CLINICOPATHOLOGICAL FACTORS AFFECTING SURVIVAL OUTCOMES OF ESOPHAGEAL CANCER PATIENTS TREATED AT A SINGLE TERTIARY RADIOTHERAPY CENTER IN IRAQ

Redeer Adnan Mikaeil [a], Kamal Ahmad Saeed [b], and Nyan Othman Saeed [a]

Submitted: 14/8/2022; Accepted: 20/2/2023; Published: 21/6/2023

ABSTRACT

Background

Carcinoma of the oesophagus is one of the top ten most prevalent and aggressive types of cancer worldwide.

Objectives

To determine the clinicopathological factors affecting the survival of oesophagal cancer.

Patients and Methods

This cross-sectional study was conducted retrospectively on 97 patients with oesophagal cancer in a single radiotherapy cancer centre in Sulaimaniyah City, Kurdistan region of Iraq, from 2010 to 2021.

Results

The mean age of the patients was 68.4 ± 12.2, ranging from 29 to 90 years old. The major histology was squamous cell carcinoma (89%), and pathological grade II disease was more prevalent (53%). Males and females were equally affected (50% for each gender). At presentation, a larger number of the patients were located in the lower (N=30) and mid (N=29) oesophagus. Stage III was the most common presenting stage (45.7%). The median follow-up time was 14 months. The 12-month and 18-month survival rates were 58.6% and 34.6%, respectively. There was a significantly better survival outcome for patients with grade 1 disease than higher grades, especially grade 2 (p value= 0.01). Chemoradiation showed significantly improved survival benefits compared with RT alone (p value= 0.03) and tri-modality therapy.

Conclusion

The most significant factors affecting 18-month actual survival in oesophagal cancer are tumour biology characteristics, especially low tumour grade, and chemoradiotherapy without surgery.

Keywords: *Esophageal cancer, clinicopathological factors, radiotherapy, survival outcomes.*

---

[a] Radiation Oncology, Zhianawa Cancer Center, Sulaimani, Kurdistan Region, Iraq.
Correspondence: redeeradnan@gmail.com.
[b] College of Medicine, University of Sulaimani. Kurdistan Region, Iraq.

https://doi.org/10.17656/jsmc.10410

INTRODUCTION

Oesophagal cancer is an aggressive tumour. It is the ninth most common cancer-related cause of death in women and the sixth most common cancer-related death in men globally [1]. According to data from the Global Cancer Observatory (GLOBOCAN), there were 572,034 new oesophagal cancer cases and 508,585 related deaths in 2018 [2].

Ninety-five per cent of cases are caused by the two main histological subtypes; squamous cell carcinoma (SCC) and adenocarcinoma (AC) [3]. In the Western world, esophageal adenocarcinoma is the most common histology. At the same time, squamous cell carcinoma is more predominant subtype in the Eastern world [4, 5], possibly due to the differences in risk factors [6]. More than half of oesophagal cancer patients is diagnosed with locally advanced disease, and approximately 20% have resectable disease at presentation [7]. Even in individuals with resectable oesophagal cancer, the prognosis is poor with surgery alone, with a 5-year survival rate of less than 30% [8, 9].

Although tri-modality therapy consisting of neoadjuvant chemoradiotherapy (nCRT) followed by resection is currently the standard treatment for locally advanced oesophagal cancer [10, 11], nevertheless, surgery is linked to morbidity and mortality.

Despite the advantages of surgery for local control (LC), no differences were found between nCRT followed by surgery and definitive CRT (dCRT) in two previous randomised trials [12, 13]. One randomised controlled trial compared the outcomes of 172 patients with oesophagal SCC who were treated by three different regimens: definitive combined chemoradiotherapy, induction chemotherapy followed by disease resection, or induction chemotherapy followed by concurrent chemoradiotherapy with escalated radiation dose. They discovered no differences in 5- and 10-year overall survival rates; however, patients who underwent surgery had higher treatment-related mortality rates [12].

Also, the FFCD 9102 study involved 444 individuals with possibly respectable oesophagal SCC who had surgery or additional chemoradiation therapy after induction chemotherapy revealed that while surgically treated individuals were less likely to require palliative care for dysphagia and had considerably reduced rates of loco-regional recurrence (LRR) (34% vs 43%), they had comparable 2-year and median survival to those who kept on chemoradiation, along with the worsening quality of life outcomes and sharply increased morbidity with the resection [13].

