regional control, disease-free survival, and survival in patients treated with 5-FU based chemotherapy. There was a positive correlation between radiation dose and locoregional control.[7] In this study, we evaluated the dose–response relationship for loco-regional control (LRC), disease-free survival (DFS), and overall survival (OS) in patients with esophageal cancer treated with chemoradiotherapy

II. MATERIALS AND METHODS

1. Patient selection

Between 1998 and June 2007, a total of 347 patients with stage I to IV esophageal carcinoma were treated with CCRT at the Yonsei Cancer Center, Yonsei University, College of Medicine (Seoul, South Korea). Patients were excluded from this analysis for the following reasons: (1) they presented with distant metastasis at the time of diagnosis (M1b); (2) they received low dose radiotherapy as a palliative intent, not a curative aim; (3) they underwent esophagectomy after CCRT; (4) they had a recurrent tumor, and received CCRT in the salvage aim; (5) They had other primary tumors. Ultimately, total 207 patients who received CCRT were included for this study.

The pretreatment evaluation included a medical history and physical examination, focusing on performance status and a history of smoking, alcohol intake, weight loss, and dysphagia. Laboratory studies included a complete blood cell count and biochemical survey. For stage work-up, barium swallow, chest computerized tomography (CT) and transesophageal endoscopic ultrasonography (US) were performed routinely. To evaluate distant metastasis, patients were evaluated with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), bone scan, upper abdomen US or abdomen CT.

2. Radiation therapy

Radiation therapy was delivered using 10 MV photon starting Day 1 of chemotherapy. Conventional fractionation schedule (5 days per week, 1.8 – 2.0 Gy/fraction daily) and cone-down techniques were used in all patients. The initial target volume encompassed the primary tumor with a margin of at least 5 cm above and below the tumor and 2 cm radially. Before the 2000, a

two-dimensional plan was used, and after that a three-dimensional plan was used. Subclinical disease was treated to at 30.6 – 41.4 Gy (median dose, 36 Gy) before the field size was reduced. To reduce irradiation dose to the lungs, anterior-posterior parallel opposite fields were used in these phases. The final target volume encompassed the primary tumor with a margin of at least 2 cm above and below the tumor and 2 cm radially. To avoid radiation-induced myelopathy, the spinal cord dose was restricted to within 45 Gy. For that, left-right parallel opposite fields or posterior two oblique fields were used in two-dimensional plan. And 3-5 multi-ports fields were used in the three-dimensional plan. Total doses of radiation therapy were 45 – 70.2 Gy (median dose, 63 Gy). For delineating gross tumor accurately, CT-PET fusion by pinnacle (Phillips Medical Systems, Andover, MA) and correlation with barium swallow were performed.

3. Chemotherapy

5-FU and cisplatin were administered to 85% of the patients (n=185), and the other patients received 5-fluorouracil mono-chemotherapy. Cisplatin was administered at 40 - 100 mg/m^2 on Days 1, and 5-FU was administered at 750 -1250 mg/m^2 daily as a continuous infusion, using a portable electronic pump on Day 1 – Day 5 during RT. Each cycle of chemotherapy was repeated every 28 days. Two cycles of chemotherapy were administered with radiotherapy. After CCRT, 79% of patients (n=163) were received maintenance chemotherapy for 1 – 4 cycles.

4. Follow-up

During radiotherapy, patients were examined weekly to monitor treatment-related toxicity and their general condition. Barium swallow, chest CT,

FDG-PET was performed within two months after the completion of radiation therapy. The following were performed until the time of disease progression: every 3 months for 1 year, every 6 months for 3 years, then yearly. A clinically complete response was defined as no clinical, radiographic, endoscopic, or histologic evidence of cancer on follow-up visits. Partial response was defined as a reduction of tumor size more than 50% in chest CT, endoscopy. No response was defined as reduction of tumor size less than 50% or no reduction or increased tumor size. Because of the protean feature of local recurrences, the sites of local failure were arbitrary allocated to one of three categories based on their patterns of recurrences; (a) “Central recurrence”, occurring within final radiation therapy field; (b) “Marginal recurrence”, within initial radiation therapy fields, but outside of the final radiation therapy field; and (c) “Out-field recurrence” occurring at outside of initial radiation therapy field. Survival duration was calculated from the date of initiation of CCRT to that of the first occurrence of the considered event (loco-regional recurrence, distant metastasis, or death).

