ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 04, pp.3076-3081, April, 2019

DOI: https://doi.org/10.24941/ijcr.34957.04.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

ROLE OF ER, PR, HER2 AND EGFR IN ESOPHAGEAL CARCINOMA

***Muneera Gull, Zubaida Rasool, Danish Rafiq, Salma Gull, Salma Yaseen and Ishrat Younis**

Department of Pathology, Dr Radhakrishnan Govt medical college Hamirpur to Sheri Kashmir Institute of Medical Sciences soura sgr

ARTICLE INFO

Article History:

Received 09th January, 2019
Received in revised form
06th February, 2019
Accepted 10th March, 2019
Published online 30th April, 2019

Key Words:

Immunohistochemistry,
ER, PR, HER2.

ABSTRACT

Introduction: Esophageal cancer is a serious malignancy with regards to mortality and prognosis. The incidence of esophageal adenocarcinoma is increasing in trends. In India, the extremely high incidence rates of esophageal cancer have been reported from the state of Jammu and Kashmir which seems to fall in the Asian esophageal-cancer belt particularly from Kashmir. The unique personal and dietary habits and environmental factors in Kashmir have been related to this high risk. Immunohistochemistry is nowadays a simple, reproducible way to assess the expression of oncogenic factors in paraffin embedded samples from cancer tissues. It is therefore more and more used customarily to study the expression of new potential therapeutic targets and to determine which patients are the most liable to answer to these specific therapies. **Aiims and objectives:** To study the expression of.ER/PR, EGFR and HER-2 in esophageal carcinoma.and to study the correlation of above mentioned markers with pathological characteristics such as tumor type, grade and lymph node status. **Materials and Methods:** It was a prospective study for a period of one and half years from June 2016 to December 2017 and retrospective study for three and half years from January 2013 to May 2016.The study was carried on resected specimens of esophagus over the period mentioned above. All esophageal carcinomas with or without nodal metastasis and other primary tumors of esophagus, tumors metastasized to esophagus and those who have received neoadjuvant therapy were taken. For the retrospective study, cases were taken from the records maintained in the Department of Pathology at SKIMS. Histopathological data was collected and relevant details were noted. Corresponding slides were collected and photographed wherever available. Prospective study comprised of fresh cases of esophageal carcinomas. In each case a brief clinical history was taken, along with other relevant investigations. The clinical data of the patient was recorded as per proforma. Samples were collected in 10% formalin for routine histopathological examination. After overnight fixation, the specimens were grossed with 3-4 sections taken from the tumor. Gross photographs of the specimen were taken. Sections from all resection margins were taken. The tissue was processed as per standard procedure for histological examination and 4-5 micron thick sections were cut on microtome and stained by routine haematoxylin and eosin stain. Immunohistochemistry was done in 30 Squamous cell carcinoma cases (out of a total of 86 cases) and all (12) Adenocarcinoma cases. After final microscopic diagnosis was made, the slides were photographed. **Results:** The study included a total of 98 cases received in our department and with the final diagnosis of esophageal carcinoma (SCC and AC). Out of 98 cases, 57 (58.2%) were males and 41 (41.8%) were females with a male to female ratio of 1.39:1. Age range was 35-75 years. The maximum number of cases was in the age group of 45-54 and 55-64 years and the least number of cases was seen in the age group of 35-44 years. Mean age was 55.9+8.92 years. Dysphagia was the main presenting complaint in majority of patients (69.4%). Most of the tumors presented as ulceroin filtrative lesions (25.5%). Most of the tumors were in the size range of 3-5 cm (49%). Middle 1/3rd of the esophagus was the most common site (48%) followed by lower 1/3rd (37.6%). Among the 98 esophagectomy cases, 83 (84.7%) were diagnosed as SCC, 12 as AC (12.2) and 3 (3.1%) as squamous cell carcinoma in situ. Most of the tumors were well and moderately differentiated. Regional lymph node involvement was present in 25% cases. Distant metastasis was not seen in any case.11 (11.2%) cases had CRM involved by the tumor. Out of the 83 cases of squamous cell carcinoma, 42 (50.6%) were T2, 39 (47.0%) were T3, 2 cases were in T1. Out of 12 AC cases, 11 (91.7%) were T3 and 1 (8.3%) was T2. Majority of the cases i.e.; 72 (73.5%) were in N0, 19 (19.4%) were in N1, 6 (6.1%) were in N2, 1 (1%) was in N3. Out of 86 SCC cases, 25 (29.1%) were in Stage IB, 24 (27.9%) were in stage IIA, 21 (24.4%) were in Stage IIB, 9 (10.5%) were in Stage IIIA, 3 (3.5%) were in Stage IIIB and 3 (3.5%) were in Stage 0. None of the cases was in Stage IV. One patient was in stage IA. Out of 12 AC cases, 7 (58.3%) cases were in Stage IIB, 3 (25%) cases were in Stage IIIB and 2 (16.7%) cases were in Stage IIIC. None of the cases was in Stage IV or Stage 0. Out of 98 esophagectomy cases, 32 (32.7%) had LVI and 29 (29.6%) had PNI. On immunohistochemistry; (IHC was done on 30 SCC and 12 AC cases), none of the 42 cases was positive for ERα or PR. For ERβ, among 12 adenocarcinoma cases, 9 cases were positive and among 30 SCC cases, 7 were positive. For EFGR, among 12 AC cases, 3 were positive and among 30 SCC cases, 17 were positive. For HER2, among 12 AC cases, 1 was positive and among 30 SCC cases, 2 were positive. Among 16 ERβ positive cases, 2 were in Grade 1, 7 in Grade 2 and 7 in Grade 3. None of the cases was of Grade 4. Among 20 EGFR positive cases, 3 were in Grade 1, 9 in Grade 2 and 8 in Grade 3. Among 3 HER2 positive cases, 1 was in Grade 1and 2 were in Grade 3. None of the cases was of Grade 2. ERβ positive cases were predominantly in N0 (8/16), followed by N2 (5/16). 2 cases were in N1 and 1 in N3. Among 20 EGFR positive cases, 7 were in N1, 6 in N2 and 7 in N0. Among 3 HER2 positive cases, 2 were in N0 and 1 was in N1. . Among the 16 ERβ positive cases, majority (7/16) were in Stage IIB. 3 were in Stage IIIB, 2 were in IIIC, 2 in IIIA and 2 in IB. None of the cases was in Stage IA or in Stage IV. Among the 20 EGFR positive cases, 7 cases were in Stage IIIA, 5 in Stage IIB, 3 in Stage IB, 3 in Stage IIIB, 1 in Stage IIA and 1 in Stage IIIC. . Among 3 HER2 positive cases, 2 were in Stage IIB and 1 in Stage IIA. ERβ expression had a significant correlation with tumor type. AC showed higher expression than SCC. EGFR had a significant correlation with tumor type, tumor grade and lymph node status. **Summary and conclusion:** The present study suggests that EGFR is a candidate for targeted therapy using anti-EGFR antibodies. Evaluation of EGFR overexpression detected by IHC may aid the selection of patients and prediction of sensitivity to adjuvant EGFR -targeted therapy for esophageal carcinoma. HER2 overexpression may also play a crucial role in the therapeutic management of both esophageal squamous cell carcinoma and esophageal adenocarcinoma. In present study, HER2 was positive in both ESCC and EAC. The sample size may have undermined statistical significance between HER2 and histopathological characteristics of esophageal carcinoma. Further studies may augment the understanding in this area.