According to earlier reports of national practice patterns, definitive chemoradiation therapy is reportedly utilised more commonly than tri-modality therapy [14, 15].

Even though the recommended dose of RT in the definitive setting has remained at 50.4 Gy based on the results of the RTOG 94-05 trial [16], the optimal radiation dose remains debatable.

Intensity-modulated RT (IMRT) is a modern form of three-dimensional conformal radiation therapy (3D-CRT) that uses non-uniform radiation beams to maximise the radiation dose of the target volume while simultaneously minimising the radiation dose of the surrounding normal tissues. However, oesophagal cancer survival rates remain dismal despite all technological advancements in RT and surgery, as well as a greater understanding of the clinical and biochemical aspects of the illness.

The current study aims to illustrate treatment outcomes for oesophagal cancer according to different clinicopathological factors in a retrospective study performed at a single tertiary radiotherapy centre in Sulaimaniyah City/Iraq.

PATIENTS AND METHODS

In a retrospective cross-sectional study from January 2010 to January 2021, 97 patients with a biopsy-proven stage II-IV primary oesophagal carcinoma who visited Zhianawa cancer centre, a tertiary radiotherapy centre in Sulaimaniyah, were reviewed. All patients treated with local radiotherapy (curative or palliative) for oesophagal cancer (AC or SCC or others) of any T, N, or M stage and any age, smokers or non-smokers, either as a sole form of treatment or in combination with chemotherapy and surgery, met the criteria for inclusion in our analysis.

All pathological specimens from surgically excised or preoperative endoscopic biopsies were examined to classify the tumour grades as well-differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3) disease.

Patients who initially received neoadjuvant radiotherapy but did not undergo subsequent surgery due to disease progression or other factors were also eligible. Five patients who did not receive radiation for various reasons were excluded.

Ultimately, 92 patients received radiotherapy and were enrolled in this analysis. Patients had to know the total radiation dose and the number of radiation fractions. The tumour staging was done according to the American Joint Committee on Cancer (AJCC) TNM staging, 8th edition, 2017.

Patients underwent a thorough pre-treatment workup for proper staging, including medical history and physical examination.

The radiation oncologists decided whether to use the IMRT or 3D-CRT technique at their discretion, primarily based on scientific team discussion and the facility available during treatment planning.

Treatment

Radiotherapy

On computed tomography (CT) simulation, a required step prior to radiotherapy for delineation of the disease targets and critical normal organs, patients were placed supine with arms up, wing board for immobilisation. A fusion with already performed diagnostic imaging, especially CT of the chest or positron-emission tomography (PET- CT) used for target delineation. CT, PET, clinical information, and endoscopic findings identified the primary tumour and any affected lymph nodes, contoured as the gross tumour volume (GTV). As per the treating radiation oncologist's decision, the clinical target volume (CTV) was defined as the GTV plus a margin of 1 cm radial and 3–4 cm craniocaudal expansion along the oesophagus. Elective nodal volumes included the celiac axis for lower tumours or the supraclavicular fossa for upper esophageal cancers. The CTV plus a 0.5-1 cm extension created the planned target volume (PTV).

Typically, curative patients are treated with 1.8–2 Gy daily fractions to a total dose of 40 to 66 Gy based upon tumour location and physician discretion, and the palliative radiotherapy dose schedules used were 35Gy in 14Fx, 30Gy in 10Fx, and 20Gy in 5Fx. Both 6MV and 18MV photon energies are used in the planning. RT planning was done in the XiO or Monaco treatment planning systems (Elekta planning software).

To maximise target dose coverage and reduce dosage to OARs, techniques like a 3D-CRT and fixed-field IMRT beam modes were utilised for each instance. The X-ray Volumetric Imaging (XVI), a low-dose computed tomography, was used as a verification image to identify and correct any patient positioning errors before treatment.

During receiving radiotherapy, a weekly follow-up was routinely conducted for assessment of patient health status and management of radiation-related toxicities. After radiotherapy completion, patients are followed every 3-6-month intervals for the first two years and then 6-12 months for the subsequent three years. Follow-up sessions included physical examination and endoscopy, and if clinically indicated, the patients were sent for chest CT, FDG PET, and barium swallow.