5. Statistical analysis

Patients were grouped by total radiation dose (≥54 Gy and <54 Gy). The survival function was performed using the Kaplan-Meier estimates, and the log–rank test was used to assess the equality of the survival function across the groups. In addition, Pearson’s chi-square test was used to assess measures of association in frequency tables.

III. Results

1. Patient characteristics and clinical profile

Of the 207 patients in our study, 65 received radiation doses of ≥54 Gy (standard dose group) and 142 received <54 Gy (high dose group). The median radiation dose of the standard dose group was 54 Gy (range, 45 – 54 Gy), and the high-dose group was 63 Gy (range, 59.4 – 70 Gy). The pretreatment patient and tumor characteristics for the two groups are listed in Table 1. No statistically significant differences were found between the groups in age, gender, histologic subtype and grade, tumor location, or clinical stage distribution. But Stage I-II patients were higher in the standard group (41% versus 19%).

2. Disease control and survival

The median disease progression free survival (PFS), and overall survival (OS) in all patients were 13 months, and 24 months, and no significant differences were found between the two groups (Figure 1-2). But the high-dose group showed significant better 2-year local control rate (68% vs. 38%, p=0.05). These data are shown in Figure 3. Two-year distant metastasis free survival (DMFS) was 85% and 60% in the standard dose group and the high-dose group, respectively (p=0.03). These data are shown in Figure 4. The clinical primary tumor responses in the two groups are summarized in Table 2. In the standard dose group, the complete response rate was 33%, the partial response rate was 57%, and the no-response rate was 10%. In the high-dose group, the complete response rate was 68%, the partial response rate was 26%, and the no-response rate was 6%. The complete response rate was significantly greater in the higher dose group (p value=0.04).

Table 1. Patient characteristics

Characteristics	No. of patients (%)		*p* value
	Standard	High dose	
	65	142	
Age (years)			**NS**
≤ 60	**19 (29)**	**41 (29)**	
> 60	**46 (71)**	**101 (71)**	
Sex			**NS**
Male	**62 (95)**	**132 (93)**	
Female	**3 (5)**	**10 (7)**	
Pathology			**NS**
SCC	**62 (95)**	**137 (96)**	
AdenoCa	**3(5)**	**5 (4)**	
Histologic grade			**NS**
Well diff.	**9 (14)**	**20 (14)**	
Moderately diff.	**8 (13)**	**48 (34)**	
Poorly diff.	**48 (73)**	**74 (52)**	
Stage			**NS**
I	**12 (18)**	**8 (6)**	
II	**15 (23)**	**18 (13)**	
III	**27 (41)**	**68 (48)**	
IVA	**11 (18)**	**48 (33)**	

Abbreviation: SCC = squamous cell carcinoma; AdenoCa = adenocarcinoma; Diff = differentiation.

Table 2. Primary tumor response to CCRT

Response to CCRT	CR (%)	PR (%)	NR (%)
Standard dose group	**33**	**57**	**10**
High-dose group	**68**	**26**	**6**

