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Impact of EGFR membranous overexpression on cervical cancer treatment outcomes

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Abstract

Purpose: This study aimed to assess the association between pretreatment EGFR overexpression in local-regional advanced cervical cancer patients treated definitively with concurrent chemoradiation (CRT) and treatment outcomes including overall survival (OS), progression free survival (PFS), distant metastases control (DM), local-regional control (LC), and distant control (DC).
Patients and Methods: This IRB approved study included cervical cancer patients treated definitively and consecutively with CRT. Evaluation of memberanous expression for EGFR was performed and scored semi-quantitatively by expert pathologists, blinded to the treatment outcomes, and incorporated both the intensity and percentage of immune-reactivity in invasive carcinoma. Treatment-outcomes were reviewed and reported.
Results: The study included 28 patients who had tissue available from the pathology core facility for immune-histochemistry. The mean patients' age was 51 $\pm$ 10 years. 53.57% of the patients had FIGO stage IIB disease. Most of the patients (78.6%) had locally advanced disease (size $\geq$ 4 cm) at presentation. The 5-year OS, PFS, LC, and DC were 57.2%, 48.1%, 72.1%, and 62.9%, respectively. Six (21.4%), and 20 patients (78.6%) had EGFR score <2 and $\geq$ 2, respectively. EGFR overexpression was associated with worse 3-year and 5-year OS (72.8% vs. 60%, and 65.59% vs. 40%), PFS (61.83% vs. 41.6%, and 51.53% vs. 41.67%), LC (77.73% vs. 41.67%, and 77.7% vs. 41.7%), and DC (77.1% vs. 41.7% and 64.3% vs. 41.67%). However, these values did not reach a statistical significance.
Conclusion: This study demonstrated a trend that EGFR overexpression is a potential prognostic marker for local-regional advanced cervical cancer patients treated definitively with CRT.

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Introduction

Cervical cancer is a major cause of morbidity and mortality worldwide, with an estimated 529,800 newly diagnosed cases and 275,100 deaths in 2011. In the United States alone, it is estimated that there will 12,360 new cases in 2014. [1, 2] Definitive concurrent chemoradiation therapy (CRT) is the standard of care for treatment of patients with local-regionally advanced cervical cancer [3-9]. However, almost all patients who develop recurrence still have a poor prognosis, despite advancements in salvage treatment. [10-12] Identification of molecular biomarkers predictive of higher relapse risk after CRT is lacking. If patients who are likely to recur could be better identified then more individualized treatments could be of great benefit to this subset. Potential molecular markers would be helpful for determining prognosis and potentially for development of individualized target therapies. [11, 12]

A recent study aimed at assessing the genetic profiles of cervical tumors by high- throughput sequencing for personalized medical care detected a mutation in a specific subpart of extracellular domain of EGFR, called the dimerization loop.[13] This loop is essential for receptor dimerization and hence activation. This mutation was shown by another study to be able to increase receptor oncogenic activity. [14] This study aimed to assess the association between pretreatment c-Met overexpression in local-regional advanced cervical cancer patients (treated definitively with CRT) and treatment outcomes including overall survival (OS), progression free survival (PFS), distant metastases control (DM), and local-regional control (LC).

Patients and Methods

The Institutional Review Board approved this retrospective study. The study aimed to evaluate the incidence and impact of EGFR oncogene mutation on the treatment outcomes of local-regional advanced cervical cancer treated consecutively and definitively with CRT. Charts were reviewed of patients with local-regionally advanced cervical cancer who presented to our department between January 1983 and December 2009. Patients were treated with definitive cisplatin-based chemotherapy and external beam radiation therapy (EBRT) followed by a low-dose-rate (LDR) brachytherapy boost (BT). Inclusion criteria included (1) a histologically proven diagnosis of cervical cancer stages IB1 through IVA locally advanced cervical carcinoma, (2) Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2, and (3) age > 18 years old. Women were excluded if treated with up-front surgery followed by adjuvant radiotherapy or CRT and also if they had prior radiotherapy for gynecologic or gastrointestinal diseases. The chart review yielded 129 eligible cervical cancer patients. Of the eligible patients, 28 had tissue available from the pathology core facility. There was no statistical significant difference between 129 eligible patients versus 28 evaluable patients regarding patients' and tumors' characteristics.