Chemotherapy

Chemotherapy is administered as definitive chemoradiotherapy (CRT), induction chemotherapy followed by concomitant CRT, or adjuvant/consolidation chemotherapy after surgery. Common regimens were either 5-fluorouracil (5-FU)–or cisplatin-based. Widespread protocols used were ECX (epirubicin, cisplatin, and capecitabine) every 21 days, induction chemo by ECF (epirubicin, cisplatin, and fluorouracil) every 21 days, or FP (5-FU and cisplatin) concurrently with RT.

Statistics

Software statistical package SPSS was performed for all statistical analysis, SPSS 18 for Windows/MAC (PASW et al. 18; SPSS, Chicago, IL). First, a descriptive analysis of the covariables was conducted, and for qualitative variables, the absolute (N) and relative (%) frequency distributions were reported. The patient's survival was calculated from the date of diagnosis until the close-out date (July 8th, 2022). The Kaplan-Meyer estimate was used to calculate the survival probability between treatment modalities, cancer location, and grades. Multivariate analysis was performed as well, with the Cox regression (Cox proportional hazards survival model) approach for analyzing overall survival differences by age, gender, smoking status, pathological grades, anatomical locations, disease stage, plan and modality of treatment, as well as RT dose and technique used. Statistical significance was defined as a p-value of ≤ 0.05.

RESULTS

Table 1 provides comprehensive information on the patients, tumours, and treatments. The mean age of 92 patients included in the study was 68.4 years old (SD 12.2 years, range: 29–90 years). There were precisely the same numbers of males and females in the cohort (46 patients – 50%), and 53% (49/92) of patients had pathological grade II disease with a predominant histology of squamous cell carcinoma (82/92, 89%). Most patients subsequently had primary tumours in the lower and middle third of the oesophagus, 32% and 31%. Smoker patients were slightly more than non-smokers, 38 vs 36. In the present study, the stages of primary tumours included stage II/stage III/stage IV/not specified stage in the following distribution: 22/42/24/4 (23.9%/45.7%/26.1%/4.3%).

All 92 patients enrolled in the analysis received radiotherapy treatment, either alone (17 patients, 18.5%), with chemotherapy (63 patients, 68.5%), or with both chemotherapy and surgery as tri-modal treatment (9 patients, 9.8%). More than half (52.2%, N=48) of patients received 35Gy or less of RT, thirty-seven (40.2%) patients treated with RT dose between 40–50.4Gy, and the remaining seven (7.6%) oesophagal cancer patients received RT dose of 54Gy or more. Only 13(14.1%) patients were treated with the IMRT technique compared to 79(85.9%) who received radiotherapy with the 3D-CRT technique.

Survival Outcomes

When the data were evaluated, 67 (72.8%) patients had died, and only 8 (8.7%) patients were still alive and censored. The other 17 (18.4%) patients had missed contact with them and their vital status was unknown. The median follow-up time for a total of 75 patients was 14 months (1-118 months), with an interquartile range of 17 months. The estimated eighteen and twelve-month overall survival was 34.6% (26/75) and 58.6% (44/75), respectively. A total of 67 patients died; in 88% (59) of them, the cause of death was distant metastasis or other disease-related complications, while in the remaining 12% (8/67), the death was reported as a result of other co-morbidities rather than oesophagal cancer itself.

Table 2 shows the differences between many variables in the survival outcome of oesophagal cancers.

There were significantly higher adjusted hazards among patients having grade 2 disease (AHR, 15.85; 95% CI, 1.66 to 151.3; P value = 0.01), and at the margin of significance for grade 3 disease (AHR, 9.89; 95% CI, 0.88 to 110.3; P value = 0.06) as compared to patients with pathological grade 1 carcinoma (Figure 1A). Lower hazards of statistical significance were noted for giving the patients both chemotherapy and radiotherapy as a bi-modality treatment (AHR, 0.19; 95% CI, 0.04 to 0.88; P value = 0.03) than RT alone and tri-modality therapy (Figure 1B). Tumours of the upper oesophagus have poorer survival outcomes than other locations but just reached the borderline of significance (AHR, 3.42; 95% CI, 0.87 to 13.41; P value = 0.07) (Figure 1C).