**Corresponding author: Muneera Gull*

***Citation*: *Muneera Gull, Zubaida Rasool, Danish Rafiq, Salma Gull, Salma Yaseen and Ishrat Younis,* 2019.** "Role OF ER, PR, HER2 and EGFR in esophageal carcinoma", *International Journal of Current Research*, 11, (04), 3076-3081.

INTRODUCTION

Esophageal cancer is one of the deadliest and eighth most common cancer worldwide (Gupta *et al*., 2017). It is the sixth most common cause of cancer related deaths with developing nations making up more than 80% of total cases and deaths (Herszenyi and Tulassay, 2010). Esophageal cancer affects more than 450,000 people worldwide and incidence is increasing rapidly (Pennathur *et al*., 2013). The incidence of esophageal carcinoma has been increasing over the past few decades, with a shift from squamous cell carcinoma arising in upper 2/3rd of esophagus to adenocarcinoma in lower 1/3rd of esophagus (Lepage *et al*., 2005). The 5-yearsurvival rate for patients with esophageal cancer ranges from 15-20%, despite many advances in diagnosis and treatment (Pennathur *et al*., 2013). The rate of high expression of HER2 in esophageal adenocarcinoma EAC (15-30%) is higher than in ESSC (5-13%) (Kato *et al*., 2013). Epidermal growth factor receptor (EGFR), required for downstream signaling, is overexpressed in 36.6%-80% of ESCC patient (Shang *et al*., 2014). EGFR participates in cellular differentiation and proliferation (Hanawa *et al*., 2006). EGFR overexpression correlates with tumor invasion and lymph nodemetastasis (Jiang *et al*., 2015; Zhang *et al*., 2014). A number of studies have shown that increased EGFR expression is associated with poor survival among patients with esophageal cancer (Zhang *et al*., 2014; Fukai *et al*., 2005; Yu *et al*., 2011). Human tissues contain two isoforms of ER, ER alpha (α) and ER beta (β) which are generated by genes located on chromosome 6q25 and chromosome 14q22-24, respectively. Several studies have identified the expression of ERs in ESCC (Ueo *et al*., 1990; Utsumi *et al*., 1989; Utsumi *et al*., 1991; Nozoe *et al*., 2007; Kalayarasan *et al*., 2008).

Aims and objectives: To study the expression of. ER/PR, EGFR and HER-2 in esophageal carcinoma. and to study the correlation of above mentioned markers withpathological characteristics such as tumor type, grade and lymph node status.

MATERIALS AND METHODS

The study entitled Role of ER, PR, HER2 and EGFR in Esophageal Carcinoma was conducted in the department of pathology at the Sher-i- Kashmir Institute of Medical Sciences (SKIMS) Srinagar, Kashmir. It was a prospective study for a period of one and half years from June 2016 to December 2017 and retrospective study for three and half years from January 2013 to May 2016.The study was carried on resected specimens of esophagus over the period mentioned above. All esophageal carcinomas with or without nodal metastasis. Other primary tumors of esophagus, tumors metastasized to esophagus and those who have received neoadjuvant therapy. For the retrospective study, cases were taken from the records maintained in the Department of Pathology at SKIMS. Histopathological data was collected and relevant details were noted. Corresponding slides were collected and photographed wherever available. Prospective study comprised of fresh cases of esophageal carcinomas. In each case a brief clinical history was taken, along with other relevant investigations. The clinical data of the patient was recorded as per proforma. Samples were collected in 10% formalin for routine histopathological examination. After overnight fixation the specimens were grossed with 3-4 sections taken from the tumor. Gross photographs of the specimen were taken. Sections from all resection margins were taken. The tissue was processed as per standard procedure for histological examination and 4-5 micron thick sections were cut on microtome and stained by routine haematoxylin and eosin stain. Immunohistochemistry was done in 30 Squamous cell carcinoma cases (out of a total of 86 cases) and all (12) Adenocarcinoma cases. After final microscopic diagnosis was made, the slides were photographed.

