



Gastrointestinal Cancer

A Study of Hormonal Receptors in Esophageal Carcinoma: Northeast Indian Tertiary Cancer Center Study

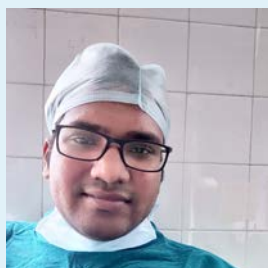
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Abstract



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Background Esophageal cancers, both squamous cell and adenocarcinoma, have poor outcomes with high morbidity and mortality. Our hospital-based registry for the year 2017 to 2018 showed that esophageal cancer constituted 22.7% of annual case-load. Most of our patients present in advanced stages. The aim of this article was to study the role of hormonal receptors in patients with esophageal cancer.

Methods This is a single-institution, prospective, observational study in patients with esophageal carcinoma. Hormonal receptors (estrogen receptor [ER]- α and progesterone receptors) were studied in tumor tissue. Of 160 patients, receptor status was analyzed in 133 patients. Chi-square test was used for the correlation of categorical variables. The value of $p < 0.05$ was considered as statistically significant.

Results A total of 133 patients was taken into the study of which 96 were males and 37 were females. The mean age of patients was 52 years. Carcinoma esophagus was predominantly seen in males. Estrogen and progesterone receptors were positive in 9.02 and 4.51% of the study population, respectively. Patients with hormonal receptor positivity presented with poor functional status, higher grades of dysphagia, higher stage, and most of the tumors were poorly differentiated with statistically significant p -values.

Conclusion Despite recent advances in various fields of oncology, outcomes of esophageal carcinoma have not improved significantly. Hence, a study of new pathways of pathogenesis in carcinogenesis of esophageal carcinoma is essential. Few recent evidences including our study shows that the hormonal milieu is responsible in the pathogenesis of carcinoma esophagus. The utilization of this data and future study of the role of hormonal therapy might lead to improved outcomes in patients with carcinoma esophagus.

Keywords

- ▶ carcinoma esophagus
- ▶ estrogen receptors
- ▶ progesterone receptors

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Introduction

Esophageal cancers, both squamous cell and adenocarcinoma, have poor outcomes with high morbidity and mortality. Global cancer statistic 2018 ranks esophageal cancer as the seventh most common cancer in terms of percentage incidence of new cases site. Over 572,034 (3.2%) new cases were reported and registered number of deaths was 508,585 (5.3%) of all sites.¹ It is expected that by 2025, incidence of esophageal cancer is expected to rise by 140%.² Our hospital-based registry for the year 2017 to 2018 showed that esophageal cancer constituted 22.7% of the annual caseload.

Squamous cell carcinoma and adenocarcinoma are the two main histopathological types.³ Estrogen through regulation of adipose tissue of the body and fat distribution is associated with increase in risk for esophageal adenocarcinoma.^{4,5} There is a lack of sufficient data on the role of the presence of hormonal receptors in esophageal carcinoma which could be a target of therapy.

In view of high esophageal cancer, load, and most patients presenting in the advanced stage, we want to study the role of estrogen and progesterone receptors in esophageal cancer patients.

Methods

This is a single-institution, prospective, observational study in patients with esophageal carcinoma, conducted by the Department of Surgical Oncology at Dr. Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India. The study period was from August 12, 2018, to September 5, 2019. A total of 160 patients was taken into the study, but data regarding only 133 patients were analyzed as the rest of the patients lost to follow-up in the initial evaluation phase. Data regarding clinical features, diagnostic and staging workup, and hormonal receptor status were collected from patient history and hospital records.

SSPS (Statistical Package for the Social Sciences IBM Corp, Chicago, USA) software, version 2017 was used. Chi-square test was used for the correlation of categorical variables. Value of $p < 0.05$ was considered as statistically significant.