No statistically significant differences in survival outcomes were observed for other clinicopathological features and treatment options like age of the patients, gender identity, smoking effect, disease stage, treatment plan, and RT dose and technique.

Table 1. Patient and Tumor Characteristics.

Variables	N	%
Gender		
Male	46	50.0
Female	46	50.0
Residency		
Sulaimaniyah	68	73.9
Erbil	4	4.3
Duhok	7	7.6
Halabja	7	7.6
Other Iraqi cities	6	6.5
Smoking history		
Yes	38	41.3
No	36	39.1
Unknown	18	19.6
Tumour histology		
SCC	82	89.1
AC	7	7.6
NET	1	1.1
Not specified	2	2.2
Anatomical location		
Lower	30	32.6
Mid	29	31.5
Upper	16	17.4
Extensive	16	17.4
Unknown	1	1.1
Grade		
Well-differentiated	10	10.9
Moderately differentiated	49	53.3
Poorly differentiated	19	20.7
Unknown	14	15.2
Stage		
II	22	23.9
III	42	45.7
IV	24	26.1
Not specified	4	4.3
Treatment plan		
Curative	46	50.0
Palliative	46	50.0
Treatment modality		
RT alone	17	18.5
RT + Chemo	63	68.5
RT + Chemo + Surgery	9	9.8
Not reported	3	3.3
Radiotherapy technique		
3D-CRT	79	85.9
IMRT	13	14.1
Radiotherapy dose (Gray)		
35 or less	48	52.2
40 - 50.4	37	40.2
54 or more	7	7.6
Vital state (now)		
Alive	8	8.7
Dead	67	72.8
Unknown	17	18.4
Age at diagnoses (years)		
Mean	68.43	...
Minimum	29	...
Maximum	90	...

N: Numbers of different characteristic; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; NET: Neuroendocrine tumo; 3D-CRT: Three-dimensional conformal radiation therapy; IMRT: Intensity-modulated radiotherapy

Table 2. Adjusted Hazard Ratios of Association between Selected Covariates and Survival in Patients with Esophageal Cancer.

Variable	AHR	95% CI	P-value
Gender			
Male	1		
Female	0.80	0.36 - 2.10	**0.79**
Smoking Status			
No	1		**0.29**
Yes	0.66	0.30 - 1.42	
Pathological Grade			
Grade 1	1		
Grade 2	15.85	1.66 - 151.3	**0.01**
Grade 3	9.89	0.88 - 110.35	**0.06**
Anatomical Location			
Lower	1		
Mid	1.05	0.38 - 2.87	**0.91**
Upper	3.42	0.87 - 13.41	**0.07**
Extensive	2.42	0.88 - 6.67	**0.08**
Disease Stage			
Stage 2	1		
Stage 3	0.91	0.27 - 3.03	**0.88**
Stage 4	0.73	0.15 - 3.58	**0.70**
Treatment Plan			
Curative	1		
Palliative	2961.2	0.01 - 2.01	**0.90**
Treatment Modality			
RT alone	1		
RT + Chemo	0.19	0.04 - 0.88	**0.03**
RT + Chemo + Surgery	0.32	0.05 - 1.78	**0.19**
RT Dose (Gray)			
35 or less	1		
40-50.4	2199.9	0.01 - 1.49	**0.91**
54 or more	151.03	0.01 - 1.05	**0.94**
RT Technique			
3D-CRT	1		
IMRT	2.20	0.61 - 7.90	**0.22**
Age (years)	2.43	0.88 – 6.70	**0.08**

3D-CRT: Three-dimensional conformal radiation therapy
IMRT: Intensity-modulated radiotherapy

