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Survival impact and toxicity of metformin in head and neck cancer: An analysis of the SEER-Medicare dataset

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Abstract

Objectives: Recent preclinical research has renewed interest in the interplay between glucose dysregulation and cancer. Metformin holds promise as an adjunctive antineoplastic agent in head and neck cancer (HNC). We aimed to explore the impact of metformin in HNC patients from a population-based dataset.

Patients & Methods: Patients diagnosed with HNC from 2008 to 2011 were identified from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset and categorized into three groups: non-diabetics (nD), diabetics not taking metformin (DnM), and diabetics taking metformin (D + M). Overall survival (OS) and cancer-specific survival (CSS) were compared between groups using Kaplan-Meier and Cox regression controlling for sociodemographic, clinical, and treatment covariates. The incidence of toxicities associated with HNC therapy was compared among groups using χ^2 analysis.

Results: Among 1646 patients, there were 1144 nD, 378 DnM, and 124 D + M. 2-year OS rates was 65.6% for nD, 57.7% for DnM, and 73.4% for D + M by Kaplan-Meier ($p < 0.01$), and corresponding rates of 2-year CSS were 73.7%, 66.1%, and 88.8% ($p < 0.01$), respectively. On Cox multivariable analysis, OS among the three groups did not significantly differ; however, CSS was significantly worse among both nD versus DnM as compared to D + M. Toxicity rates were not significantly increased among D + M.

Conclusion: HNC patients with diabetes taking metformin experience improved CSS. Prospective investigation of the addition of metformin to standard-of-care HNC therapy is warranted.

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Conflict of interest statement
None declared.

Keywords

Metformin; Diabetes; Head and neck cancer; Warburg effect

Introduction

The past decade has witnessed both a growing prevalence of head and neck cancer (HNC) driven by the human papillomavirus (HPV) [1,2] and a series of innovations [3–7] that have enhanced the therapeutic ratio in this disease; however, survival outcomes in the United States remain suboptimal. At a national level, 5-year relative survival rates from cancers of the oral cavity, pharynx, and larynx remain at or below 66% [8], while even on recent prospective clinical trials, patients with advanced HNC experience 3-year overall survival (OS) and progression-free survival rates that fail to exceed 76% and 62%, respectively [9]. Novel therapeutic approaches will therefore prove essential to improving outcomes in HNC.

Building on a hypothesis initially formulated half a century ago [10], recent preclinical data have implicated dysregulation of glucose metabolism in stimulating tumor growth and proliferation [11]. It follows that disorders of glucose homeostasis, chiefly diabetes mellitus, may adversely affect outcomes in cancer patients. Clinical data support this hypothesis and suggest that premorbid diabetes confers a worse prognosis in the setting of a new diagnosis of cancer [12].

These data give rise to the possibility of using antihyperglycemic agents to improve outcomes in HNC. Metformin, a biguanide agent, has generated particular interest due to preclinical studies demonstrating its activity against multiple oncogenic pathways [13,14]. Retrospective analyses have demonstrated improved outcomes in cancer patients with diabetes taking metformin across a variety of disease sites including breast, prostate, lung, colorectum, uterus, and pancreas [15–21]. Recently, attention has also turned to the application of metformin in HNC [22]. However, data regarding its impact in this disease are conflicting, with some studies suggesting no effect of metformin on recurrence, survival, or second malignancy [23], and others demonstrating oncologic outcomes among diabetic patients taking metformin (D + M) that are not only superior to those with diabetes not taking metformin (DnM) but also comparable to those of non-diabetic patients (nD) [24,25]. These latter studies are limited, however, by their focus on single disease sites (larynx and oropharynx), study populations drawn from one or two institutions, and in the case of one series, uniform treatment approach with organ preservation.

We therefore aimed to evaluate the survival impact of metformin and associated toxicity in a national cohort of HNC patients managed with a variety of approaches by comparing recent outcomes among nD, DnM, and D + M patients using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset.

Patients and methods

Data source

The linked SEER-Medicare dataset combines two data sources. SEER uses population-based cancer registries to collect information on cancer cases occurring in approximately 28% of the U.S. population [26], including demographics, tumor characteristics, treatment, census tract-level socioeconomic measures, mortality, and cause of death. Medicare claims provide longitudinal data on diagnoses, procedures, and prescription drugs. Diagnoses and procedures are reported using the *International Classification of Diseases, Ninth Revision (ICD-9)*, *Clinical Modification* codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS). In 2006, Medicare initiated the optional Part D drug benefit, which covers outpatient prescription drugs to supplement traditional Medicare and Medicare Advantage plans [27]. Part D claims are filed for each event in which a prescription is filled and include the date of service.