All patients had a cervical biopsy with pathologic confirmation of cervical carcinoma and underwent appropriate staging work-up. Concurrent cisplatin-based EBRT was to a total dose of 45 Gy, in 1.8 Gy/fraction, 5 fractions per week for a total of 5 weeks. Parametrial boost and nodal boosts were added at the treating physician's discretion. As part of the definitive management, LDR Fletcher-Suit tandem and ovoid BT implant (s) were performed with Cs-137 sources, in one or two implants. The dose was prescribed according to the Manchester System with dose prescribed to point A based on patient and tumor characteristics. Doses to point B and the rectal and vaginal doses were also calculated. The brachytherapy treatment duration ranged from 40-70 hours, during which time the patients were admitted to the hospital. The details of pretreatment evaluation, treatment technique and treatment parameters of the entire cohort of 129 patients were described in detail in an earlier report.[8]

For the 28 patients whom cervical cancer tissue was available, we report treatment-induced acute adverse events including gastrointestinal, genitourinary, and skin toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC AE) and treatment outcomes including OS, PFS, LC, and DC. Outcomes were also stratified by EGFR mutation as well as other relevant tumor characteristics.

Immunohistochemistry

Evaluation of cytoplasmic immunoreactivity for c-Met was performed and scored semi-quantitatively by expert pathologists, and incorporated both the intensity and percentage of immunoreactivity in invasive carcinoma (H-score).[15] The immunointensity was defined as negative (0), weak (1+), moderate (2+), and high (3+) positive (Figure 1). The H-score consisted of a sum of combination of immunoreactivity for intensity multiplied by percentages. A score of ≥ 2 was used as a cut off value for positive staining. All pathologists were blinded to the treatment outcomes.

Statistical analysis

Means, standard deviations, medians, and ranges summarized continuous variables. Categorical variables were summarized by frequencies and percentages. OS, PFS, LC, and DC rates were obtained via the Kaplan-Meier method and differences between groups were evaluated by the log-rank test. Hazard ratios associated with these rates were obtained via Cox regression for both univariate and multivariate analyses.

Results

The mean patient age in this cohort was 51 $\pm$ 10 years. 53.57% of the patients had FIGO stage IIB disease. Almost two thirds of the patient had clinical node negative disease. Most of the patients (78.57%) had locally advanced disease (size $\geq$ 4 cm) at presentation. Detailed patients and tumor characteristics are presented in Table 1. Six patients (21.5%) had EGFR $\geq$ 2 and 20 patients (78.5%) had EGFR <2.

Treatment outcomes

Tables 2 and 3 detail the treatment outcomes (OS, PFS, LC, and DC) for all patients stratified by EGFR mutation (EGFR $\geq$ 2 versus <2), as well as other patients and tumor characteristics. The 5-year OS, PFS, LC, and DC in the entire cohort were 57.2% (CI 34.1% - 74.8%), 48.1% (CI 25.5% - 67.5%), 72.1% (CI 50% - 85.7%), and 62.9% (CI 36.3% - 80.8%), respectively. As shown in table 2, there was a trend towards worse outcomes represented as worse association between EGFR $\geq$ 2 and worse 3-year and 5-year OS, PFS, LC, and DC. The log-rank test demonstrated a significant association between smoking and OS (p = 0.04), PFS (p=0.02), LC (p=0.047), and DC (p=0.03). There was also a significant association between OS and tumor stage (p=0.03), as well as treatment breaks (> 3 days throughout the treatment course) (p=0.04) as shown in Table 3. Additionally, there was a significant association between PFS and tumor stage (p = 0.01), tumor size (p=0.052), and treatment breaks (0.051).

Treatment induced adverse events

Treatment induced adverse events according to CTCAE are detailed in Table 4. Two patients (7.14%), and 11 patients (39.29%) experienced CTCAE grade 3-4 acute, and chronic gastrointestinal adverse events, respectively.