RESULTS

The mean age of patients was Mean±SD (Range)=55.9± 8.92 (35-75) years. Out of 98 cases, 57 (58.2%) were males and 41 (41.8%) were females with a male to female ratio of 1.39:1. In the present study, 68 (69.4%) patients presented with dysphagia alone, 9 (9.2%) with weight loss and 8 (8.2%) with generalized weakness. Dysphagia along with epigastric discomfort was present in 5 (5.1%) patients. Dysphagia with hoarseness, and dysphagia with generalized weakness were present in 4 (4.1%) and 3 (3.1%) respectively. Least common complaint was epigastric discomfort and recurrent vomiting together (1%). In terms of tumor location, 47 (48.0%) of the tumors were located in the middle 1/3rd of the esophagus, 36 (36.7%) in lower 1/3rd of the esophagus and 15 (15.3%) in the upper 1/3rd of the esophagus. In our study, out of 98 esophagectomy cases, majority of the cases i.e.; 48 (49.0%) had a tumor size of 3-5 cm,27 cases (27.6%) had a tumor size of >5 cm and 23 cases (23.5%) had a tumor size of1-3cm. Based on the gross appearance, the tumors were classified into ulceroproliferative, ulceroinfiltrative, polypoidal, etc.In our study out of the 98 esophagectomy specimens, 25 (25.5%) were ulceroinfiltrative, 19 (19.4%) were ulceroproliferative, 18 (18.4%) were ulcerative, 13 (13.3%) were diffusely ulcerative, 10 (10.2%) were diffusely infiltrative, 8 (8.2%) were polypoidal and 5 (5.1%) were infiltrative. Out of 98 esophagectomy cases, 83 (84.5%) cases were of squamous cell carcinoma and 12 (12.2%) were of adenocarcinoma. 3 cases (3.1%) were squamous cell carcinoma in situ. There was no case of adenosquamous carcinoma type in this study. In our study, out of the 98 esophagectomy cases, 11 (11.2%) caseshad CRM involved by the tumor. Out of the 83 cases of the squamous cell carcinoma (Squamous cell carcinoma in situ cases constituting 3 in number having been excluded), majority were moderately differentiated/G2i.e; 42 (50.6%), 33 (39.8%) were well differentiated/G1and 8 (9.6%) were poorly differentiate d/G3..Out of the 12 cases of adenocarcinoma, 5 (41.7%) were well differentiated, 4 (33.3%) were poorly differentiated and 3 (25.0%) were moderately differentiated. None of the cases was undifferentiated. Out of the 83 cases of squamous cell carcinoma, 42 (50.6%) cases had invasion into muscularis propria (T2), 39 (47.0%) had invasion into adventitia (T3), 1 (1.2%) had invasion into submucosa (T1) and 1 (1.2%) into lamina propria (T1). 3 cases had no invasion (Tis). Out of 12 AC cases, 11 (91.7%) had invasion into adventitia (T3) and 1 (8.3%) into Muscularis propria (T2). None of the cases was limited to submucosa or lamina propria. In our study, out of 86 SCC cases, 25 (29.1%) were in Stage IB, 24 (27.9%) were in stage IIA, 21 (24.4%) were in Stage IIB, 9 (10.5%) were in Stage IIIA, 3 (3.5%) were in Stage IIIB and 3 (3.5%) were in Stage 0. None of the cases was in Stage IV. One case was in stage IA.

Out of 12 AC cases, 7 (58.3%) cases were in Stage IIB, 3 (25%) cases were in Stage IIIB and 2 (16.7%) cases were in Stage IIIC. None of the cases was in Stage IV or Stage 0.In our study, out of 42 cases, all the 42 were negative for ERα. All the 42 were also negative for PR. ERβ was positive in 16 (38.1%) cases. EGFR was positive in 20 (47.6%) cases & HER2 was positive in 3 (7.1%) cases. In our study, out of the 12 adenocarcinoma cases, none was positive for ERα. Among the 30 cases of SCC, none was positive for ERα. For ERβ, among 12 adenocarcinoma cases, 9 cases were positive and among 30 SCC cases, 7 were positive. ERβ had a significant correlation with tumor type (p-value 0.017).For PR, none of the 42 cases (30 SCC+ 12 AC) was positive. For EFGR, among 12 AC cases, 3 were positive and among 30 SCC cases, 17 were positive. EGFR had statistically a significant correlation with tumor type (p- value 0.048). For HER2, among 12 AC cases, 1 was positive and among 30 SCC cases, 2 were positive. Among 16 ERβ positive cases, 2 were in Grade 1, 7 in Grade 2 and 7 in Grade 3. None of the cases was of Grade 4.Among 20 EGFR positive cases, 3 were in Grade 1, 9 in Grade 2 and 8 in Grade 3. EGFR had statistically a significant correlation with tumor grade (p-value 0.026). Among 3 HER2 positive cases, I case was in Grade 1and 2were inGrade3.None of the cases was of Grade 2. In our study, ERβ positive cases were predominantly in N0 (8/16), followed by N2 (5/16). 2 cases were in N1 and 1 in N3. ERβ had statistically a significant correlation with lymph node status (p- value 0.008). Among 20 EGFR positive cases, 7 were in N1, 6 in N2 and 7 in N0. EGFR had statistically a significant correlation with lymph node status (p-value 0.014). Among 3 HER2 positive cases, 2 were in N0 and 1 was in N1. In our study, among the 16 ERβ positive cases, majority (7/16) were in Stage IIB. 3 were in Stage IIIB, 2 were in IIIC, 2 in IIIA and 2 in IB. None of the cases was in Stage IA or in Stage IV. Among the 20 EGFR positive cases, 7 cases were in Stage IIIA, 5 in Stage IIB, 3 in Stage IB, 3 in Stage IIIB, 1 in Stage IIA and 1 in Stage IIIC. Among 3 HER2 positive cases, 2 were in Stage IIB and 1 in Stage IIA.