Sample selection

From our initial cohort of cancers of the head and neck diagnosed through 2013, we selected patients whose first and only primary tumor was a non-metastatic squamous cell carcinoma (International Classification of Diseases for Oncology ICD-O-3 morphology codes 8050–8089) of the head and neck (ICD-O-3 topography codes C00-C14) diagnosed from 2008 through 2011 ($n = 12,367$). We selected 2008 as the earliest year of diagnosis to ensure that at least one full year of Part D data was available prior to diagnosis (without using data from 2006, the initial year of the program), and 2011 was selected as the latest year of diagnosis to ensure most patients would have 24 months of follow-up. Patients with unknown diagnosis dates ($n = 41$), negative survival time ($n < 11$), or diagnoses identified by autopsy or death certificate ($n < 11$) were excluded. To capture patients with complete Medicare data, we included only beneficiaries who were least 66 years old at diagnosis and continuously enrolled in fee-for-service Medicare Parts A, B, and D for both 12 months before and 12 months following the month of diagnosis (or until death if within 12 months of diagnosis). Patients with no paid claims during the 12-month observation period were excluded ($n < 11$), leaving 2003 patients with complete claims data to examine prior health status, treatment, and outcomes of interest.

We used CPT, HCPCS, ICD-9, and NDC codes reported in the Medicare Provider Analysis and Review (MEDPAR), Outpatient, National Claims History (NCH) Physician/Supplier, Durable Medical Equipment (DME), and Part D (PDESAF) claims to identify patients undergoing definitive-intent therapy, which we defined as surgery, radiotherapy, or chemotherapy initiated within six months after diagnosis ($n = 1726$). Lastly, we excluded patients with unknown race, unknown census tract, unknown nodal stage, or nodal stage of “Not Applicable” ($n = 80$), leaving a sample of 1648 (Fig. 1).

Outcomes

The initial analysis examined the characteristics associated with diabetes and metformin. Our primary focus centered on diabetes status and metformin use; however, we also incorporated statin usage and dyslipidemia status as covariates in light of recent Danish data

[28], in addition to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARB) and comorbid hypertension or chronic kidney disease. Prescription drugs were identified using generic names, brand names, and NDC codes on PEDSAF claims. Medication use was defined as having three or more prescriptions filled in the 12 months prior to diagnosis and three or more prescriptions filled in the year since diagnosis, unless a patient died less than a year from diagnosis, in which case we required at least one prescription filled for every four months of survival. The associated chronic conditions were identified using the ICD-9 diagnosis codes used in the Chronic Conditions Data Warehouse algorithms [29]. We considered a patient with at least one diagnosis reported on a MEDPAR, outpatient, or NCH claim in the year prior to diagnosis to have the condition. We classified patients with respect to diabetes status and metformin usage into three categories: (1) negative for diabetes and negative for metformin, i.e. nD; (2) positive for diabetes and negative for metformin, i.e. DnM; and (3) positive for diabetes and positive for metformin, i.e. D + M. As few patients were negative for diabetes and positive for metformin, these 2 patients were dropped from the sample. In total, 1646 patients met final inclusion criteria, including 1144 (69.5%) nD, 378 (23.0%) DnM, and 124 (7.5%) D+ M.

The primary outcome of interest was two-year OS, measured as the number of months from diagnosis until death due to any cause, with patients surviving more than two years censored after 24 months. As Medicare-reported death data are more robust than those reported in SEER, we used the former to assess OS through 2011. However, only SEER captures data regarding cancer-specific survival (CSS). For this outcome, patients dying of causes other than cancer were censored at the time of death. Due to the limited time for follow-up, patients diagnosed in 2011 were excluded from cancer-specific survival analyses.

Toxicity events and conditions associated with HNC therapy and occurring within six months of the initiation of any definitive treatment were examined as a secondary outcome. Specific events were identified using claim procedure and diagnosis codes. Events included gastrostomy or feeding tube placement, tracheostomy or airway obstruction, weight loss, antiemetic prescription, dysphagia, speech pathology, or any emergency department visit. We also included hospital or emergency department visits with symptoms of dehydration, malnutrition, or nausea/emesis as toxicity events.

Control variables

In all multivariate analyses, we adjusted for patient gender, age, race, marital status, SEER registry, population density (metropolitan, urban, and rural), census tract percentage of population with high school education only, census tract percentage of population below poverty, primary tumor site, and AJCC T and N categories. Using Medicare claims, we also identified and controlled for whether the primary treatment facility was a teaching hospital. To address potential differences in overall health, Medicare claims from the year prior to diagnosis were used to calculate Charlson Comorbidity Index (CCI) values according to the National Cancer Institute adaptation of the algorithm described by Klabunde et al. [30].