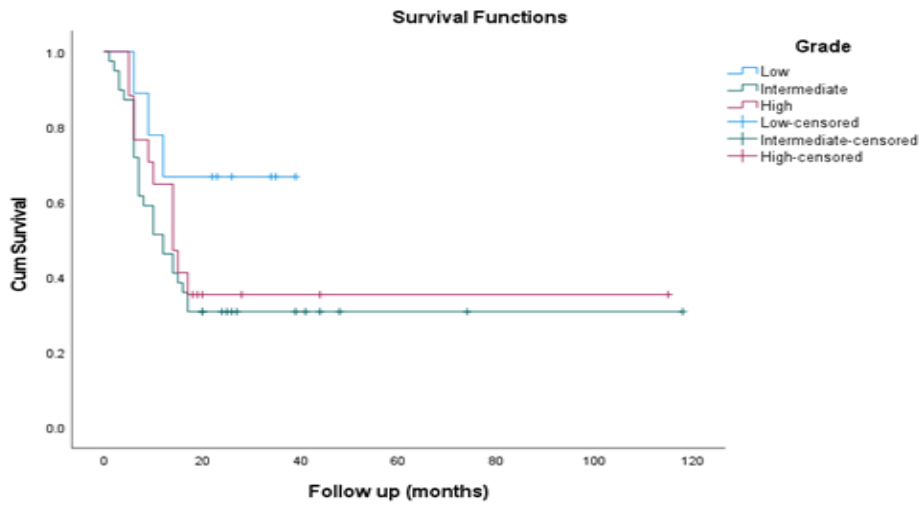

Figure 1 A

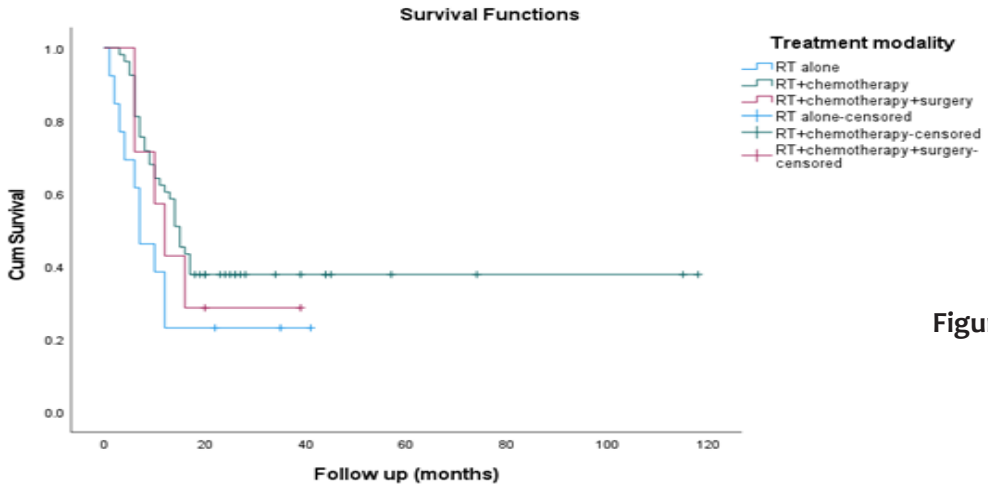

Figure 1 B

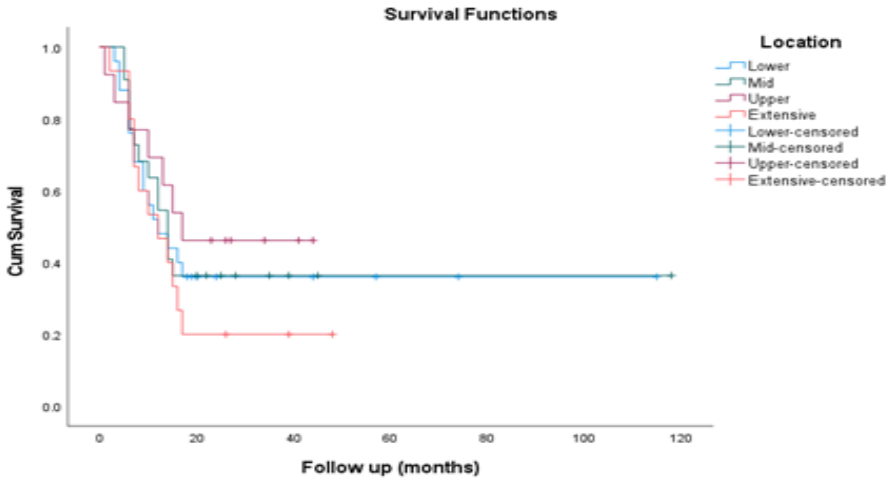

Figure 1 C

Figure 1. A. Kaplan-Meier curve of overall survival by tumor grades. B. Kaplan-Meier curve of overall survival by treatment modality. C: Kaplan-Meier curve of overall survival by anatomical locations.