Table 1. Immunohistochemical markers in esophageal carcinoma

		Frequency	Percentage
ERα	Positive	0	0
	Negative	42	100
ERβ	Positive	16	38.1
	Negative	26	61.9
PR	Positive	0	0
	Negative	42	100
EGFR	Positive	20	47.6
	Negative	22	52.4
HER2	Positive	3	7.1
	Negative	39	92.9

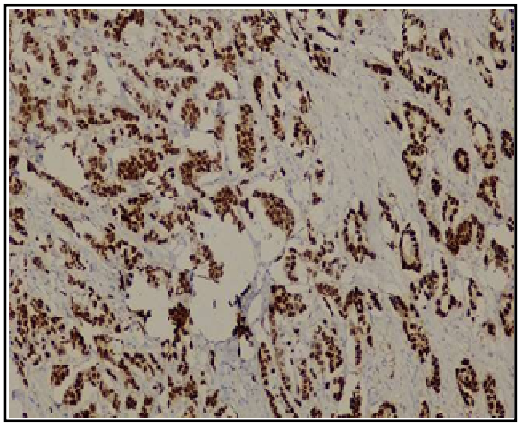

Fig. 1. Positivity for ERβ in Esophageal Adenocarcinoma

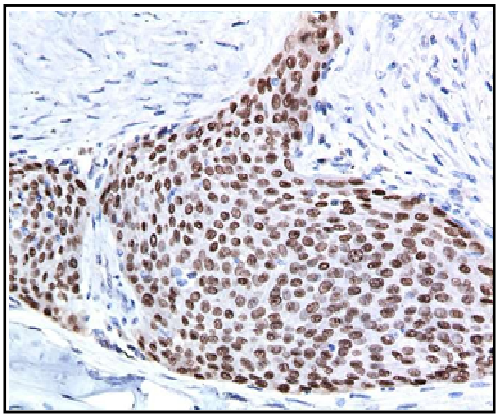

Fig. 2. Positivity for ERβ in Esophageal SCC

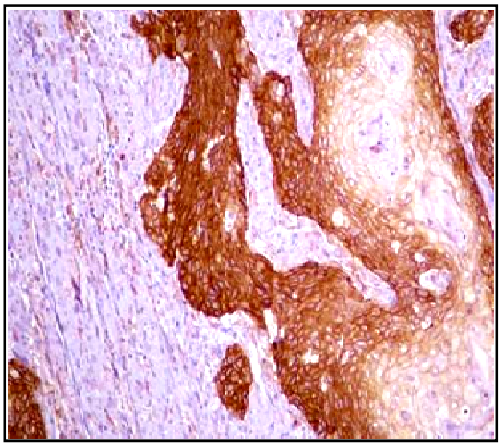

Fig. 3. Positivity for EGFR in Esophageal SCC

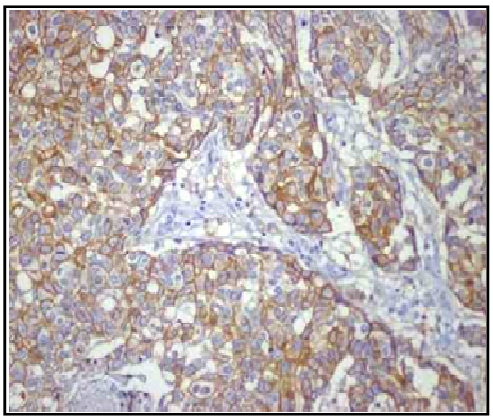

Fig. 4. Positivity for EGFR in Esophageal Adenoca

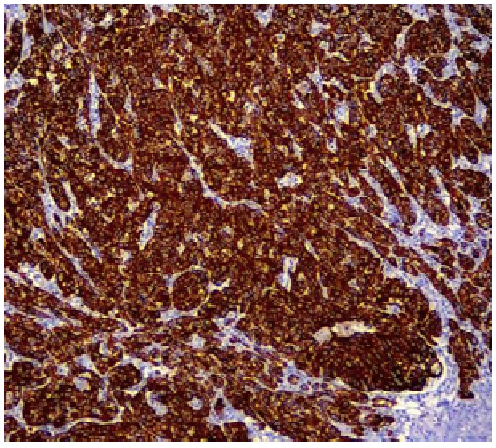

Fig. 5. Positivity for HER2in Esophageal SCC

DISCUSSION

Esophageal cancer is a serious malignancy with regards to mortality and prognosis. Squamous cell carcinoma is the most prevalent esophageal cancer worldwide, while in certain developed countries like Australia, France, Finland, United States and United Kingdom, adenocarcinoma predominates. 17A drop of 30% in incidence of squamous cell carcinoma is observed in USA between 1973 and 2002, while there is 4-fold increase in adenocarcinoma over the same period.4Thus the incidence of esophageal adenocarcinoma is increasing in trends. In India, the extremely high incidence rates of esophageal cancer have been reported from the state of Jammu and Kashmir which seems to fall in the Asian esophageal-cancer belt particularly from Kashmir (Alema and Iva, 2014).

