

## RESEARCH ARTICLE

# Survival in Patients Treated with Definitive Chemo-Radiotherapy for Non-Metastatic Esophageal Cancer in North-West Iran

Seyed Kazem Mirinezhad<sup>1\*</sup>, Mohammad Hossein Somi<sup>1</sup>, Farshad Seyednezhad<sup>2</sup>, Amir Ghasemi Jangjoo<sup>2</sup>, Morteza Ghojzadeh<sup>1</sup>, Mohammad Mohammadzadeh<sup>2</sup>, Ali Reza Naseri<sup>2</sup>, Behnam Nasiri<sup>2</sup>

### Abstract

**Background:** Areas of Iran have among the highest incidences of esophageal cancer in the world. Definitive chemo-radiotherapy (DCRT) is used for locally advanced esophageal cancer and for inoperable tumors as an alternative to surgical treatment. **Materials and Methods:** This retrospective study was conducted in North-West Iran 2006-2011, including 267 consecutive patients with non-metastatic esophageal cancer. Eligible inoperable patients were treated with DCRT or definitive radiotherapy (DRT) alone. Radiotherapy (RT) was delivered at 1.8-2 Gy/day for five consecutive days in a given week. Chemotherapy (CT) consisted of cisplatin and 5-fluorouracil. **Results:** The median survival was 12.7 months with 1, 3 and 5 year survival rates of 55%, 18% and 11%, respectively. On univariate analysis, relations with age at diagnosis ( $p=0.015$ ), N-stage ( $p=0.04$ ), total dose of RT ( $p=0.001$ ), fraction ( $p<0.001$ ), Gap status ( $p=0.025$ ), chemotherapeutic regimens ( $P=0.027$ ), and 5-Fu  $\text{Mg/m}^2$  ( $P=0.004$ ) were apparent. Comparing DCRT to DRT, there was a significant difference in survival. Multivariate analysis was performed for comparison between DCRT and DRT showed significant association with age group  $\geq 65$  to  $<65$  ( $P=0.02$ ; OR: 1.46), the total RT dose (Gy)  $\geq 50$  to  $<50$  ( $P=0.01$ ; OR: 0.65) and the fraction group  $\geq 25$  to  $<25$  ( $P<0.001$ ; OR: 0.54). **Conclusions:** The survival rates of esophageal cancer treated with DCRT in North West of Iran is poor; therefore, early detection and improved treatment methods, with clinical trials are a high priority.

**Keywords:** Survival - esophageal cancer - definitive chemo radiotherapy - North-West Iran

*Asian Pacific J Cancer Prev*, 14 (3), 1677-1680

### Introduction

Esophageal cancer is one of the three most common cancers among Iranian people (Sadjadi et al., 2010). The five-year survival rate in the northern part of Iran is 13% (Ghadimi et al., 2011). DCRT as primary treatment modality is offered to esophageal cancer patients, as an alternative for patients considered medically unfit for surgery or having irresectable tumors (Smit et al., 2012). Although DCRT has not been compared directly with surgery in randomized trials, outcomes from published studies are similar to those seen in surgical trials in terms of survival and quality of life (Gwynne et al., 2011). Despite 45 years of the establishment of the regional center of RT, the effect of DCR in survival patients with esophageal cancer has been unknown. The purpose of the current study is to evaluate the effects of DCRT on survival of patients

with locally advanced inoperable esophageal cancer and compare two modality treatment.

### Materials and Methods

This retrospective study was conducted in North-West of Iran from March of 2006 to March of 2011, included of 267 consecutive patients with locally advanced inoperable esophageal cancer. Clinical staging consisted of endoscopy, endoscopic ultrasound, barium swallow, computed tomography scan of the abdomen and thorax. Patients with metastatic diseases and those treated with palliative intent (radiation dose  $<30$  Gy) have been excluded. Eligible inoperable patients were treated with DCRT or DRT alone. Clinicopathological variables and survival times were patient's medical records and collected by telephone contact.

<sup>1</sup>Liver and Gastrointestinal Disease Research Center, <sup>2</sup>Radiation Oncology Therapy of IMAM REZA (AS) Hospital, Tabriz University of Medical Sciences, Tabriz, Iran \*For correspondence: [mirinezhad@gmail.com](mailto:mirinezhad@gmail.com)

## Treatment protocol

Treatment protocol, consisting of either DCRT or DRT was begun immediately after diagnosis. RT was delivered by linear accelerator at 9 MV at 40°C Gy/min. The initial 44 Gy dose was administered using a conventional AP-PA. RT was delivered at 1.8-2 Gy/day for five consecutive days in a given week. Patients lay supine, with the tumor volume and surrounding nodes included within the RT field with longitudinal and lateral margins of 5 and 3 cm, respectively. The spinal cord dose was limited to 44 Gy. RT consisted of two course of Cisplatin (100 mg/m<sup>2</sup> per d) plus 5-FU (1000 mg/m<sup>2</sup> per day) for three consecutive days, beginning 1-5 week after concurrent with RT. Cisplatin was administered as a bolus over 30 min, simultaneously started with the 5-FU, with adequate hydration and anti-emetic drugs.