DISCUSSION

The factors impacting the survival of patients with esophageal cancer (EC) were examined retrospectively in this study. The results of our analysis have the benefit of applying to the future affected people with oesophagal cancer. In this population-based study, we discovered an 18-month overall survival difference among patients with oesophagal cancer in Iraq in terms of tumour grade and treatment modality. In contrast, when adjusted for gender, smoking history, disease stage, tumour location, treatment plan, RT dose, and RT technique, no statistically significant differences were found.

In addition, the age of the patients in general and without making them into groups did not affect 18-month survival so much. However, the main limitations of this study were: Unknown performance state and co-morbidities of patients, no details about chemotherapy treatment, and the inclusion of palliative treatment and stage IV disease.

Traditionally, oesophagal cancer has been recognised as a disease of the elderly, with a peak incidence occurring between the sixth and seventh decades of life. In the Western world, it has been noted that the peak incidence shifts from 65–70 to 70–79 years of age, and 30% of oesophagal cancer patients are 75 years of age or older [17, 18]. However, our data showed that in this part of Iraq, oesophagal cancer incidence peaked between 70 and 80. Unsurprisingly, increasing age was associated with decreased overall survival rates in previous studies [19, 20]. However, the inclusion of patients with oesophagal obstruction and the lack of advanced surgical interventions for our patients may be behind no age-related disparities in survival (P value: 0.08).

Reported previously that gender was a strong and independent prognostic factor, and males had significantly worse survival rates than females [21]. However, in our analysis, the impact on mortality was unrelated to gender identity among Iraqi citizens.

SCC remains the most prevalent histological type in many developing countries, even though the incidence of AC has increased in developed countries in recent decades [22]. The same results were noticed in our developing country regarding the incidence, and 89.1% of the cases were SCC, but since the number of adenocarcinomas was very small (N = 7, 7.6%), the survival comparison was scientifically unreasonable, of note, different outcomes and clinical and molecular characteristics are suspected between SCC and AC [1, 23, 24].

The current study shows that the most significant factor affecting 18-month overall survival in oesophagal cancer may be tumour biology characteristics, particularly favourable tumour grade (P value = 0.01). Kim et al. observed that less aggressive pathologic tumours in well- or well-moderately differentiated tumours have significant long-term survival rates in esophageal cancer [25].

When adenocarcinoma of the oesophagus is treated with chemoradiation, the clinical outcome is significantly worse than with squamous cell cancer [11]. In comparison, trials on patients with oesophagal squamous cell carcinoma have indicated that surgery may not provide any additional benefits over definitive chemoradiation [12, 13]. In the current analysis, EC patients treated with definitive chemoradiotherapy had significantly better lifetime survival outcomes than RT alone and chemoradiation plus resection. This result is the same as in several trials that showed a trend toward chemoradiation [26 -28]. It is important to note that due to medical co-morbidities, many patients referred for definitive chemoradiation are not candidates for surgery. That is why we still agree that treatment of EC can vary considerably and is dictated by disease stage, surgical candidacy, and patients` preferences. Neoadjuvant therapies, part of triple lines of treatment, are often added to treatment plans for locally advanced malignancies that have metastasized to the lymph nodes [29 – 31].

Regarding the impact of RT dose on oesophagal cancer survival, significant variations were not seen in assessing treatment efficacy. Numerous studies using the National Cancer Data Base have found conflicting findings regarding the effect of radiation dose on the survival rate in oesophagal carcinoma patients who received chemoradiation treatment [32 – 35]; three studies revealed that irradiation dosage had no effect on survival outcomes, and one study even came to the conclusion that 41.4 Gy is linked with better overall survival than 50.4 Gy [32].

Concerning the tumour's location, we found no 18-month EC-specific survival benefits. Otterstatter et al. found that whether the tumour was located in the upper, middle, or lower oesophagus, the 5-year survival rates for oesophagal cancer in Canada were similar [36].

Also, Doki et al. looked at 501 patients with squamous cell carcinoma as their primary cancer and discovered that the three sites' survival rates were comparable [37]. However, they observed that the tumour's location has a role in the recurrence mode of the disease.

In conclusion, the 12-month and 18-month survival rates were 58.6% and 34.6%, respectively. Chemoradiation has a superior 18-month survival outcome compared to RT alone and a combination of chemoradiotherapy and surgery in treating stage II-IV oesophagal cancers. A low-grade or well-differentiated cancer cell is oesophagal cancer's most important survival predictor. Other factors like gender, age, smoking, tumour stage and location, and RT dose and technique have no significant impact on the survival of the disease. For better results, additional more extensive prospective randomised clinical trials are required.