The unique personal and dietary habits and environmental factors in Kashmir have been related to this high risk. Immunohistochemistry is nowadays a simple, reproducible way to assess the expression of oncogenic factors in paraffin – embedded samples from cancer tissues. It is therefore more and more used customarily to study the expression of new potential therapeutic targets and to determine which patients are the most liable to answer to these specific therapies. The age range in our study was 35 to 75 years. Maximum number of cases in our study was seen in 45-54 years age group and the mean age in our study was 55.9 ±8.92SD. Our study results were in conformity with many other studies. In a study conducted by Kumar *et al*. (2016), the mean age was 59.1 years and the age range was 32 to 80 years. Alema, Iva (2014) found maximum cases in age group of 40 to59 years with mean age of 55.5±SD 11.8. In our study the male female ratio was 1.39:1.00 with males constituting 57 cases and females 41 cases. Our results were comparable with other study results like Shi *et al*. (2014) in which male to female ratio was 1.88:1.00 with males constituting 34 cases and females 18 cases, Vishal *et al*. (2017) in which male to female ratio was 1.80:1.00 with males constituting 65 cases and females 36 cases. In our study the most common clinical presentation was dysphagia (69.4%) followed by weight loss (9.2%). Our results were comparable to other studies like Renovat *et al*. (2016). Where dysphagia was the most common complaint (94%) followed by weight loss (47%), Michal S *et al*. (2017) who found dysphagia as the most common complaint (81%) followed by weight loss (70%) and Mabula *et al*. (2013) where also dysphagia was the most common complaint followed by weight loss.

In our study 48% (47/98) of the cases occurred in the middle esophagus, 36.7% (36/98) in lower esophagus and 15.3% (15/98) in upper esophagus. Our results were comparable with other studies like Alema, Iva (2014) in which 53.52% cases were seen in middle esophagus, 38.03% cases occurred in lower esophagus and 8.45% in upper esophagus. In our study, tumor size was 3-5cm in majority of cases. Our results were comparable with a study conducted by Kumar *et al*. (2016), where majority of the cases had a tumor size of 2-5cm. In a study conducted by Takako (2006), majority of the cases had a tumor size of 2.5-4.5cm, followed by > 4cm. In our study, out of 98 esophagectomy specimens, 25 (25.5%) were ulceroinfiltrative, 19 (19.4%) were ulceroproliferative and 18 (18.4%) were ulcerative. Our results were coherent with a study conducted by Kumar (2016) in which 13 (37.1%) were ulceroinfiltrative followed by 8 (22.9%) ulceroproliferative lesions.

In a study conducted by Mabula *et al*. (2013), 40% of the lesions were ulcerative. In our study, the most common histopathological subtype of esophageal cancer was squamous cell carcinoma, constituting 84.7% followed by adenocarcinoma which constituted 12.2%. Kumar A *et al*. (2016), in their study found that out of 35 esophagectomy cases, 30 (85.7%) were of SCC and 5 (14.3%) were of AC. Muninder *et al*. (2017) in their study found that 92% of cases were of SCC and only 4% cases had adenocarcinoma. Mabula DM *et al*. (2013) in their study found squamous cell carcinoma as the most common histopathological type (96%) followed by adenocarcinoma (4%). Vishal G *et al* (2017)1in their study also found SCC as the most common type constituting 61 (60.4%) cases out of a total of 101 cases, followed by AC constituting 38(37.6%) cases.

In our study, among 83 squamous cell carcinoma cases, 42 (50.6%) were moderately differentiated, 33(39.8%) were well differentiated and 8(9.6%) were poorly differentiated. Our findings were coherent with a study conducted by Vishal *et al*. (2017) where 45(73.8%) out of 61 cases were moderately differentiated, 10(60.4%) were well differentiated followed by 6(9.8%) poorly differentiated cases. Our results were comparable to other studies like Meysam *et al*. (2013) where moderately differentiated squamous cell carcinoma was the most common (61.8%), followed by well differentiated (21.8%) and poorly differentiated being the least common (16.4%). In our study, adenocarcinoma cases were predominantly well and moderately differentiated together constituting 66.7% of the adenocarcinoma cases. Poorly differentiated constituted the least common type (33.3%). Similar results were found in a study conducted by Yoon *et al*. (2012). In our study, CRM was involved in 11(11.2%) cases. In the reviewed literature, a wide range of CRM involvement (8.6–83.1%) has been reported. The difference can be explained by the varying pathologic classification systems (Royal College Of Pathologists/RCP and College of American Pathologists/CAP criteria) being used.28n our study, out of 98 esophagectomy cases, majority i.e.; 93 (94.9%) were T2 and T3. Our findings were coherent with many other studies. In a study conducted by Kumar *et al*. (2016), out of 35 esophagectomy cases, 33 (94.3%) cases were of T2 and T3. Konig AM *et al*. (2013), in their study found that majority of cases were T2 and T3 (136/158 cases i.e., 86%).