Statistical analysis

All statistical analyses were performed using SPSS V24.0 (SPSS Inc., Chicago, IL).

Conditions and medications.—Pearson chi-square tests were used to assess univariate associations between categorical variables and diabetes/metformin categories.

Toxicity.—We report results as predicted marginals, which are calculated by averaging the estimated probabilities of toxicity for a standardized set of patient covariates [31]. Predicted marginals standardize outcomes to the entire study sample for covariance imbalance [31,32] and can be interpreted as percentages for logistic models and means for linear models. Statistically significant trends were determined using the Wald test at $p < 0.05$.

Survival.—OS and CSS were first examined using the Kaplan Meier method. Univariate survival analysis was performed with the log-rank test and unadjusted Cox proportional hazards models to estimate hazard ratios (HR) with corresponding 95% confidence intervals (95%CI). Cox Proportional Hazard regression analysis was used to estimate survival, evaluated at a significance level of $p < 0.05$. The proportional hazards assumption was assessed using a test of Schoenfeld residuals for covariates in all final models and returned no significant results [33].

Results

Among the 1646 patients meeting inclusion criteria, 1144 (69.5%) were nD, 378 (23.0%) were DnM, and 124 (7.5%) were D + M (Table 1). Most patients were male, white non-Hispanic, and non-married, and a majority resided in metropolitan areas. Most had oral cavity as their primary site, N0 disease, and comorbidity scores of 0. A majority of patients received surgery (59.1%) and radiotherapy (64.9%), but most (54.8%) did not receive chemotherapy.

Across diabetes/metformin groups, 2-year rates of OS were lowest among DnM patients at 57.7% and highest among D + M at 73.4%, with nD patients falling in between at 65.6% ($p < 0.01$). Similarly, rates of CSS at 2 years were lowest among DnM patients at 66.1% and highest among D + M at 88.8%, with nD patients again falling in between at 73.7% ($p < 0.01$). Kaplan-Meier curves for OS and CSS are depicted in Fig. 2A and B, respectively.

In multivariate Cox proportional hazard regression for OS (Table 2), neither non-metformin group experienced significantly different OS from the D + M group, although there was a trend toward worse survival in the DnM group (nD: HR 1.13, 95%CI 0.78–1.65, $p = 0.53$; DnM: HR 1.36, 95% CI 0.92–2.00, $p = 0.12$). However, statin usage, receipt of care at a teaching hospital, surgery, and radiotherapy were each associated with improved OS, while age ≥ 75 , non-married status, increasing T-and N-classification, comorbidity score ≥ 1 , and poorer census tract were each associated with worse OS.

On multivariate Cox regression for CSS (Table 3), both nD and DnM experienced significantly worse CSS as compared D + M (nD: HR 2.33, 95%CI 1.16–4.65, $p = 0.02$; DnM: HR 3.03, 95% CI 1.49–6.16, $p < 0.01$). Improved CSS was associated with oropharyngeal primary site and surgery, while age ≥ 75 , female sex, increasing T-and N-classification, comorbidity score ≥ 1 , and poorer census tract were each associated with worse CSS.

Toxicity outcomes are depicted in Table 4. The most common toxicity events were dysphagia (47.4%), antiemetic prescription (46.8%), gastrostomy (38.3%), and weight loss (34.5%), with the incidence of every other event falling below 30%. Toxicity rates were generally consistent across between metformin and non-metformin groups, as the incidence of each assessed toxicity did not significantly differ between them.

Discussion

In a nationally-representative cohort of HNC patients, we identified improved OS and CSS among D + M as compared not only to nD but also to DnM. Even after controlling for imbalanced covariates on MVA, D + M appeared to experience improved CSS as compared to DnM or nD.

It may not be surprising that patients with diabetes taking metformin (D + M experience improved outcomes as compared to their counterparts not taking metformin) [22]. After all, patients who take metformin may also be more likely to exhibit other health behaviors associated with improved outcomes in HNC, including abstinence from tobacco or alcohol and adherence to oncologist-recommended care. What is remarkable, however, is our finding that diabetic patients taking metformin experience a significant CSS advantage over patients without diabetes. This provocative result suggests that metformin may not only overcome the negative impact of diabetes in HNC, but may also confer additional anticancer benefit beyond promoting normoglycemia.