## Statistical analysis

Descriptive analysis was done for demographic, pathology and clinical features. Results were expressed as means±standard deviation and percentage. The probability curves for survival were calculated according to the Kaplan–Meier Method and compared by the log-rank test. Multivariate analysis was carried out using the Cox proportional hazard model. P<0.05 was considered as statistically significant. The data were analyzed using by SPSS.v.16 software.

## Results

Outcome data were available on all 267 patients who underwent DCRT, 175 patients (65.5%) received CRT, and 92 patients (34.5%) received RT as well. The mean age of the patients at diagnosis was 67.4±12.1 years (range, 35-90 years); 123 women (46.1%) and 144 males (53.9%). The most common tumor histology was squamous cell carcinoma (SCC) (95.1%), and most tumors (51.3%) were located in the lower thoracic region. The radiotherapy dose of ≥50 Gy in ≥25 fractions was prescribed in 105 (39%) patients. The median radiation dose was 44 Gy (range, 19.8-100.8 Gy). A total of 178 (66.7%) patients died during the period of study.

## Univariate analysis

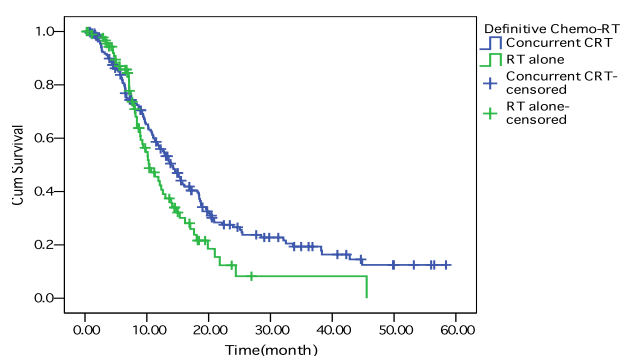
The median survival was 12.73±0.92 (95%CI=10.92-14.54) months with 1, 3 and 5 year survival rates of 55%, 18% and 11%, respectively. As shown in Table 1, on univariate analysis for identifying potential prognostic factors related to age at diagnosis (p=0.015), N-stage (p=0.04), total dose of RT (p=0.001), Fraction (p<0.0001), Gap status (p=0.025), Chemotherapeutic regimens (P=0.027), 5-Fu Mg/m<sup>2</sup> (P=0.004) and Comparing DCRT to DRT, There was a significant difference in survival between the two treatment groups (Figure 1). Fifty-eight of the 92 patients in the radiation-therapy group (63%)