Acknowledgement

The author gratefully acknowledges the assistance of Dr Jagar Jasem, asst. Prof., University of Colorado, for statistical analysis.

REFERENCES

1. Torre LA; Bray F; Siegel RL; Ferlay J; Lortet-Tieulent J; Jemal A; Global cancer statistics, 2012 [Internet]. CA: a cancer journal for clinicians. U.S. National Library of Medicine; [cited 2022 Oct18]. Available from: https://pubmed.ncbi.nlm.nih.gov/25651787/

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018, 68:394-424. 10.3322/caac.21492

3. Pohl H, Sirovich B, Welch HG: Esophageal adenocarcinoma incidence: Are we reaching the peak? Cancer Epidemiol Biomarkers Prev. 2010, 19:1468-70. 10.1158/1055-9965.EPI-10-0012

4. Brown LM, Devesa S S, Chow W H. Incidence of adenocarcinoma of the oesophagus among white Americans by sex, stage, and age. J Natl Cancer Inst. 2008; 100 (16): 1184–7.

5. Gholipour C, Shalchi R A, Abbasi M. A histopathological study of oesophagal cancer on the western side of the Caspian littoral from 1994 to 2003. This Esophagus. 2008; 21 (4): 322–7.

6. Löfdahl HE; Lane A; Lu Y; Lagergren P; Harvey RF; Blazeby JM; Lagergren J; Increased population prevalence of reflux and obesity in the United Kingdom compared with Sweden: A potential explanation for the difference in the incidence of oesophagal adenocarcinoma [Internet]. European Journal of Gastroenterology & Hepatology. U.S. National Library of Medicine; [cited 2022 Oct18]. Available from: https://pubmed.ncbi.nlm.nih.gov/21178778/

7. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003; 349:2241-52.

8. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the oesophagus. N Engl J Med. 1997; 337:161-7.

9. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for oesophagal cancer: CALGB 9781. J ClinOncol. 2008; 26:1086-92.

10. Ajani JA; D'Amico TA; Bentrem DJ; Chao J; Corvera C; Das P; et al. Esophageal and Esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology [Internet]. Journal of the National Comprehensive Cancer Network: JNCCN. U.S. National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/31319389/

11. Van Hagen P; Hulshof MC; van Lanschot JJ; Steyerberg EW; van Berge Henegouwen MI; Wijnhoven BP; et at. Preoperative chemoradiotherapy for oesophagal or junctional cancer [Internet]. The New England Journal of Medicine. U.S. National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/22646630/

12. Stahl M;Stuschke M;Lehmann N;Meyer HJ;Walz MK;Seeber S et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the oesophagus [Internet]. Journal of clinical oncology: Official American Society of Clinical Oncology journal. U.S. National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/15800321/.

13. Bedenne L, Michel P, Bouché O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the oesophagus: FFCD 9102. Journal of Clinical Oncology. 2007;25(10):1160–8.

14. Suntharalingam M, Moughan J, Coia LR, Krasna MJ, Kachnic L, Haller DG, et al. Outcome results of the 1996-1999 Patterns of Care survey of the national practice for patients receiving radiation therapy for carcinoma of the oesophagus. Journal of Clinical Oncology. 2005;23(10):2325–31.

15. Smith GL, Smith BD, Buchholz TA, Liao Z, Jeter M, Swisher SG, et al. Patterns of care and loco-regional treatment outcomes in older oesophagal cancer patients: THE SEER-medicare cohort. International Journal of Radiation Oncology*Biology*Physics. 2009;74(2):482–9.

16. National Comprehensive Cancer Network - Home [Internet]. NCCN. [cited 2022Oct18]. Available from: http://nccn.org/

17. vanBlankenstein M, Looman CW, Siersema PD, Kuipers EJ, Coebergh JW. Trends in the incidence of adenocarcinoma of the oesophagus and cardia in the Netherlands 1989–2003. Br J Cancer. 2007; 96:1767–71.