Our findings are therefore in line with the published literature suggesting that metformin exerts antitumor effects in HNC [14]. Preclinical evidence demonstrates that metformin activates adenosine monophosphate-activated protein kinase (AMPK) [34], which in turn suppresses the Warburg effect and inhibits tumor growth [35]. Via both AMPK-dependent and AMPK-independent pathways, metformin downregulates mammalian target of rapamycin (mTOR), thereby suppressing cell proliferation, growth, and survival [36]. These antineoplastic effects (and others) may underlie the improved outcomes among patients taking metformin observed in our study and others [24,25].

Intriguingly, the prolonged survival we observed among metformin users did not appear to come at the cost of increased toxicity, in contrast to previous studies [37]. Our findings are therefore consistent with metformin being well-tolerated in general. Unlike other drugs classes used in the management of diabetes, biguanides have an antihyperglycemic mechanism of action, rather than a hypoglycemic one [38], rendering hypoglycemic episodes rare. This is an important consideration in patients undergoing therapy for HNC, who tend to experience mucosal toxicity that can limit oral nutrition and may therefore be predisposed to hypoglycemia. Indeed, the most serious adverse effect of metformin is lactic acidosis, which is fortunately rare among metformin users and typically occurs in patients inappropriately selected for metformin therapy [39,40].

Our study joins others that support the repurposing of drugs traditionally used in non-cancer settings for the treatment of cancer [41]. Notably, preclinical data have demonstrated that statins exert an anticarcinogenic effect [42] (including against HNC specifically [43]), and a

recent study from Denmark identified improved cancer mortality among statin users [28]. It is therefore notable that the effect of metformin in our study persisted even after adjusting for statin usage. The expanded use of typically generic (and therefore inexpensive) medications whose pharmacokinetic and pharmacodynamic properties are well-characterized holds appeal as our health care system strains under the burden of escalating costs for oncology care [44–46].

There are limitations inherent to SEER-Medicare that should be noted. First, as a retrospective analysis, our study is subject to selection bias, and it is possible that unmeasured confounders may have influenced our findings. Second, established prognostic factors such as performance status, HPV status, tobacco usage, and high-risk pathologic features are unavailable in SEER-Medicare and may have been imbalanced between diabetes/metformin groups. Third, SEER-Medicare only captures patients eligible for Medicare (typically ages 65 and up), and we only included patients enrolled on fee-for-service Medicare, which both limit the generalizability of our findings to younger patients or those on Medicare Advantage plans. Finally, oncologic outcomes from SEER-Medicare are limited to survival and cause of death. As such, we are unable to compare locoregional control, distant metastases, or disease-free survival between diabetes/metformin groups. Moreover, the particular selection criteria and covariates (including comorbidities and medications) we applied may also introduce bias beyond that specific to SEER-Medicare itself.

In light of these limitations, our study can only be considered hypothesis-generating, and prospective validation of our findings is warranted. Two prospective, single-arm trials are evaluating the addition of metformin to standard-of-care cisplatin-based chemoradiotherapy for HNC (P,). Should these pilot trials demonstrate the safety of metformin in this setting, they will justify subsequent phase II-III trials randomizing patients to standard-of-care chemoradiation $\pm$ metformin, analogous to the cooperative group study in the realm of locoregionally-advanced non-small cell lung cancer [47] that recently met its accrual goal.

In summary, this population-based study of the effect of metformin on survival in HNC demonstrated that diabetic patients taking metformin experienced significant prolongation in cancer-specific survival and nonsignificant prolongation of overall survival as compared to both nondiabetic patients and diabetic patients not taking metformin. Moreover, metformin was not associated with excess treatment-related toxicity. These findings therefore justify current prospective investigations adding metformin to standard-of-care therapy in HNC.

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SEER cases of HNC diagnosed 2008-2011
(12,367)

unknown date of diagnosis
(41)

negative survival time
(<11)

diagnosis on autopsy or death certificate
(<11)

inadequate Medicare claims data
(10,320)

no definitive therapy
(277)

missing covariate data
(80)

taking metformin without DM diagnosis
(<11)

Final Sample (1,646)

- nD (1,144)
- DnM (378)
- D+M (124)

Fig. 1. Cohort Derivation. Abbreviations: SEER, Surveillance, Epidemiology, and End Results; HNC, head and neck cancer; DM, diabetes mellitus; nD, non-diabetic; DnM, diabetic not taking metformin; D + M diabetic taking metformin.

Fig. 2.

(A) Overall Survival and (B) Cancer-Specific Survival. Abbreviations: nD, non-diabetic; DnM, diabetic not taking metformin; D + M diabetic taking metformin.

Patient Characteristics (χ^2).

