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"Does diabetes mellitus influence pathologic complete response and tumor downstaging after neoadjuvant chemoradiation for esophageal and gastroesophageal cancer? A two-institution report"

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Running Title: Diabetes and response to neoadjuvant therapy in esophageal cancer.

Key words: gastroesophageal cancer, diabetes mellitus, neoadjuvant chemoradiation

ABSTRACT

Background: Esophageal carcinoma is an aggressive disease that is often treated with neoadjuvant therapy followed by surgical resection. Diabetes mellitus (DM) has been associated with reduced efficacy of chemoradiation (CRT) in other gastrointestinal cancers. The goal of this study was to determine if DM affects response to neoadjuvant CRT in the management of gastroesophageal carcinoma.

Methods: We retrospectively reviewed the esophageal cancer patient databases and subsequently analyzed those patients who received neoadjuvant CRT followed by surgical resection at two institutions, Thomas Jefferson University (TJUH) and Fox Chase Cancer Center (FCCC). Comparative analyses of rates of pathologic complete response rate (pCR) and pathologic downstaging in DM patients versus non-DM patients was performed.

Results: Two hundred and sixty patients were included in the study; 36 patients had DM and 224 were non-diabetics. The average age of the patients was 61 years (range 24-84 years). The overall pCR was 26%. The pCR rate was 19% and 27% for patients with DM and without DM, respectively (p= 0.31). Pathologic downstaging occurred in 39% of study patients, including of 33% of DM patients and 40% of non-DM patients (p=0.42).

Conclusions: Although the current analysis does not demonstrate a significant reduction in pCR rates or pathologic downstaging in patients with DM, the observed trend suggests that a potential difference may be observed with a larger patient population. Further studies are warranted to evaluate the influence of DM on the effectiveness of neoadjuvant CRT in esophageal cancer.

INTRODUCTION

Over the past two decades, diabetes mellitus (DM) has become endemic throughout the United States and globally. It is estimated that by the year 2010, 221 million people will be affected with diabetes; up from 124 million in 1997 [1]. Because an increasing number of cancer patients will also carry the diagnoses of DM, it is important to fully understand the implications that DM has on the prognosis and treatment of cancer treatment.

In 2004, Coughlin *et al,* in a large prospective cohort study, found that diabetes mellitus was an independent predictor of mortality from multiple cancers, including cancer of the colon, breast, liver, pancreas, and bladder. Diabetes is often considered to be a common risk factor for esophageal adenocarcinoma. A recent meta-analyses comparing overall survival in all cancer patients with and without preexisting diabetes found that diabetic patients are at an increased risk for long-term, all-cause mortality compared with non-diabetic patients [2].

Esophageal cancer is the eighth most common cause of cancer worldwide [3]. It often presents at an advanced stage and therefore tends to be incurable. For resectable disease, surgery is the gold standard treatment. Even with improving resection rates and decreasing postoperative mortality rates, 5-year survival after esophagectomy is only 25-

35% [3-6]. Neoadjuvant chemotherapy and radiation therapy are often added to the treatment of patients with resectable esophageal cancer, although the benefits remain small [7-9].

Response to neoadjuvant therapy is a valuable marker of tumor biology and prognosis. Numerous studies have shown that the subset of esophageal cancer patients that are able to achieve a complete pathologic response (pCR) after neoadjuvant therapy have significantly better outcomes [10-14]. It is therefore imperative to determine if there are any patient related factors that may affect individual ability to achieve pCR. In 2008, Caudle *et al* demonstrated that although diabetic patients had a similar rate of downstaging after neoadjuvant therapy compared to non-diabetics, no diabetic patients achieved a pCR. The authors concluded that neoadjuvant therapy in rectal cancer is less effective in diabetic patients than in non-diabetic patients. The goal of the current study was to determine if diabetes mellitus had an influence on the rate of pCR and tumor downstaging in the treatment of esophageal cancer. To our knowledge this relationship in esophageal cancer has never been reported in the literature.