***p* value: 0.04**

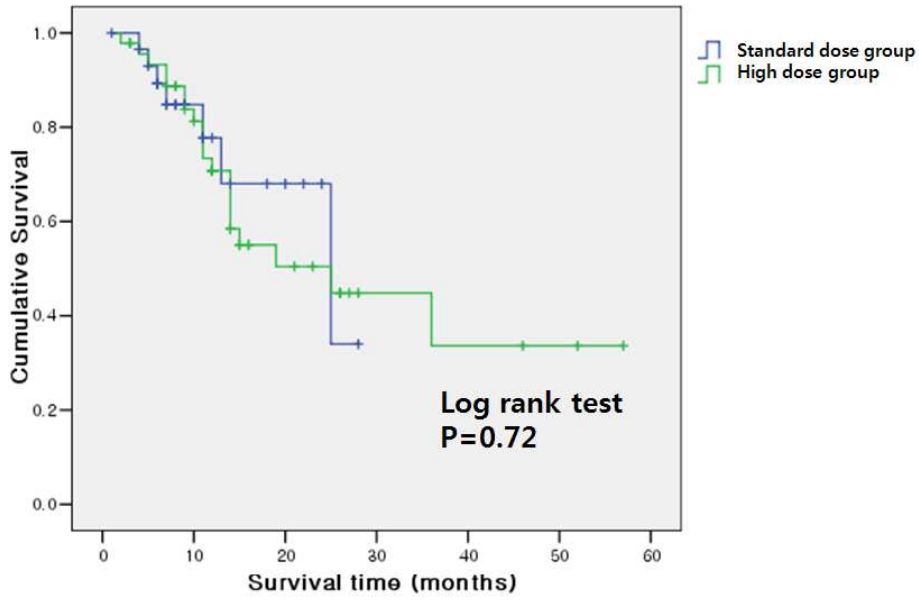

Figure 1. Overall survival

3. Patterns of failure

The loco-regional failure rate was 55% and 41% in the standard-dose group, and the high-dose group, respectively. The distant metastasis rate was 15% and 53%. These reached statistical significance (p=0.001). In local recurrence, patterns of failure were shown in Table 3. In the high-dose group, the central failure rate is lower than in the standard-dose group (27% versus 44%). But this was not significant statistically.