Table 1. Patients and tumor characteristics

Characteristics			
Age		51 ± 10 51 (32,74)	
		N	**%**
Race	White	14	50.00
	African American	7	25.00
	Hispanic	6	21.43
	Others	1	3.57
Smoking	Current Smoker	10	35.71
	< 20 p/y	2	20.00
	20-40 p/y	4	40.00
	> 40 p/y	4	40.00
	Ex-Smoker	5	17.86
	< 20 p/y	2	40.00
	20-40 p/y	2	40.00
	> 40 p/y	1	20.00
	Non Smoker	13	46.43
Tumor Stage	IB1	1	3.57
	IB2	2	7.14
	IIA	0	0.00
	IIB	15	53.57
	IIIA	0	0.00
	IIIB	5	17.86
	IVA	3	10.71
	IVB	2	7.14
Nodal Status	Node negative	18	64.29
	Pelvic	4	14.29
	Para-aortic	1	3.57
	Both (Pelvic and PA)	5	17.86
Positive node location	Unilateral	9	32.14
	Bilateral	18	64.29
	Unknown	1	3.57
Tumor Grade	1	1	3.57
	2	13	46.43
	3	8	28.57
	N/A	6	21.43

Table 1. Patients and tumor characteristics (continued)

Characteristics		N	%
Tumor morphology	Exophytic	24	85.71
	Endophytic	3	10.71
	N/A	1	3.57
Tumor Histology	Squamous Cell Carcinoma	25	89.29
	Adenocarcinoma	3	10.71
Tumor Size in cm	< 4 cm	4	14.29
	≥ 4 cm	22	78.57
Pretreatment Anaemia	Yes (<12)	17	60.71
	No (≥ 12)	11	39.29
Body mass index	≤ 18.5	1	3.57
	18.5 – 24.9	9	32.14
	25.0 – 29.9	6	21.43
	≥ 30	12	42.86

Table 2. Treatment outcomes (Overall Survival, Progression Free Survival, Local Control and Distant Control) for all patients and stratified by Met expression (H index ≤ 30 versus > 30)

	All patients (N=28; N events=10)	EGFR ≥ 2 (N=6; N events=3)	EGFR < 2 (N=20; N events=6)	p-value
3-yr OS	63.53% (CI 41.29% - 79.24%)	60.00% (CI 12.57%, 88.18%)	72.87% (CI:46.43%,87.77%)	**0.25**
5-yr OS	57.18% (CI 34.06% - 74.82%)	40.00% (CI 5.20%, 75.28%)	65.59% (CI:38.18%,83.13%)	
	All patients (N=28; N events=13)	**EGFR ≥ 2 (N=6; N events=3)**	**EGFR < 2 (N=20; N events=9)**	
3-yr PFS	61.04% (CI 39.51% - 76.91%)	41.67% (CI 5.60%, 76.65%)	61.83% (CI:35.96%,79.78%)	**0.53**
5-yr PFS	48.07% (CI 25.50% - 67.52%)	41.67% (CI 5.60%, 76.65%)	51.53% (CI:23.93%,73.54%)	
	All patients (N=28; N events=7)	**EGFR ≥ 2 (N=6; N events=3)**	**EGFR < 2 (N=20; N events=4)**	
3-yr LC	72.11% (CI 49.96% - 85.73%)	41.67% (CI 5.60%, 76.65%)	77.73% (CI:50.67%,91.09%)	**0.17**
5-yr LC	72.11% (CI 49.96% - 85.73%)	41.67% (CI 5.60%, 76.65%)	77.73% (CI:50.67%,91.09%)	
	All patients (N=28; N events=9)	**EGFR ≥ 2 (N=6; N events=3)**	**EGFR < 2 (N=20; N events=6)**	
3-yr DMFS	71.83% (CI 49.45% - 85.60%)	41.67% (CI 5.60%, 76.65%)	77.19% (CI:49.48%,90.92%)	**0.24**
5-yr DMFS	62.85% (CI 36.33% - 80.82%)	41.67% (CI 5.60%, 76.65%)	64.33% (CI:30.10%,85.03%)	

Table 3. Treatment outcomes (Overall Survival, Progression Free Survival, Local Control and Distant Control) stratified by patients and tumor characteristics.