In our study, out of 98 esophagectomy cases, majority of the cases i.e.; 72 (73.5%) were in N0, 19 (19.4%) were in N1, 6 (6.1%) were in N2,1 (1%) in N3.Similar results were found in other studies conducted by Lin *et al*. (2015), Kato *et al*. (2013) and Taghizadeh *et al*. (2016). In our study, out of 86 SCC cases, majority i.e;45 (52.3%) were in Stage II, followed by Stage I i.e. 26 (30.2%) cases. 12 (12.9%) cases were in Stage III and 3(3.4%) cases were in Stage 0. None of the cases was in Stage IV. In our study, out of 12 AC cases, 7 (58.3%) were in Stage II followed by 5 (41.7%) cases in Stage III. None of the cases was in Stage 0, Stage I or Stage IV. Our findings were coherent with the results of a study conducted by Taghizadeh *et al*. (2016) in which out of 64 SCC cases, 43 (67.2%) were in Stage II, 13 (20.3%) were in Stage I and 8 (12.5%) were in Stage III. None of the cases was in Stage IV. In our study, out of 98 esophagectomy cases, 32 (32.7%) had LVI. PNI was present in 29 (29.6%) cases. Our results were coherent with other studies. In a study, conducted by Gibault *et al*. (2005), LVI was present in 35 out of 107(32.7%) cases. Taghizadeh *et al*. (2016) in their study found LVI in 17 out of

64 (26.5%) cases and PNI in 12 (18.8%) cases. In contrast to our study, Sarbia *et al*. (1995) reported 48.5% LVI in their study. This slight discrepancy could be explained by large sample size (161) in their study.In our study none of the 42 cases was positive for ERα or PR. In a study conducted by Kalyarasan *et al*. (2008), out of 45 cases, none was positive for ERα. Similarly none was positive for PR. Boone *et al*. (2009), in their study found that out of 108 SCC cases, none was positive for ERα. Likewise, none was positive for PR. However, few studies show results contrary to our study. In a study, conducted by Zuguchi *et al*. (2012) in Japan, out of 90 SCC cases 38 (42.2%) were positive for ERα. In our study, out of 12 AC cases, 9(75%) were positive for ERβ. And out of 30 SCC cases, 7 (23.3%) were positive for ERβ. Tadahiro *et al*. (2007) in their study in Japan reported that out of 73 ESCC cases, 21(28.8%) were positive for ERβ. Dong *et al*. (2013) in their study in China reported that out of 89 ESCC cases, 44 (49.4%) were positive for ERβ.

The reason for this large variation in the expression of ER subtypes and PR in esophageal carcinoma is multifactorial such as difference in populations studied, different sample sizes, differences in immunohistochemical protocols, different sources of antibodies used or different criteria for evaluation of expression. Regarding the correlation of ER (ERα and ERβ) and PR with tumor type, tumor grade, lymph node status and tumor stage, there is paucity of publications. In our study, we found a significant correlation between ERβ and tumor type (p-value 0.017). AC showed higher expression for ERβ than SCC. Kalyarasan *et al*. (2008), in their study reported a higher mean score for ERβ expression as compared with SCC.In our study, no significant correlation was found between ERβ expression and tumor grade (p-value 0.271). Also no significant correlation was found between ERβ expression and tumor stage (p-value 0.169). However, a significant correlation was found between ERβ expression and lymph node status (p-value 0.008). In our study, out of 42 esophageal carcinoma cases, 20(47.6%) were positive for EGFR.

In a study conducted by Qichun *et al*. (2007), 63% cases were positive for EGFR. In our study, out of 30 ESCC cases, 17(56.7%) were positive for EGFR. Our findings were consistent with many other studies. Lin *et al*. (2015) in their study in China reported that out of 56 ESCC cases, 30 (53.6%) were positive for EGFR. In a study conducted by Wei *et al*. (2007), out of 40 ESCC cases, 27(67.5%) were positive for EGFR. In our study, out of 12 AC cases, 3(25%) were positive for EGFR. In a study conducted by Wei *et al*. (2007), out of 6 EAC cases, 2(33.3%) were positive for EGFR. A study conducted by Daniel *et al*. (2012) found that out of 37 EAC cases, 16 (43%) were positive for EGFR. The discrepancy could be explained by the limited number of adenocarcinoma (12) cases in our study.In our study, EGFR had a significant correlation with tumor type (p-value 0.048), tumor grade (p-value 0.026) and lymph node status (p- value 0.014). No significant correlation was found between EGFR expression and tumor stage (p- value 0.007).

In a study conducted by Jiang *et al*. (2015), a significant correlation was found between EGFR expression and lymph node status (p-value 0.006). Zhang W *et al*. (2014) conducted a study and reported that the expression of EGFR is correlated with depth of tumor invasion (p=0.005), lymph node metastasis ($p < 0.001$), and pathologic stage ($p<0.001$). In our study, out of 42 cases, 3 (7.1%) were positive for HER2. Similar results were found in a study conducted by Qichun *et al*. (2007) where out of 45 esophageal carcinoma cases, 4(8.89%) were positive for HER2. In our study, out of 30 ESCC cases, 2(6.7%) were positive for HER2. Similar results were found by many other studies. Nagaraja *et al*. (2016) in their study found that out of 27 ESCC cases, 1(3.7%) was positive for HER2. In a study conducted by Wei *et al*. (2007), out of 40 ESCC cases, 3(7.5%) were positive for HER2. Konig *et al*. (2013) in their study reported that out of 68 SCC cases, 5(7.4%) were positive for HER2. In our study, out of 12 AC cases, only 1 case (8.3%) was positive for HER2. In a study conducted by Wei *et al*. (2007), out of 6 EAC cases, 1 (16.7%) case was positive for HER2. Konig *et al*. (2013) in their study reported that out of 90 EAC cases, 9(10%) were positive for HER2.In our study, no significant correlation was found between HER2 expression and tumor type, tumor grade, lymph node status and tumor stage. A study conducted by Kumar *et al*. (2016), also found no statistically significant correlation between tumor grade and HER2 positivity. Also in the same study, no correlation was found with tumor stage and lymph node status. However, Taghizadeh *et al*. (2016) in their study found a significant correlation between tumor grade and HER2 positivity. Hiroaki *et al*. (2013) and Jun-Xing *et al*. (2013). Have not reported a significant correlation between tumor grade and HER2 positivity.