The workup for all patients included a detailed history; physical examination; standard blood workup; upper gastrointestinal biopsy; and contrast-enhanced computed tomography of the neck, chest, and abdomen. On an average, five samples of tumor tissue from the different location were taken. The staging was done according to the eighth edition of the American joint committee on Cancer for esophageal cancer. Dysphagia score was graded as grade-1: able to swallow some solids, grade-2: able to swallow only semisolids, grade-3: able to swallow liquids only, and grade-4: unable to swallow anything or total dysphagia. Functional status of patients was assessed according to the Eastern Cooperative Oncology Group (ECOG) score as ECOG-0 as fully active and able to carry all predisease activity. Grade-1: able to carry out light household work, grade-2: unable to carry out any activities and about >50% waking hours, grade-3: capable of limited self-care and confined to chair >50% of waking hours, grade-4: completely disabled, and grade-5: dead.

Immunohistochemistry (IHC) for estrogen receptor (ER)- α and progesterone receptors has been performed on deparaffinized, formalin-fixed paraffin-embedded tissues (**Fig. 1**). IHC was done by the manual method using cell mark Specific Protein -1 (SP-1) clone (rabbit monoclonal) for ER- α and Y85 (rabbit monoclonal) clone for progesterone receptor staining. The reporting of positive staining for both ER- α and progesterone receptor was done based on the percentage of cells with nuclear positivity of weak, moderate, or strong intensity in >1% of tumor cells taking breast slide as control.

Results

A total of 133 patients were taken into the study of which 96 were males and 37 were females. The mean age of patients was 52 years. The mean hemoglobin of patients was 9.3 (g/dL), and the mean albumin was 3.2 (g/dL). Around 74 patients presented with ECOG-1 functional status, 44 patients had ECOG-2 status, and ECOG-3 status in 15 patients (**Table 1**).

Dysphagia grades 1, 2, 3, and 4 were seen in 28.6, 40.6, 24.8, and 6% of patients, respectively (**Table 1**). Histopathological analysis showed 116 patients with squamous cell carcinoma, 13 patients with adenocarcinoma, and adenosquamous cell carcinoma, signet-ring cell carcinoma, and neuroendocrine

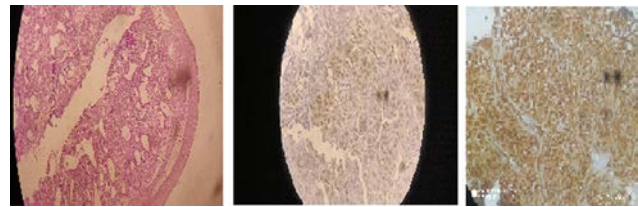


Fig. 1 Histopathology and immunohistochemistry slide of carcinoma esophagus with estrogen- and progesterone-receptor positivity.

Table 1 Demographic, clinical presentation data of patients ($n = 133$)

Characteristics	n (%)
Gender	
Male	96 (72.2)
Female	37 (27.8)
Mean hemoglobin (g/dL)	9.3
Mean albumin (g/dL)	3.2
ECOG status	
1	74 (55.6)
2	44 (33.1)
3	15 (11.3)
Dysphagia grades	
1	38 (28.6)
2	54 (40.6)
3	33 (24.8)
4	8 (6)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2 Histopathology and stage of patients (*n* = 133)

Characteristics	<i>n</i> (%)
Histology	
Squamous cell carcinoma	116
Adenocarcinoma	13
Adenosquamous	2
Neuroendocrine carcinoma	1
Signet ring cell carcinoma	1
Grade	
Well differentiated	32 (24.1)
Moderately differentiated	87 (65.4)
Poorly differentiated	14 (10.5)
Stage	
I	11 (8.3)
II	69 (51.9)
III	44 (33.1)
IVA	2 (1.5)
IVB	7 (5.3)

Table 3 Hormonal receptor status (*n* = 133)

Characteristics	<i>n</i> (%)
ER- α clone	
Positive	12 (9.02)
PR	
Positive	6 (4.51)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

carcinoma in 2, 1, and 1 patients, respectively. Grades of differentiation included well-differentiated adenocarcinoma in 24.1% of patients, moderately differentiated in 65.4% of patients, and poorly differentiated in 10.5% of patients (►Table 2).