Treatment Outcomes		Median in months	2-years (%)	3-years (%)	5-years (%)	Log-rank P value
Overall Survival (OS)						
OS according to tumor stage						
	I	NA	100% (100%, 100%)	50.00% (0.60%, 91.04%)	50.00% (0.60%, 91.04%)	0.03
	II	NA	77.38% (44.93%, 92.11%)	77.38% (44.93%, 92.11%)	77.38% (44.93%, 92.11%)	
	III	27 (7, 127)	60.00% (12.57%, 88.18%)	30.00% (1.23%, 71.92%)	30.00% (1.23%, 71.92%)	
	IVA	NA	66.67% (5.41%, 94.52%)	66.67% (5.41%, 94.52%)	66.67% (5.41%, 94.52%)	
	IVB	11 (8, 14)	0.00%	0.00%	0.00%	
OS according to Lymph node status						
	Negative	NA	79.41% (53.97%, 91.75%)	72.79% (46.01%, 87.82%)	63.70% (34.58%, 82.56%)	0.08
	Positive	18 (7, 124)	33.33% (4.61%, 67.56%)	33.33% (4.61%, 67.56%)	33.33% (4.61%, 67.56%)	
OS according to tumor size						
	< 4 cm	NA	100%	100%	100%	0.12
	≥4 cm	NA	58.93% (34.30%, 77.00%)	52.38% (27.98%, 72.02%)	52.38% (27.98%, 72.02%)	
OS according to pretreatment anemia						
	Yes (<12)	NA	75.00% (46.34%, 89.80%)	67.50% (38.35%, 85.11%)	67.50% (38.35%, 85.11%)	0.30
	No (≥12)	42 (7, 147)	57.14% (21.72%, 81.46%)	57.14% (21.72%, 81.46%)	42.86% (11.40%, 71.85%)	
OS according to treatment breaks						
	Yes	NA	77.92% (45.90%, 92.32%)	77.92% (45.90%, 92.32%)	77.92% (45.90%, 92.32%)	0.04
	No	27 (8, 90)	57.14% (25.38%, 79.58%)	42.86% (12.64%, 70.67%)	28.57% (4.90%, 59.44%)	
Progression Free Survival (PFS)						
PFS according to tumor stage						
	I	70 (42, 97)	100% (100%, 100%)	50.00% (0.60% , 91.04%)	50.00% (0.60%, 91.04%)	0.01
	II	NA	77.92% (45.90%, 92.32%)	77.92% (45.90%, 92.32%)	77.92% (45.90%, 92.32%)	
	III	19 (3, 127)	20.00% (0.84%, 58.19%)	20.00% (0.84%, 58.19%)	20.00% (0.84%, 8.19%)	
	IVA	57 (5, 57)	66.67% (5.41%, 94.52%)	66.67% (5.41%, 94.52%)	0.00%	
	IVB	6 (3,8)	0.00%	0.00%	0.00%	

Table 3. Treatment outcomes (Overall Survival, Progression Free Survival, Local Control and Distant Control) stratified by patients and tumor characteristics (continued)