**Table 1. Univariate Analysis of the 267 Patients Undergoing Definitive Chemoradiotherapy**

| Variable                    | Sub groups | No  | (%)    | Median Survival<br>mo (CI 95%) | Survival raet%<br>3 year | 5 year | P value<br>(Log-rank) |
|-----------------------------|------------|-----|--------|--------------------------------|--------------------------|--------|-----------------------|
| Age group                   | <65        | 92  | (34.5) | 15.03 (12.07-17.98)            | 30                       | 17     | 0.01                  |
|                             | 65 ≥       | 174 | (65.2) | 12.2 (10.1-14.3)               | 12                       | 9      |                       |
| Sex                         | Female     | 123 | (46.1) | 11.8 (8.98-14.62)              | 16                       | 8      | 0.52                  |
|                             | Male       | 144 | (53.9) | 13.43 (11.06-15.8)             | 19                       | 14     |                       |
| Tumor Histology             | SCC        | 254 | (95.1) | 12.93 (11.07-14.79)            | 18                       | 12     | 0.88                  |
|                             | AC         | 13  | (4.9)  | 10.27 (5.03-15.51)             | 29                       | -      |                       |
| T stage                     | T2         | 5   | (1.9)  | 19.57 (---)                    | 43                       | 43     | 0.09                  |
|                             | T3         | 26  | (9.7)  | 18.47 (10.47-26.47)            | 25                       | -      |                       |
| N stage                     | N0         | 16  | (6)    | 20.53 (18.28-22.78)            | 53                       | 31     | 0.04                  |
|                             | N1         | 15  | (5.6)  | 12.2 (4.05-20.35)              | -                        | -      |                       |
| Tumor Differentiation       | well       | 98  | (36.7) | 14.1 (10.78-17.42)             | 22                       | 12     | 0.44                  |
|                             | Moderate   | 49  | (18.4) | 11.3 (8.52-14.08)              | 15                       | 15     |                       |
|                             | poor       | 11  | (4.1)  | 20.9 (---)                     | -                        | -      |                       |
| Tumor Site                  | Upper      | 35  | (13.1) | 11.07 (1.00-22.63)             | 27                       | 14     | 0.46                  |
|                             | Middle     | 94  | (35.2) | 15.17 (12.27-18.06)            | 22                       | 13     |                       |
|                             | Lower      | 138 | (51.3) | 11.8 (9.8-13.8)                | 12                       | 9      |                       |
| Radiation therapy dose (Gy) | <50        | 156 | (58.4) | 10.3 (8.92-11.68)              | 14                       | 7      | 0.001                 |
|                             | ≥50        | 111 | (41.6) | 15.77 (12.36-19.18)            | 22                       | 15     |                       |
| Fraction group              | <25        | 142 | (53.2) | 10.17 (8.98-11.36)             | 13                       | 6      | <0.001                |
|                             | ≥25        | 125 | (46.8) | 16.9 (13.52-20.28)             | 23                       | 16     |                       |
| Gap Status                  | No         | 186 | (69.7) | 11.07 (9.3-12.84)              | 15                       | 10     | 0.02                  |
|                             | Yes        | 81  | (30.3) | 14.67 (12.92-16.42)            | 22                       | 13     |                       |
| Chemotherapeutic Regimens   | 5-FU       | 23  | (13.1) | 9.67 (8.21-11.13)              | -                        | -      | 0.02                  |
|                             | Cisplatin  | 23  | (13.1) | 11.6 (10.39-12.8)              | 22                       | -      |                       |
|                             | 5-FU + Cis | 123 | (71.4) | 15.17 (12.27-18.1)             | 22                       | 16     |                       |
|                             | Other      | 4   | (2.4)  | 8.83 (11.6-16.2)               | -                        | -      |                       |
| 5-Fu Mg/m <sup>2</sup>      | <5000      | 56  | (38.4) | 10.8 (5.5-16.1)                | 11                       | 11     | 0.004                 |
|                             | ≥5000      | 90  | (61.6) | 18.2 (15.22-21.18)             | 32                       | 17     |                       |
| Cisplatin Mg/m <sup>2</sup> | <120       | 66  | (45.2) | 12.93 (9.54-16.32)             | 16                       | 10     | 0.06                  |
|                             | ≥120       | 80  | (54.8) | 16.07 (12.44-19.7)             | 27                       | 18     |                       |
| Definitive therapy          | CRT        | 175 | (65.5) | 13.93 (11.79-16.06)            | 20                       | 14     | 0.03                  |
|                             | RT         | 92  | (34.5) | 10.4 (8.09-12.71)              | 10                       | -      |                       |

**Table 2. The Cox Regression – Definitive CRT Compared with Definitive RT**

| Variable                          | Sub groups | Median Survival time by life table (mon) |       | Exp (B) | Multi variate (Cox Regression) (95%CI) P-value |        |
|-----------------------------------|------------|--|-------|---------|--|--------|
|                                   |            | DCRT                                     | DRT   |         | Lower  | Upper  |
| Age group                         | <65        | 18.22                                    | 11.45 |         |  |        |
|                                   | ≥65        | 13.86                                    | 12.00 | 1.46    | 1.06-2.02                                      | 0.020  |
| N-Stage                           | N0         | 36.92                                    | -     |         |  |        |
|                                   | N1         | 19.50                                    | -     | 2.11    | 0.66-4.23                                      | 0.230  |
| Total Radiation therapy dose (Gy) |            |  |       |         |  |        |
| Fraction group                    | <50        | 10.57                                    | 11.56 |         |  |        |
|                                   | ≥50        | 18.62                                    | 12.60 | 0.65    | 0.47-0.90                                      | 0.010  |
| Gap Status                        | <25        | 9.30                                     | 11.74 |         |  |        |
|                                   | ≥25        | 19.19                                    | 11.50 | 0.54    | 0.38-0.76                                      | <0.001 |
| Gap Status                        | No         | 12.69                                    | 11.50 |         |  |        |
|                                   | Yes        | 18.27                                    | 13.50 | 0.75    | 0.53-1.04                                      | 0.080  |

**Figure 1. Kaplan-Meier Compare of Survival on Definitive Therapy Analysis are Shown CRT and RT Alone**

died, as compared with 120 of the 175 patients in the combined-therapy group (68.6%). The median survival in the radiation-therapy group was 10.4 months, as compared with 13.9 months in the combined-therapy group ( $P=0.03$  by the log-rank test).