Conclusion

The present study suggests that EGFR is a candidate for targeted therapy using anti-EGFR antibodies. Evaluation of EGFR overexpression detected by IHC may aid the selection of patients and prediction of sensitivity to adjuvant EGFR - targeted therapy for esophageal carcinoma. HER2 over expression may also play a crucial role in the therapeutic management of both esophageal squamous cell carcinoma and esophageal adenocarcinoma. In present study, HER2 was positive in both ESCC and EAC.

RERERENCES

Alema, ON. and Iva, B. 2014. Cancer of the esophagus: histopathological sub-types in northern Uganda. *African Health sciences,* 14(1).

Boone, J., Van Hillegersberg, R., Offerhaus, GJ., Van Diest, PJ., Borel Rinkes, IH. and Ten Kate, FJ. 2009. Targets for molecular therapy in esophageal squamous cell carcinoma: an immunohistochemical analysis. *Dis Esophagus,* 22(6): 496.

Boone, J., Van Hillegersberg, R., Offerhaus, GJ., Van Diest, PJ., Borel Rinkes, IH. and Ten Kate, FJ. 2009. Targets for molecular therapy in esophageal squamous cell carcinoma: an immunohistochemical analysis. *Dis Esophagus.,* 22(6): 496-504.

Dong, J., Jiang, S. and Niu, Y. 2013. Expression of estrogen receptor α and β in esophageal squamous cell carcinoma. *Onc Reports.,* 30: 2771-76.

Eguchi, T., Nakanishi, Y. and Shimoda, T. 2006. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: Analysis of 464 surgically resected cases Modern, *Pathology.,* 19(3): 475-80

Fukai, Y., Masuda, N., Kato, H., Fukuchi, M., Miyazaki, T., Nakajima, M., *et al*., 2005. Correlation between laminin-5 gamma2 chain and EGFR expression in esophageal squamous cell carcinoma. *Oncology*, 69:71-80.

Gibault, L. and Metges, JP. 2005. V Conan-Charlet. Diffuse EGFR staining is associated with reduced overall survival in

locally advanced oesophageal squamous cell cancer. *British Journal of Cancer,* 93: 107 – 115.

Gupta, V., Bhardwaj, S. and Bhagat, O K. 2017. Pattern of esophageal cancer in tertiary care hospital in North India: a clinicopathological study. *Int J Res Med Sci.,* 5(4):1405-1409.

Hanawa, M., Suzuki, S., Dobashi, Y., Yamane, T., Kono, K., Enomoto, N., *et al*., 2006. EGFR protein overexpression and gene amplification in squamous cell carcinoma esophagus. *Int J Cancer.,* 118: 1173-1180.

Haung, J X., Zhao, K. and Lin, M. 2013. HER2 gene amplification in esophageal squamous cell carcinoma is less than in gastroesophageal junction and gastric adenocarcinoma. *Oncol Lett.,* 6(1): 13-18.

Herszenyi, L. and Tulassay, Z. 2010. Epidemiology of gastrointestinal and liver tumors. *Eur Rev Med Pharmacol Sci.,* 14:249-58.

Jiang, D., Li, X., Wang, H., Shi, Y., Xu, C., Lu, S., *et al*., 2015. The prognostic value of EGFR overexpression and amplification in esophageal squamous cell carcinoma. *BMC Cancer,* 15:377.

Kalayarasan, R., Ananthakrishnan, N., Kate, V. and Basu, D. 2008. Estrogen and progesterone receptors in esophageal carcinoma. *Dis Esophagus.,* 21: 298-303.

Kato, H., Arao, T., Matsumoto, K., Fujita, Y., Kimura, H., Hayashi, H., *et al*., 2013. Gene amplification of EGFR, HER2 FGFR2 and MET in esophageal squamous cell carcinoma. *Int. J Oncol.,* 42: 1151- 8.

Kermani, AT., Vakili, R. and Dadkhah, S. 2016. HER-2/neu Overxpression in Esophageal Squamous Cell Carcinoma (ESCC) and Its Correlation with Patient's Clinicopathological Features. *Iran J Cancer Prev.,* October; 9(5): e5007.

Konig, A M., Reeh, M. and Dancau, A M. 2013. Concordance of HER2 Status in Primary Tumor and LymphNode Metastases in Patients with Esophageal Carcinoma: *Anticancer Research*, 33: 4975-82.

Kumar, A., Manjunath, GV. and Mahinderu, K. 2016. A Study of evaluation of immunoreactivity of C-ERBB-2 and Histopathological Parameter in Esophageal Carcinoma. *IOSR Journal of Dental and Medical Sciences,* August. 15(8): 53-61.

Lepage, C., Bouvier, AM., Manfredi, S., Coatmeur, O., Chenyel, N. and Faivre, J. 2005. Trends in incidence and management of esophageal adenocarcinoma in a well-defined population. *GastroenterolClin Biol.,* 29:1258-63.