METHODS

Institutional Review Board approved esophagectomy databases at both institutions were searched to identify patients with esophageal cancers who received CRT followed by surgical resection. Dates of surgical resections included the time periods of 1994-2006 (TJUH) and 1992-2002 (FCCC). Medical records were reviewed, including office notes, operative dictations and pathology reports. Data recorded included demographics, medical history, length of stay, chemotherapeutic regimen, type of esophagectomy, completeness of resection, histologic diagnosis, tumor location, initial stage, pathologic stage, pathologic complete response, total lymph nodes, number of positive lymph nodes, time to recurrence and survival. Patients were classified as having DM or not based on past medical history as listed in hospital or clinic notes as well as examination of medication lists (including oral hypoglycemic agents and/or insulin) during the time that they underwent CRT.

Pretreatment or initial stage was determined using a combination of computed tomography (CT) scan, endoscopic ultrasound (EUS) and sometimes positron emission tomography (PET) scans. Staging was by the American Joint Committee on Cancer (AJCC) TNM staging, sixth edition. The neoadjuvant chemotherapy most often included a 5-fluoruracil, taxol and platinum (cisplatinum or carboplatinum) regimen, in concurrence with phase I and II trials at the two institutions [15, 16]. These regimens were most commonly given concurrently with external beam radiation therapy to a dose of 45 Gy. The individual surgical method was left to the discretion of the operating surgeon. Surgery was performed approximately four to six weeks after the completion of CRT and re-staging to ensure no metastatic disease. Post-treatment staging was determined by

pathologic review. A pCR was defined as no residual tumor cells in the surgical specimen including the primary site and surrounding lymph nodes. Downstaging was defined as patients whose tumors underwent significant regression down to T1 tumors with no nodal involvement. Chi-square test was used as a comparative analysis of rates of pathologic complete response rate (pCR) and pathologic downstaging in DM patients versus non-DM patients.

RESULTS

Two hundred and sixty patients were included in this retrospective study. Thirty-six (13.8%) patients had DM and 224 (86.2%) were nondiabetics (non-DM). The average age for the overall patient population was 61 years (61 years for DM group (range=41-78) and 60 years (range=24-84) for non-DM group). Overall, the male to female ratio was 5.6:1. Of note, the male to female ratio was 17:1 in the DM group and 5.5:1 in the non-DM group. The location of the tumors was not appreciably different between the two patient groups. The majority of tumors were located at the distal esophagus and gastroesophageal junction (Table 1). All patients in both groups completed neoadjuvant therapy. Surgical resection followed neoadjuvant therapy in all patients in this study.

The groups did not have statistically different differences in the initial clinical stage or the pathological stage; the majority of patients in both groups presented with stage 2 disease. There were 12 patients with initial stage IVa disease. The majority of stage 2 patients were those with T3N0 disease. Among the non-diabetic patients, there were 44 with T2, 149 with T3, and 9 with T4 disease. In contrast there were 7 T2, 27 T3, and one T4 patient in the diabetic group. There were no significant differences in pre-treatment nodal staging either with the non-diabetics group having 21% Nx, 36% N0, and 43% N1, and the diabetic group having 27%Nx, 40% N0, and 33% N1.

There were a total of 44 patients with squamous cell carcinoma (SCC, 17%). Of these 44, only one was diabetic, and this patient did not have a partial or complete response. Among the 44 patients with SCC, the pCR rate was 32% (14 of 44). A total of 43% of SCC patients achieved a significant partial or complete response. By contrast, the

majority of patients in this series had adenocarcinoma (n=216, 83%) which reflects national trends. The pCR rate among patients with adenocarcinoma was 25% and the significant responder rate was 39%.