Stages of patients according to tumor–node metastasis (TNM) eighth edition include stages I, II, III, IVA, and IVB in 8.3, 51.9, 33.1, 1.5, and 5.3%, respectively (►Table 2). ER- α clone was analyzed in esophageal tumor tissue; of 133 patients, ER was positive in 12 (9.02%) patients. Progesterone receptors were positive in six (4.51%) of the study population (►Table 3).

Correlation of various factors related to ER and progesterone receptor positivity was done. ER positivity was seen more in male patients, with a male-to-female ratio of 2:1 ($p = 0.655$), whereas progesterone receptor positivity showed male-to-female ratio of 1:1 ($p = 0.347$). In patients with ER positivity, around 75% of patients presented with initial functional status of ECOG-2 and above ($p = 0.001$), whereas in patients with progesterone receptor positivity around 83.3% presented with functional status of ECOG-3 ($p = 0.000$; ►Table 4). Correlation of dysphagia scores with receptor positivity showed dysphagia grade of 3 and above

in 83.3% with estrogen and progesterone receptor positivity ($p = 0.000$; ►Table 4).

When pathological grade was correlated with receptor positivity, ER positivity had grades of well-differentiated, moderately differentiated, and poorly differentiated tumors in 8.3, 33.3, and 58.3%, respectively ($p = 0.000$), whereas patients with progesterone receptor positivity had 16.7, 16.7, and 66.7%, respectively, ($p = 0.000$). Stage-wise correlation of patients with ER positivity for stages I, II, III, IVA, and IVB was 0, 8.3, 50, 16.7, and 25%, respectively ($p = 0.000$), and for patients with progesterone receptor positivity was 0, 16.7, 33.3, 16.7, and 33.3%, respectively ($p = 0.000$; ►Table 4).

Discussion

Esophageal cancers, both squamous cell and adenocarcinoma, have poor outcomes with high morbidity and mortality. Our hospital-based registry for the year 2017 to 2018 showed that esophageal cancer constituted 22.7% of the annual case-load. Global cancer statistic 2018 ranks esophageal cancer as the seventh most common cancer in terms of percentage incidence of new case sites. Over 572,034 (3.2%) new cases were reported, and the registered number of deaths was 508,585 (5.3%) of all sites.¹

Esophageal squamous cell carcinoma and adenocarcinoma constitute two major histological types with differences in the prevalence of both according to geographical variation.⁶ Different modalities of treatment include surgical resection, definitive chemoradiotherapy, and palliation with the best supportive care for patients who present in late stages.⁷ Although there are advances in various fields of oncology and multidisciplinary approach, most of the patients with esophageal carcinoma, present in advanced stage outcomes, still remain poor.⁸

As current treatment modalities have not led to significant outcomes, the study of new means of approaches with understanding of factors or pathways associated with the disease process and introduction of new treatment measures, which can lead to improved outcomes in patients with esophageal carcinoma, is of utmost need.

Influence of hormonal milieu on pathogenesis of esophageal carcinoma though has been studied, very limited data exist in literature regarding this and no conclusive outcomes has been established yet, in view of high burden of esophageal cancer in the Northeastern part of India, we wanted to study effect of hormonal linkage in our set of esophageal cancer patients.

ER is a type of steroid receptor class of nuclear receptor superfamily. The effect of estrogen is predominantly mediated through ER- α and ER- β isoforms.⁹⁻¹¹

Demographic data from our study show that around 72.2% of patients were males, which suggests some hormonal milieu might be involved apart from common risk factors for esophageal carcinoma pathogenesis. Due to nonavailability of reagent for ER- β and cost issues, only ER- α isoform was analyzed in our patients. There are limited data regarding the immunohistochemical expression of estrogen- α and