#### Multivariate analysis

Multivariate analysis was performed for Comparison between DCRT and DRT with covariates significantly associated with Age group  $\geq 65$  to  $< 65$  ( $P=0.02$ ; Odds Ratio (OR): 1.46; 95%IC=1.06-2.02), the total radiation therapy dose (Gy)  $\geq 50$  to  $< 50$  ( $P=0.01$ ; Odds Ratio (OR): 0.65; 95%IC=0.47-0.9) and fraction group  $\geq 25$  to  $< 25$  ( $P \leq 0/001$ ; Odds Ratio (OR): 0.54; 95%IC=0.38-0.76) (Table 2).

#### Discussion

Esophageal cancer is the second and third most common malignancy in Iranian males and females, respectively (Sadjadi et al., 2010). The 5 years survival is reported to be only 12% East Azerbaijan province of Iran (Mirinezhad et al., 2012). Unfortunately, patients suffering from esophageal cancer often refer to medical care when it is unfit for surgery or having irresectable tumors and so DCRT to treat them. In our study, the one, three and the five year survival rates were 55, 18 and 11%, respectively

which are slightly lower as compared to those reported from other studies (Gwynne et al., 2011; Motoori et al., 2012; Semrau et al., 2012). This result could be explained by the fact that Iranian patients generally seek a medical advice with a delay and the diagnosis is made when the disease has reached an advanced stage (Ghadimi et al., 2011). This study revealed that, aging was one of the risk factors ( $P=0.02$ ; OR=1.46 by the cox regression analysis) and again age was inversely associated with the survival rate ( $P=0.01$ ), which is consistent with previous studies (Aghcheli et al., 2011; Ghadimi et al., 2011). We showed that nodal stage was an important prognostic factor; this was reported from another studies as well ( $P=0.04$ ) (Gwynne et al., 2011; Semrau et al., 2012). Result in the current study did not show any statistical significance according to histology this is consistent with several prior studies (Gwynne et al., 2011; Semrau et al., 2012). There was no statistically significant difference in gender and tumors site of the upper, middle or lower esophagus this is consistent with other studies respectively (Byun et al., 2011; Semrau et al., 2012). Higher doses of radiation, was one of the Protective factors ( $P=0.005$ ; OR=0.62 by the cox regression analysis) and was associated with a higher survival rate ( $P<0.001$ ), as report by other study and may improve local control as well as survival (Byun et al., 2011; Gwynne et al., 2011; Semrau et al., 2012). We found a significant survival advantage for patients who received a combination of CT and RT as compared with RT alone ( $p=0.03$ ), this is consistent with other report (Semrau et al., 2012). Results of our study were limited by the lack of recorded toxicity data in a standardized fashion. In conclusion, the survival rates of esophageal cancer treated with DCRT in North West of Iran is poor; therefore, early detection and improved treatment methods, with performed clinical trial study.

#### Acknowledgements

This study was funded by a grant from Liver and Gastrointestinal Disease Research Center, Tabriz University of medical sciences. We thank Dr.Sara Farhang and all of the Tabriz Radiotherapy center personnel for helping us in conducting this study.

#### References

- Aghcheli K, Marjani A, Nasrollahzadeh D, et al (2011). Prognostic factors for esophageal squamous cell carcinoma-a population-based study in Golestan province, Iran, a High Incidence Area. *PLoS ONE*, **6**, 1-7.
- Byun SJ, Kim JH, Kim OB, et al (2011). Concurrent chemoradiotherapy in locally advanced esophageal cancer. *Society for Therapeutic Radiology and Oncology*, **29**, 20-7.
- Ghadimi M, Rasouli M, Mahmoodi M, et al (2011). Prognostic factors for the survival of patients with esophageal cancer in Northern Iran. *J Res Med Sci*, **16**, 1261-72.
- Gwynne S, Hurty C, Evans M, et al (2011). Definitive chemoradiation for oesophageal cancer - a standard of care in patients with non-metastatic oesophageal cancer. *Clinical Oncology*, **23**, 182-8.
- Mirinezhad SK, SomiMH, Ghasemi JA, et al (2012). Survival rate and prognostic factors of esophageal cancer in east

*Seyed Kazem Mirinezhad et al*

Azerbaijan province, north-west of Iran. *Asian Pac J Cancer Prev*, **13**, 3451-4.

Motoori M, Yano M, Ishihara R, et al (2012). Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. *Ann Surg Oncol*, **19**, 2135-41.

Sadjadi A, Marjani H, Semnani S, et al (2010). Esophageal cancer in Iran: A review. *Middle East J Cancer*, **1**, 5-14.

Semrau R, Herzog SL, Vallböhmer D, et al (2012). Prognostic factors in definitive radiochemotherapy of advanced inoperable esophageal cancer. *Dis Esophagus*, **25**, 545-54.