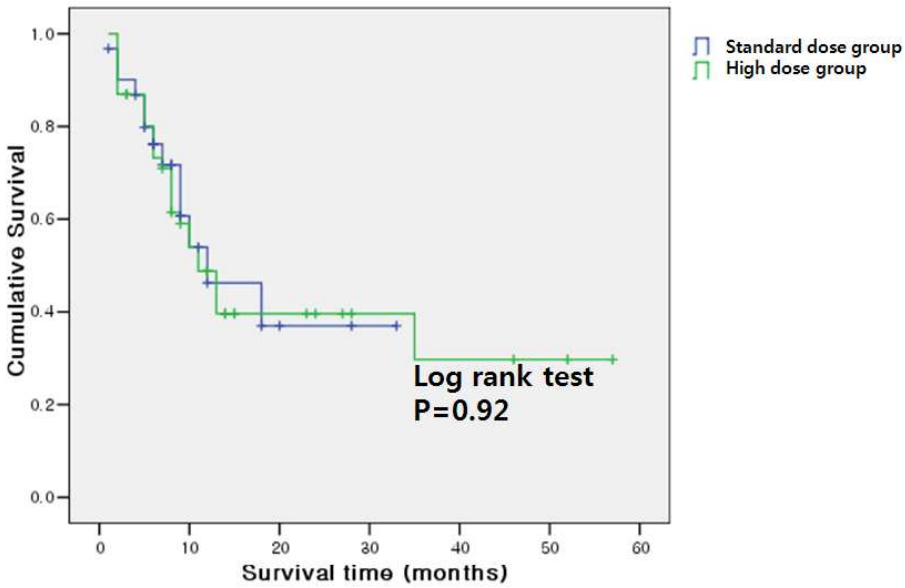

Figure 2. Progression free survival

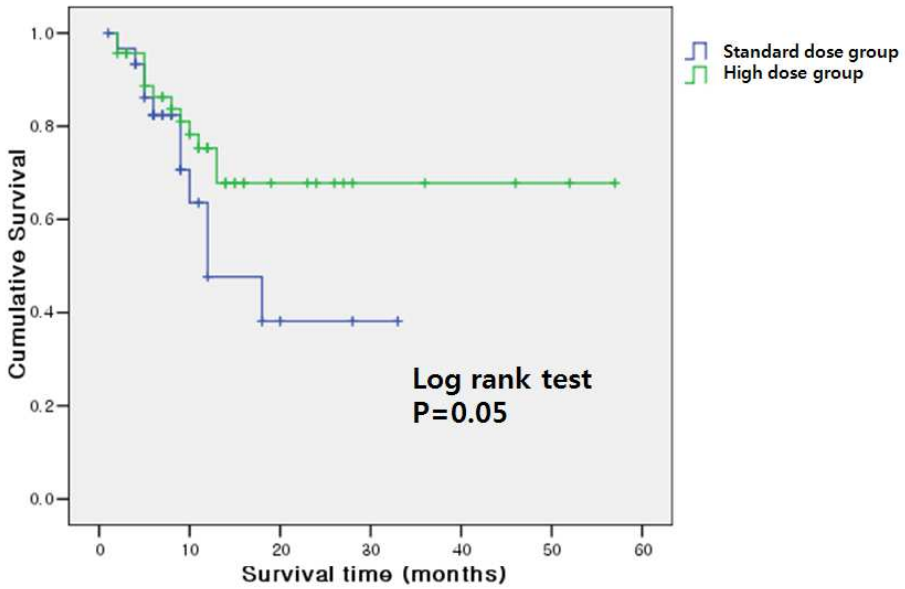

Figure 3. Local recurrence free survival

Table 3. Patterns of failure for local recurrence

	No. of patients (%)	
	Standard dose	**High-Dose**
Central failure	**29/65 (44)**	**38/142 (27)**
Marginal failure	**0/65 (0)**	**8/142 (6)**
Outfield failure	**7/65 (11)**	**12/142 (8)**
Total	**36/65 (55)**	**58/142 (41)**

***p* value: 0.21**

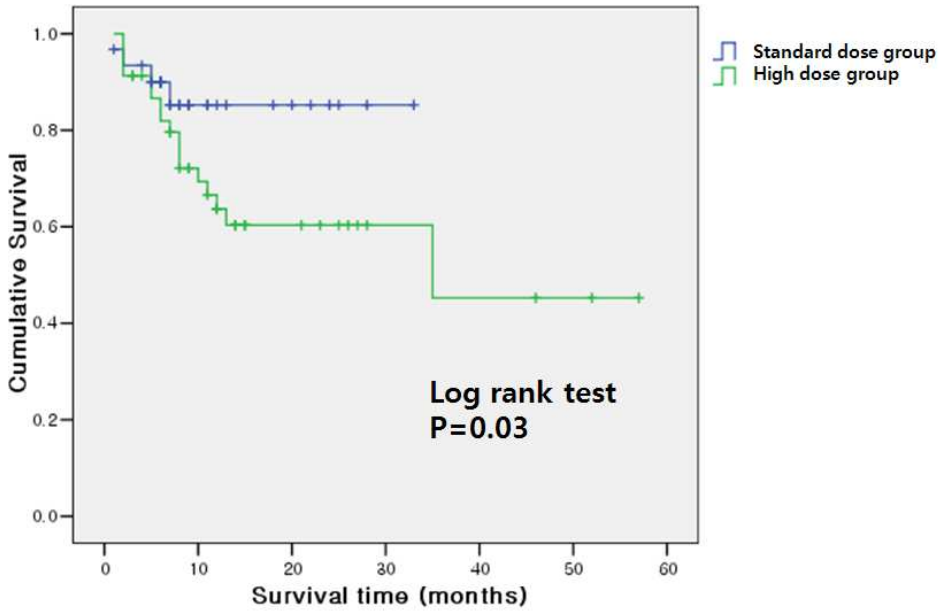

Figure 4. Distant metastasis free survival

IV Discussion

In the setting of CCRT, the optimal radiation dose for treating esophageal cancer is controversial. Sun et al. reported a clear association between a higher radiation dose and improved 5-year survival when RT was the sole therapeutic modality in patients with Stage II or III esophageal cancer. The 5-year survival rate was 10.6% for patients who received 60–69 Gy, and about 2% for those who received 50 –59 Gy.[8] In the series of Coia and associates, patients received 5-FU, mitomycin C, and 60 Gy of radiation. Importantly, their trial was the only combined-modality trial in which patients with clinically early-stage esophageal cancer (Stage I and II) were treated and analyzed separately. The results of that trial demonstrated a very low local failure rate of 25%, a 5-year actuarial survival rate of 30%, and a 5-year actuarial local relapse-free survival rate of 70% for patients with Stage I disease.[9] However, in a study of 30 patients with clinical Stage I–III disease, John et al. reported a similar local failure rate 27% with a lower radiation dose: 40 –50 Gy. The 2-year actuarial survival rate was 29%.[10] Radiation doses of as much as 66 Gy after three cycles of cisplatin and bleomycin have also been used.[11]