Among the patients with DM, there were only six patients who required insulin and the rest (n=30) patients taking oral hypoglycemic agents. Unfortunately due to the retrospective nature of this study, it is difficult to examine glycemic control. HgA1c levels were not routinely evaluated and therefore are not available to examine. Most patients received long-term continuous infusion 5-FU at a dosage of 225 mg/m2/day during the entire course of radiation therapy. As part of various ongoing clinical trials many patients received additional chemotherapy agents. These included paclitaxel (doses ranging from 30 to 60 mg/m2 given weekly), carboplatinum (AUC=5, given on day 1 and 29), and cisplatinum (75mg/m2).

After appropriate neoadjuvant therapy, 19.4% of the diabetic patients and 26.8% of the nondiabetic patients had no detectable residual disease in the pathologic specimen. In the diabetic group, 11 patients (30%) had stage 0 or 1 residual disease, while 89 (40%) of the non-diabetics had stage 0 or 1 residual disease (p= 0.36). In the diabetic group, 33.3% had positive lymph nodes, while in the nondiabetic group 37.7% had positive lymph nodes (Table 2).

The overall rate of achieving a complete pathologic response for the entire patient population was 26%. There was a trend for a decrease in the rate of pCR in the diabetic group, 19% versus 27% in the nondiabetic group. This trend was not statistically significant (p= 0.31).

Overall, pathologic downstaging occurred in 39% of study patients. The rate of pathologic downstaging was lower in diabetic patients (33%) compared to nondiabetic patients (40%), although this was not statistically significant (p= 0.42).

DISCUSSION

Preoperative CRT followed by surgical resection is the treatment regimen employed in most patients with resectable esophageal cancer. Achieving pCR and node negative status are two major determinants of outcome following neoadjuvant CRT [14, 17]. Our analysis does not demonstrate a significant difference between diabetic and nondiabetic patients in terms of achieving pCR and pathologic downstaging. However, the observed trend does suggest that diabetic patients have an inferior response to neoadjuvant therapy when compared to nondiabetic patients. In this study, diabetic patients had a lower rate of both pCR and pathologic downstaging, although neither was statistically significant. The data reported by Caudle *et al*, demonstrated that neoadjuvant therapy was less effective in achieving pCR in diabetic rectal cancer patients than in their nondiabetic counterparts. Although the exact mechanism remains unknown, their data, and the data presented in this study, do implicate diabetes as a predictor of poor response to neoadjuvant therapy [18].

Unlike with colorectal cancers, there is no published data that illustrates a similar relationship between DM and esophageal cancer [19]. There are ample data that support that diabetes is an independent patient characteristic predictive of increased morbidity and mortality after esophagectomy [6, 20-22]. The incidence of esophageal cancer is increasing [23] and a large majority of these patients are treated with CRT. Unfortunately the mortality rate of esophageal cancer remains high. It is therefore of paramount importance to determine the factors that influence patient response to CRT. The exact mechanism of the relationship between diabetes and decreased response to CRT remains unknown. Possible explanations for the negative effect that diabetes has on cancer patients' ability to appropriately respond to CRT include the molecular effects of insulin and insulin-like growth factor on tumor growth, and the relationship between the effects of DM on the body and the ability to effectively deliver neoadjuvant treatment.

Diabetes mellitus, especially Type II, is often coupled with obesity and hyperinsulinemia. Hyperinsulinemia is known to cause an increase in insulin-like growth factor (IGF), a well-studied survival factor for cancer cells. In 2002 Liu *et al* published *in vitro* work showing that IGF, which is upregulated in cancer patients, is able to stimulate tumor growth. IGF was also shown to prevent the expected apoptosis in esophageal cancer cells that had been treated with commonly used chemotherapeutic drugs such as 5-fluorouracil and cisplatin [24]. This preclinical work is especially relevant because hyperinsulinemia and increased levels of IGF in DM and non-DM patients have been shown to be a risk factor for developing gastroesophageal adenocarcinoma as well as other gastrointestinal cancers [25, 26]. In this retrospective study we did not measure insulin or IGF levels in our patients or in their tumor specimens. Future prospective

clinical studies that include this information have the potential to clarify the relationship between DM, hyperinsulinemia, IGF levels and response to neoadjuvant therapy.