Treatment Outcomes		Median in months	2-years (%)	3-years (%)	5-years (%)	Log-rank P value
Progression Free Survival (PFS)						
PFS according to Lymph node status						
	Negative	97 (19, 127)	69.02% (43.37%, 84.83%)	69.02% (43.37%, 84.83%)	50.33% (22.34%, 73.01%)	0.23
	Positive	8 (4, 124)	33.33% (4.61%, 67.56%)	33.33% (4.61%, 67.56%)	33.33% (4.61%, 67.56%)	
PFS according to tumor size						
	< 4 cm	NA	100%	100%	100%	0.052
	≥4 cm	NA	49.33% (26.15%, 68.92%)	49.33% (26.15%, 68.92%)	39.46% (16.02%, 62.37%)	
PFS according to pretreatment anemia						
	Yes	NA	63.03% (35.42%, 1.44%)	63.03% (35.42%, 81.44%)	50.42% (20.43%, 74.44%)	0.55
	No	42 (4,127)	58.33% (22.98%, 82.07%)	58.33% (22.98%, 82.07%)	43.75% (11.87%, 72.57%)	
PFS according to treatment breaks						
	Yes	NA	79.44% (48.79%, 92.89%)	79.44% (48.79%, 92.89%)	66.20% (29.87%, 86.87%)	0.051
	No	27 (8,9 0)	38.10% (12.09%, 64.35%)	38.10% (12.09%, 64.35%)	25.40% (4.69%, 54.13%)	
Local-regional Control (LC) rate						
LC according to tumor stage						
	I	NA	100%	100%	100%	0.08
	II	NA	83.92% (49.40%, 95.73%)	83.92% (49.40%, 95.73%)	83.92% (49.40%, 95.73%)	
	III	19 (4, 128)	40.00% (5.20%, 75.28%)	40.00% (5.20%, 75.28%)	40.00% (5.20%, 75.28%)	
	IVA	NA	66.67% (5.41%, 94.52%)	66.67% (5.41%, 94.52%)	66.67% (5.41%, 94.52%)	
	IVB	NA	NA	NA	NA	
LC according to Lymph node status						
	Negative	NA	74.77% (49.46%, 88.68%)	74.77% (49.46%, 88.68%)	74.77% (49.46%, 88.68%)	0.33
	Positive	NA	66.67% (19.46%, 90.44%)	66.67% (19.46%, 90.44%)	66.67% (19.46%, 90.44%)	

Table 3. Treatment outcomes (Overall Survival, Progression Free Survival, Local Control and Distant Control) stratified by patients and tumor characteristics (continued)

Treatment Outcomes		Median in months	2-years (%)	3-years (%)	5-years (%)	Log-rank P value
LC according to tumor size						
	< 4 cm	NA	100%	100%	100%	0.18
	≥4 cm	NA	62.64% (36.58%, 80.45%)	62.64% (36.58%, 80.45%)	62.64% (36.58%, 80.45%)	
LC according to pretreatment anemia						
	Yes	NA	80.88% (51.27%, 93.48%)	80.88% (51.27%, 93.48%)	80.88% (51.27%, 93.48%)	0.26
	No	NA	58.33% (22.98%, 82.07%)	58.33% (22.98%, 82.07%)	58.33% (22.98%, 82.07%)	
LC according to treatment breaks						
	Yes	NA	79.44% (48.79%, 92.89%)	79.44% (48.79%, 92.89%)	79.44% (48.79%, 92.89%)	0.40
	No	NA	59.52% (23.51%, 83.04%)	59.52% (23.51%, 83.04%)	59.52% (23.51%, 83.04%)	
Distant Control (DC) rate						
DC according to tumor stage						
	I	NA	NA	NA	NA	0.07
	II	NA	83.33% (48.17%, 95.55%)	83.33% (48.17%, 95.55%)	83.33% (48.17%, 95.55%)	
	III	27 (7, 127)	60.00% (12.57%, 88.18%)	30.00% (1.23%, 71.92%)	30.00% (1.23%, 71.92%)	
	IVA	NA	NA	NA	NA	
	IVB	15 (8, 15)	0.00%	0.00%	0.00%	
DC according to Lymph node status						
	Negative	NA	77.04% (49.72%, 90.72%)	68.48% (38.94%, 85.90%)	68.48% (38.94%, 85.90%)	0.55
	Positive	NA	50.00% (5.79%, 84.49%)	50.00% (5.79%, 84.49%)	50.00% (5.79%, 84.49%)	
DC according to tumor size						
	< 4 cm	NA	100%	100%	100%	0.12
	≥4 cm	NA	61.39% (33.16%, 80.60%)	52.62% (24.68%, 74.48%)	52.62% (24.68%, 74.48%)	
DC according to pretreatment anemia						
	Yes	NA	75.21% (40.72%, 91.37%)	75.21% (40.72%, 91.37%)	75.21% (40.72%, 91.37%)	0.10