Table 4 Characteristics of patients with hormonal receptor positivity

Characteristics	ER- α positive (n = 12) n (%)	p	PR positive (n = 6) n (%)	p
Sex				
Male	8	0.655	3	0.347
Female	4	0.737	3	0.347
ECOG status				
1	3 (25)	0.001	1 (16.7)	0.00
2	4 (33.3)	0.001	0	0.00
3	5 (41.7)	0.001	5 (83.3)	0.00
Dysphagia grade				
1	0	0.000	0	0.000
2	2 (16.7)	0.000	1 (16.3)	0.000
3	6 (50)	0.000	2 (33.3)	0.000
4	4 (33.3)	0.000	3 (50)	0.000
Pathological grade				
Well differentiated	1 (8.3)	0.000	1 (16.7)	0.000
Moderately differentiated	4 (33.3)	0.000	1 (16.7)	0.000
Poorly differentiated	7 (58.3)	0.000	4 (66.7)	0.000
Stage				
I	0	0.000	0	0.000
II	1 (8.3)	0.000	1 (16.7)	0.000
III	6 (50)	0.000	2 (33.3)	0.000
IVA	2 (16.7)	0.000	1 (16.7)	0.000
IVB	3 (25)	0.000	2 (33.3)	0.000

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor, PR, progesterone receptor.

estrogen- β isoforms. A study by Nozoe et al showed that an inverse relationship exists between the expression of ER- α and ER- β receptor isoforms,¹² whereas studies of Kalayarasan et al did not report any expression of ER- α isoform.¹³ Analysis of our data from 133 patients of esophageal carcinoma has shown ER- α isoform positivity in 9.02% of patients. Our set of patients showed positivity for ER- α isoform, as seen in studies of Nozoe et al. Data regarding progesterone receptor positivity have not shown any conclusive results yet. Our study has shown a progesterone receptor positivity of 6%.

Correlation of various factors has been done with hormonal receptor positivity. The male-to-female ratio of receptor positivity for ER- α isoform was 2:1, while the same for progesterone receptor positivity was 1:1 with nonsignificant *p*-value. When compared with patients with receptor-negative status, most of the patients with hormonal receptor positivity presented with poor functional score, with statistically significant *p* = 0.001 and 0.00 for ER- α and progesterone receptor positivity, respectively.

Correlation of dysphagia scores for ER- α and progesterone receptor positivity showed that most of the patients whose receptor status was positive presented with higher

dysphagia grades with statistically significant *p*-value (*p*=0.000). When correlation was done with pathological grade of tumors, it was observed that among patients with hormonal receptor positivity, both for ER- α and progesterone receptors, significant number of patients was poorly differentiated with statistically significant *p*-value (*p* = 0.000). When hormonal receptor positivity was correlated with the stage of presentation of carcinoma in accordance with AJCC (American Joint Committee on Cancer) TNM eighth edition, most of the patients presented with stage III and above with statistically significant *p*-value.

In view of the major bulk of carcinoma esophagus in our part of the country with annual new case registration of 22.7% of hospital load, it is of utmost importance for us to find new pathways of linkage for the pathogenesis of esophageal carcinoma to improve outcomes in our patients. This study is such an attempt. In the current study, the positivity of ER- α receptor has been observed in 9.02% of patients. Based on the above background, we are planning to study even ER- β isoforms and a pilot study to see feasibility and outcomes of hormonal therapy in patients with carcinoma esophagus which may improve outcomes in patients with esophageal carcinoma.

Strengths and Limitations

The advantages of our study are, it is a prospective study, and it is the only study till date in our literature search with data of the highest number (133) of patients studied to see the role of hormonal receptor status in carcinoma esophagus. Disadvantages of our study are, we could not study the expression of ER- β isoform which showed positivity in previous studies due to logistical issues.

Conclusion

Despite recent advances in various fields of oncology, outcomes of esophageal carcinoma have not improved significantly. Hence, a study of new pathways of pathogenesis in carcinogenesis of esophageal carcinoma is essential. Few recent evidences, including our study, show that hormonal milieu is responsible for the pathogenesis of carcinoma esophagus, utilization of this data, and future study of the role of hormonal therapy that might lead to improved outcomes in patients with carcinoma esophagus. Further large-scale studies are required to confirm these results.

Funding

Nil.

Conflicts of Interest

There are no conflicts of interest to declare.

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