Herskovic and colleagues reported a trial where one hundred and twenty-one patients were randomized to 50 Gy with concurrent chemotherapy with 5-fluorouracil (5-FU) (1000 mg/m^2 for 4 days) and cisplatin (75 mg/m^2) or to irradiation with 64 Gy alone (RTOG 85-01). At 5 years, 27% of the combined-modality patients were alive, compared with none of the patients in the irradiation only group. The median survival time for the combined-modality arm was 14.1 months, compared with 9.3 months for irradiation alone.[4] This trial established the superiority of CCRT to RT alone.

A RTOG trial 94-05[6], a follow-up to RTOG 85-01, investigated the possibility of intensification of the radiation dose. In the 94-05 trial, 236 patients with stage I-III squamous cell carcinoma (85%) or adenocarcinoma (15%) of the

esophagus without tumor extension to within 2 cm of the stomach, were randomized to a standard dose combined-modality therapy using a slight modification of the combined-modality therapy arm of RTOG 85-01 (50.4 Gy plus concurrent 5-FU and cisplatin on Weeks 1 and 4, repeated 4 weeks after RT completion) or high-dose RT (64.8 Gy) and the same chemotherapy regimen. That trial failed to show any benefit in terms of survival in the high-dose arm. No statistically significant differences were found between the high-dose and standard-dose arms in the median survival time (13.0 vs. 18.1 months), 2-year survival rate (31% vs. 40%), or rate of locoregional failure or locoregional disease persistence (52% vs. 56%). However, 7 of the 11 treatment-related deaths in the high-dose arm of the RTOG 94-05 trial occurred in patients who had received radiation doses of <50.4 Gy. In addition, a statistically significant prolongation of treatment time occurred because of the breaks required for recovery from side effects after correction for the number of RT sessions, and a statistically significant lower dose of 5-FU was given to patients in the high-dose arm. The authors believed that these factors might have contributed, at least in part, to the lack of benefit for patients who received high-dose vs. standard-dose RT. Therefore, the findings from the RTOG 94-05 trial were inconclusive regarding whether a radiation dose effect exists in the treatment of cancer of the esophagus.

Zhang et al. reported that statistically significant better LRC, DFS, and OS were seen in patients who received >51 Gy.[7] But many patients were treated with rapid fractionation (30 Gy given in 10 fractions within 2 weeks). The median radiation dose of the lower dose group (≤51 Gy) was 30 Gy, so it did not represent a standard radiation dose group.

It is generally accepted that 50 Gy at 1.8–2 Gy per fraction within 5 weeks is adequate to control >90% of subclinical disease in patients with squamous cell carcinoma of the upper aerodigestive tract. At least 60–70 Gy given at the same fractionation is needed to treat gross tumors. For better clinical outcomes, a

higher dose than 63 Gy might be required.

In our study, high-dose RT more than 54 Gy showed improved LRC and higher complete response rate, but did not show improved DFS, OS. This could be explained by the higher proportion of advanced stage patients in the high-dose group.

Esophageal cancer has high rates of local recurrence and distant metastasis when either RT or surgery is used[12, 13]. For improving outcomes of esophageal carcinoma, effective chemotherapy might be necessary. Combined therapy with an epidermal growth factor receptor (EGFR) antagonist showed an improved survival in locally advanced head and neck squamous cell carcinoma[14]. In esophageal cancer, tyrosine kinase inbitors (TKI) or monoclonal antibodies (mAb) with chemotherapy, radiotherapy, or both, is currently under evaluation[15, 16].