Table 4.Treatment-induced adverse events:

	None		Acute CTC AE Grade 3 - 4		Chronic CTC AE Grade 3 - 4	
	N	%	N	%	N	%
Skin	20	71.43	7	25.00	1	3.57
GI Toxicity	15	53.57	2	7.14	11	39.29
GU Toxicity	23	82.14	0	0.00	4	14.29

Discussion

This study of 28 cervical cancer patients treated definitively with CRT followed by a boost with LDR BT demonstrated a trend for inverse association between EGFR mutation and poor OS, PFS, LC, and DC.

In the setting of local-regional advanced cervical cancer, image-guided brachytherapy (IGBT) after EBRT is becoming more widely utilized. Results of MRI-based IGBT have demonstrated improved local control while minimizing treatment-induced adverse events. However, there still needs to be definitive clinical evidence of superior survival advantage compared to conventional two-dimensional historical planning.[9, 16] Overall, treatment endpoints continue to be significantly worse in the setting of locally recurrent and metastatic cervical cancer. With a median OS up to 13 months, outcomes in these patients remain poor. This is despite numerous clinical trials investigating different chemotherapeutic regimens before the era of individualized molecular medicine. Currently targeted therapies aiming to knock-down specific molecular targets have emerged as an important therapeutic approach that allow tailoring treatment towards the applicable patient on an individual level with an ultimate goal of better treatment outcomes. [12, 17, 18] The Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG) – now part of NRG - as well as various other groups have recognized the importance of identifying novel molecular therapeutic agents targeting specific pathways in order to improve the treatment outcomes in both the local-regional advanced and recurrent/metastatic settings. The majority of these studies have utilized bevacizumab in an attempt to target EGFR and interrupt angiogenesis with translation to a survival advantage. This potential target was reported in considerable number of reports including GOG Protocol 227-C[19], and recently in RTOG 0417 [20], GOG 240[12]. The GOG 240 study, reported by Tewari et al., randomized 452 advanced cervical cancer patients to standard chemotherapy with or without bevacizumab at a dose of 15 mg/kg. The addition of bevacizumab to chemotherapy was associated with increased OS (17.0 months vs. 13.3 months; HR for death, 0.71; 98% CI, 0.54 to 0.95; P=0.004) and higher response rates (48% vs. 36%, P=0.008). The authors concluded that the addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median OS. [12] Based on this, the FDA approved bevacizumab to treat patients with persistent, recurrent or late-stage (metastatic) cervical cancer on August 14, 2014. Although there is a growing body of evidence that targeting angiogenesis using bevacizumab might play an important role in optimizing treatment outcomes, identifying other molecular targets in different pathways in cervical carcinogenesis might add to therapeutic options and help improve treatment outcomes.

Interestingly, it was shown that Met gene amplification is one of the most relevant mechanisms involved in EGFR – Tyrosine Kinase Inhibitors (EGFR-TKI) acquired resistance. Engelman et al[21] correlated the resistance to EGFR-TKI agents in lung cancers to the focal amplification of the c-Met proto-oncogene, and proved that inhibition of c-Met signaling in these cancer cells restored their sensitivity to EGFR-TKI. In a study by Bean et. al, [22] c-Met amplification was found in 21% of lung cancer patients with acquired resistance to EGFR-TKI and only in 3% of untreated patients, confirming that c-Met could be a relevant therapeutic target for individuals with acquired resistance to EGFR-TKIs.

Would novel molecular therapy that targets both angiogenesis through EGFR and c-Met oncogene add benefit to local-regional advanced, recurrent and / or metastatic cervical cancer patients? The answer to this question requires further controlled clinical trials to assess both the safety and efficacy of such agents with an ultimate goal of better and more effective individualized treatment options for patients.

Conclusion

This study showed that EGFR mutation is a potential prognostic marker for local-regional advanced cervical cancer patients treated definitively with CRT. Controlled clinical trials are worthwhile to verify of its potential value as a therapeutic target for this patients population.

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