Lepage, C., Rachet, B., Jooste, V., Faivre, J. and Coleman, MP. 2008. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. *Am J Gastroenterol.,* 103: 2694-99.

Lin, G., Sun, XJ. and Han, QB. 2015. Epidermal growth factor receptor protein overexpression and gene amplification are associated with aggressive biological behaviors of esophageal squamous cell carcinoma. 901-906.

Lin, G., Sun, XJ. and Han, QB. 2015. Epidermal growth factor receptor protein overexpression and gene amplification are associated with aggressive biological behaviors of esophageal squamous cell carcinoma. 901-906.

Mchembe, M D., Rambau, P F. and Chalya, P L. 2013. Endoscopic and clinicopathological patterns of esophageal cancer in Tanzania: experiences from two tertiary health institutions. *World Journal of Surgical Oncology*, 11: 2.

Moghbeli, M., Abbaszadegan, MR. and Farshchian, M. 2013. Association of PYGO2 and EGFR in esophageal squamous cell Carcinoma. *Med Oncol.,* 30: 516.

Nagaraja, V., Shaw, N. and Morey, AL. 2016. HER2 expression in oesophageal carcinoma and Barrett's oesophagus associated adenocarcinoma: An Australian study. *Eur J Surg Oncol.,* 42(1): 140-8.

Negi, M., Negi, RR., and Raina, S K. 2017. Profiling Esophageal Carcinoma (EC) among Patients Presenting to a Medical College in Rural Area of North-West India. *Public Health Research*, 7(1): 35-37.

Nozoe, T., Oyama, T., Takenoyama, M., Hanagiri, T., Sugio, K. and Yasumoto, K. 2007. Significance of immunohistochemical expression of estrogen receptors alpha and beta in squamous cell carcinoma of the esophagus. *Clin Cancer Res.,* 13: 4046-4050.

Ntagirabiri, R., Karayuba, R. and Ndayisaba, G. 2016. Esophageal Cancer: Epidemiological, Clinical and Histopathological Aspectsover a 24-Years Period at Kamenge University Hospital, Bujumbura, Burundi. *Open Journal of Gastroenterology,* 6:106-110.

Pennathur, A., Gibson, MK., Jobe, BA. and Luketich, JD. 2013. Oesophageal carcinoma. *Lancet,* 381:400-12.

Sarbia, M., Porschen, R. and Borchard, F. 1995. Incidence and prognostic significance of vascular and neural invasion in squamous cell carcinomas of the esophagus. *International Journal of Cancer,* 61(3): 333-6.

Sarfaty, M., Lankry, E. and Moore, A. 2017. Esophageal Cancer in Israel has Unique Clinico-Pathological Features: *A Retrospective Study Journal of Cancer,* 8(13): 2417-2423.

Shang, L., Liu, HJ., Hao, JJ., Jiang, YY., Shi, F., Zhang, Y., *et al*., 2014. A panel of overexpressed proteins for prognosis in esophageal squamous cell carcinoma. *PloS One*, 9:1110-45.

Shi, HY., Zhu, SC. and Shen, WB. 2014. Pathological characteristics of esophageal cancer. *Oncology Letters,* June 4, 533-538.

Ueo, H., Matsuoka, H., Sugimachi, K., Kuwano, H., Mori, M. and Akiyoshi, T. 1990. Inhibitory effects of estrogen on the growth of a human esophageal carcinoma cell line. *Cancer Res.,* 50: 7212-7215.

Utsumi, Y., Nakamura, T., Nagasue, N., Kubota, H. and Morikawa, S. 1989. Role of estrogen receptors in the growth of humanesophageal carcinoma. *Cancer,* 64: 88-93.

Utsumi, Y., Nakamura, T., Nagasue, N., Kubota, H., Harada, T. and Morikawa, S. 1991. Effect of 17 beta-estradiol on the growth of an estrogen receptor-positive human esophageal carcinoma cell line. *Cancer,* 67:2284-2289.

Washington, K., Berlin, J., Branton, P. and Lawrence, B. Protocol for the Examination of Specimens from Patients with Carcinoma of the Esophagus.

Wei, Q., Chen, L. and Sheng, L. 2007. EGFR, HER2 and HER3 expression in esophageal primary tumors and corresponding metastases. *Int. J of Onc.,* 31: 493-499.

Yoon, H H., Shi, Q. and Sukov, W R. 2012. Association of HER2/ErbB2 Expression and Gene Amplification with Pathologic Features and Prognosis in Esophageal Adenocarcinomas. *Clin Cancer Res.,* 18(2): 546–54.

Yu, WW., Guo, YM., Zhu, M., Cai, XW., Zhu, ZF., Zhao, WX., *et al*., 2011. Clinicopathological and prognostic significance of EGFR overexpression in esophageal squamous cell carcinoma: a meta- analysis. *Hepato-gastroenterology,* 58:426-31.

Zhang, L., Wang, L. and Bai, G. 2015. The relationship between the expression of VEGF, EGFR, and HER-2 mRNA in esophageal squamous cell carcinoma (ESCC) and clinicopathological features of different ethnic groups in Xinjiang. *Tumor Biol.,* 36(12): 9277–83.

Zhang, W., Zhu, H., Liu, X., Wang, Q., Zhang, X., He, J., *et al*., 2014. EGFR is a prognosis predictor in patients with esophageal squamous cell carcinoma. *Ann Thorac Surg.,* 98:513-9.

Zuguchi, M., Miki, Y. and Onodera, Y. 2012. Estrogen receptor α and β in esophageal squamous cell carcinoma: 1349-7006.

****