A more tangible yet hypothetical possibility to explain the relationship between DM and patient response to neoadjuvant therapy is the long-term effect that diabetes has on patients' microvasculature. The relative hypoxic environment created by vascular disease may reduce the effectiveness of radiation therapy. Additionally, the compromised blood flow could limit the delivery of chemotherapy. DM contributes to the development of microvascular disease as has been shown by multiple studies to contribute to morbidity and mortality in patients undergoing esophagectomy [6, 20-22]. The complications caused by microvasculature disease could also lead to decreased delivery of radiosensitizing drugs. This may compound the hypoxic environment of the tumor and diminish the efficacy of radiation therapy. For example, microvascular disease is felt to contribute to the higher rate of anastomotic leak seen in diabetic patients after rectal surgery [27]. Additionally, in cervical cancer, rectal dysfunction is increased in diabetic patients after radiotherapy in comparison to non-diabetics[28]. These functional consequences may help to explain the role of microvascular disease in the decreased drug delivery to the tumor and therefore a decreased response to therapy.

There are numerous factors that will need to be further studied as we attempt to elucidate this relationship. If increased insulin levels do indeed promote tumor growth, then it would seem important that glucose levels be tightly controlled during neoadjuvant therapy. Due to the retrospective nature of this study, HbA1c levels were not routinely followed in these patients. Also, patients undergoing neoadjuvant therapy for esophageal cancer often have severe dysphagia at the commencement of therapy and will have

derangements in their diet—either decreased calories or an increased carbohydrate load in those patients receiving jejunostomy tube feeds. These serve to cause wide fluctuations in glucose and insulin levels. Prospective study of these phenomena will be important.

The results of this study suggest diabetic patients with esophageal cancer have a decreased ability to respond to CRT. This is the first study which demonstrates that there could be a relationship between diabetes mellitus and response to neoadjuvant chemoradiation; this study raises a hypothesis that warrants future investigations with a larger patient population.

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TABLE 1—Demographics

	Diabetic Patients	**Nondiabetic Patients**
Total number	36	224
Average age	61 (range 41-78)	60 (range 24-84)
Gender (male:female ratio)	17:1	5.5:1
Location of tumor		
Proximal	0 (0%)	2 (0.9%)
Middle	2 (5.6%)	26 (11.6 %)
Distal	16 (44.4%)	92 (41%)
GE Junction	14 (38.9%)	84 (37.5%)
Cardia	4 (11.1%)	20 (8.9%)
Surgical Procedure		
Ivor-Lewis	19 (52.8%)	107 (47.8%)
Transhiatal	8 (22.2%)	46 (20.5%)

3-Hole	5 (13.9%)	62 (27.7%)
Other	4 (11.1%)	9 (4.0%)

TABLE 2—Patient Staging

	Diabetic Patients (n=36)	**Nondiabetic Patients (n=224)**
Initial clinical Stage*		
1	0 (0%)	2 (0.96%)
2	21 (61.8%)	124 (59.6%)
3	11 (32.4%)	72 (34.6%)
4	2 (5.9%)	10 (4.8%)
Pathologic Stage		
No Residual Disease	7 (19.4%)	60 (26.8%)
1	4 (11.1%)	29 (13.0%)
2	14 (38.9%)	72 (32.1%)
3	10 (27.8%)	49 (21.9%)
4	1 (2.8%)	14 (6.3%)
Positive lymph node status**	12 (33.3%)	83 (37.7%)

* Data unavailable for 2 diabetic and 16 nondiabetic patients
** Data unavailable for 4 nondiabetic patients

TABLE 3—Response to chemoradiotherapy

	Diabetic Patients (n=36)	**Nondiabetic Patients (n=224)**	**p value**
pCR*	7/36 (19.4%)	60/223 (27%)	0.42
Pathologic downstaging	12/36 (33%)	90/224 (40%)	0.47

* Data unavailable for 1 nondiabetic patient