18. Guardino JM, Khandwala F, Lopez R, Wachsberger DM, Richter JE, Falk GW. Barrett's oesophagus at a tertiary care centre: association of age on incidence and prevalence of dysplasia and adenocarcinoma. Am J Gastroenterol. 2006; 101:2187–93.

19. Gavin AT, Francisci S, Foschi R, Donnelly DW, Lemmens V, Brenner H, et al. Oesophageal cancer survival in Europe: A EUROCARE-4 study. Cancer Epidemiol. 2012; 36:505–12.

20. Wo JY, Hong TS, Kachnic LA. Impact of age and co-morbidities on the treatment of gastrointestinal malignancies. SeminRadiatOncol. 2012; 22:311–20.

21. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer. 2009; 45:1017–27.

22. Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, et al. Trends in oesophagal adenocarcinoma incidence and mortality. Cancer. 2012;119(6):1149–58.

23. Bashash M, Hislop T G, Shah A M, Le N, Brooks-Wilson A, Bajdik C D. The prognostic effect of ethnicity for gastric and oesophagal cancer: the population-based experience in British Columbia, Canada. BMC Cancer 2011; 11: 164.

24. Zhang H Z, Jin G F, Shen H B. Epidemiologic differences in oesophagal cancer between Asian and Western populations. Chin J Cancer 2012; 31 (6): 281–6.

25. Kim T; Grobmyer SR; Smith R; Ben-David K; Ang D; Vogel SB; Hochwald SN; Esophageal cancer--the five-year survivors [Internet]. Journal of surgical oncology. U.S. National Library of Medicine; [cited 2022 Oct18]. Available from: https://pubmed.ncbi.nlm.nih.gov/21259254/

26. Price EL, Etienne PL, Meunier B, Maddern G, Hassel MB, Gedouin D, et al. A randomised study of chemotherapy, radiation therapy, and surgery versus surgery for localised squamous cell carcinoma of the oesophagus. Cancer. 1994;73(7):1779–84.

27. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomised trial of preoperative chemoradiation versus surgery alone in patients with Loco-regional oesophagal carcinoma. Journal of Clinical Oncology. 2001;19(2):305–13.

28. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable oesophagus cancer: A randomised controlled phase iii trial. The Lancet Oncology. 2005;6(9):659–68.

29. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (cross): Long-term randomised controlled trial results. The Lancet Oncology. 2015;16(9):1090–8.

30. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New England Journal of Medicine. 2006;355(1):11–20.

31. Ychou M, Boige V, Pignon J-P, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. Journal of Clinical Oncology. 2011;29(13):1715–21.

32. Ji KSY, Thomas SM, Roman SA, Czito B, Anderson KL Jr, Frakes J, et al. Low- vs high-dose neoadjuvant radiation in trimodality treatment of locally advanced oesophagal cancer. J Gastrointest Surg. (2019) 23:885–94. doi: 10.1007/s11605-018-4007-3

33. Haque W, Verma V, Butler EB, Teh BS. Radiation dose in neoadjuvant chemoradiation therapy for oesophagal cancer: patterns of care and outcomes from the National Cancer Data Base. J GastrointestOncol. (2018) 9:80–9. doi: 10.21037/jgo.2017.09.12

34. Semenkovich TR, Samson PP, Hudson JL, Subramanian M, Meyers BF, Kozower BD, et al. Induction radiation therapy for oesophagal cancer: Does dose affect outcomes? Ann Thorac Surg. (2019) 107:903–11. doi: 10.1016/j.athoracsur.2018.09.064

35. Worrell SG, Towe CW, Dorth JA, Machtay M, Perry Y, Linden PA. Higher doses of neoadjuvant radiation for oesophagal cancer do not affect the pathologic complete response rate or survival: a propensity-matched analysis. Ann SurgOncol. (2020) 27:500–8. doi: 10.1245/s10434-019-07849-z

36. Otterstatter MC, Brierley JD, De P, Ellison LF, MacIntyre M, Marrett LD, et al. Oesophagal cancer in Canada: Trends according to morphology and anatomical location. Canadian Journal of Gastroenterology. 2012;26(10):723–7.

37. Doki Y, Ishikawa O, Takachi K, Miyashiro I, Sasaki Y, Ohigashi H, et al. Association of the primary tumour location with the site of tumour recurrence after curative resection of thoracic oesophagal carcinoma. World Journal of Surgery. 2005;29(6):700–7.