Due to radiation tolerance of the esophagus, higher dose irradiation is a challenging problem. Recently FDG-PET has been widely used for detection of carcinoma, and the follow-up treatment response. FDG-PET is a functional image study where tumor cell viability and density can be estimated. Because sensitivity and specificity of FDG-PET are high in esophageal cancer[17, 18], accurate target volume delineation for radiotherapy might be possible by using FDG-PET. By accurate target volume delineation using FDG-PET and advanced radiation therapy technique such as intensity modulated radiation therapy, focal high-dose irradiation for esophageal cancer may improve survival with acceptable toxicities.

Loco-regional recurrences in esophageal cancer can deteriorate patients' quality of life by dysphagia. Even if high-dose radiotherapy cannot improve survival, it might be required for loco-regional control. Because retrospective data cannot account for patients' quality of life exactly, further randomized trials will be required.

V. Conclusion

In our study, high-dose radiotherapy did not show improved DFS, OS. But the local control rate and the complete response rate was higher, and significant treatment-related late toxicity was not noted in the high-dose group. Our data indicate a need for further study of the optimal radiation dose in a prospective randomized trial, with emphasis on improving treatment outcomes, and decreasing the treatment-related toxicity of CCRT in patients with esophageal cancer.

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ABSTRACT (IN KOREAN)

식도암에 대한 동시병용 방사선-항암화학요법에서 고선량 방사선 치료와 표준선량 방사선치료의 비교

〈지도교수 이창걸〉

연세대학교 대학원 의학과

서양권

목적: 식도암 환자에 대한 동시병용 방사선-항암화학요법에서 고선량 방사선 치료의 효과를 알아보고자 하였다.

재료 및 방법: 1996년부터 2007년까지 식도암으로 동시병용 방사선-항암화학요법을 받은 207명의 환자를 대상으로 분석하였다. 207명중 65명은 54 Gy 이하의 방사선을 조사받았으며 (표준선량군), 142 명은 59.4 Gy 이상의 방사선을 조사받았다 (고선량군). 표준선량군과 고선량군의 중앙 방사선 선량은 각각 54 Gy (범위, 45 – 54 Gy) 와 63 Gy (범위, 59.4 -70 Gy) 였다. 5-fluorouracil (5-FU)와 cisplatin이 전체환자의 85%에서 처방되었으며 그 외의 환자에서는 5-FU 단독 항암화학치료가 시행되었다. 국소재발은 다음의 3가지로 분류하였으며, 최종 방사선 조사야 내의 재발은 중심부위 재발 (central recurrence), 최종 방사선 조사야 바깥이지만 초기 방사선 조사야 내의 재발은 경계부위 재발 (marginal recurrence), 그리고 초기 방사선 조사야 외의 재발은 조사야

외 재발 (out-field recurrence)로 정의하였다.
결과: 표준선량군과 고선량군 간에 환자의 나이, 성별, 병리학적 특성에 통계적으로 유의한 차이는 없었다. 그러나 1-2 기의 환자는 표준선량군에서 많은 빈도를 보였다 (41% versus 9%). 모든 환자의 무병 생존율, 생존율은 각각 중앙값 13 개월, 24 개월이었으며 두 군간에 통계적으로 유의한 차이는 관찰되지 않았다. 국소 조절율은 고선량군에서 더 높았다 (75% vs. 64%, p=0.05). 국소 재발의 패턴은 유사하였으며 (central, 44% versus 27%; marginal, 0% versus 6%; outfield 11% versus 8%) 원발병소의 완전 관해율은 고선량군이 더 높았다 (68% versus 33%, p=0.04). 치료와 연관된 만성 합병증은 두 군에서 모두 관찰되지 않았다.
결론: 본 연구에서 고선량군이 향상된 생존율은 보이지 못했지만, 진행된 병기의 환자들이 고선량군에 많았음에도 불구하고 좋은 생존율과 표준선량군보다 더 높은 국소 조절율과 완전 관해율을 보였다. 따라서 본 연구는 향후의 전향적 무작위 임상연구에 지침을 제공할 수 있을 것이다.

핵심되는 말 : 식도암, 방사선치료, 항암화학치료