Table 1

	All Patients			nD			DnM			D + M			p (D + M v nD)		p (D + M v DnM)	
	N	%	n	%	n	%	n	%	n	%	n	%				
All Patients	1646	100.0	1144	100.00	378	100.0	124	100.0								
Age																
66-69	400	24.3	286	25.0	84	22.2	30	24.2					0.85		0.84	
70-74	455	27.6	325	28.4	97	25.7	33	26.6								
75+	791	48.1	533	46.6	197	52.1	61	49.2								
Sex																
Female	682	41.4	490	42.8	150	39.7	42	33.9					0.05		0.25	
Male	964	58.6	654	57.2	228	60.3	82	66.1								
Race																
White Non-Hispanic	1318	80.1	949	83.0	279	73.8	90	72.6					<0.01		0.79	
Non-White or Hispanic	328	19.9	195	17.1	99	26.2	34	27.4								
Marital Status																
Non-Married	892	54.2	619	54.1	218	57.7	55	44.4					0.04		0.01	
Married	754	45.8	525	45.9	160	42.3	69	55.7								
Geographic Region																
East	277	16.8	175	15.3	77	20.4	25	20.2					0.46		0.65	
Midwest	208	12.6	143	12.5	53	14.0	12	9.7								
South	452	27.5	316	27.6	101	26.7	35	28.2								
West	709	43.1	510	44.6	147	38.9	52	41.9								
Population Density																
Metropolitan	1305	79.3	897	78.4	301	79.6	107	86.3					0.04		0.10	
Non-Metropolitan	341	20.7	247	21.6	77	20.4	17	13.7								
Year of Diagnosis																
2008	382	23.2	264	23.1	89	23.5	29	23.4					0.84		0.55	
2009	394	23.9	269	23.5	96	25.4	29	23.4								
2010	394	23.9	279	24.4	81	21.4	34	27.4								
2011	476	28.9	332	29.0	112	29.6	32	25.8								
Primary Site																
Oral Cavity	835	50.7	583	51.0	180	47.6	72	58.1					0.29		0.05	
Oropharynx	585	35.5	397	34.7	153	40.5	35	28.2								
Other	226	13.7	164	14.3	45	11.9	17	13.7								
T-Classification																
T0-1	472	28.7	344	30.1	95	25.1	33	26.6					0.15		0.57	
T2	489	29.7	330	28.9	118	31.2	41	33.1								
T3-4	467	28.4	330	28.9	109	28.8	28	22.6								
Unknown	218	13.2	140	12.2	56	14.8	22	17.7								

	All Patients			nD			DnM			D + M			<i>p</i> (D + M v nD)	<i>p</i> (D + M v DnM)
	N	%	n	%	n	%	n	%	n	%	n	%		
N-Classification														
N0	910	55.3	625	54.6	211	55.8	74	59.7	0.41	0.52				
N1	281	17.1	197	17.2	62	16.4	22	17.7	.	.				
N2-3	455	27.6	322	28.2	105	27.8	28	22.6	.	.				
Comorbidity Index														
0	1037	63.0	766	67.0	191	50.5	80	64.5	0.58	0.01				
1+	609	37.0	378	33.0	187	49.5	44	35.5	.	.				
Teaching Hospital														
No or Unknown	748	45.4	519	45.4	178	47.1	51	41.1	0.37	0.25				
Yes	898	54.6	625	54.6	200	52.9	73	58.9	.	.				
Tract % High School Only														
Median	823	50.0	583	51.0	174	46.0	66	53.2	0.63	0.16				
> Median	823	50.0	561	49.0	204	54.0	58	46.8	.	.				
Tract % Below Poverty														
Median	824	50.1	587	51.3	169	44.7	68	54.8	0.46	0.05				
> Median	822	49.9	557	48.7	209	55.3	56	45.2	.	.				
Surgery														
No	673	40.9	459	40.1	164	43.4	50	40.3	0.97	0.55				
Yes	973	59.1	685	59.9	214	56.6	74	59.7	.	.				
Chemotherapy														
No	902	54.8	632	55.2	201	53.2	69	55.7	0.93	0.63				
Yes	744	45.2	512	44.8	177	46.8	55	44.4	.	.				
Radiotherapy														
No	578	35.1	408	35.7	124	32.8	46	37.1	0.75	0.38				
Yes	1068	64.9	736	64.3	254	67.2	78	62.9	.	.				
ACEi/ARB														
No	1069	65.0	794	69.4	233	61.6	42	33.9	<0.01	<0.001				
Yes	577	35.1	350	30.6	145	38.4	82	66.1	.	.				
Statin														
No	1061	64.5	795	69.5	225	59.5	41	33.1	<0.01	<0.01				
Yes	585	35.5	349	30.5	153	40.5	83	66.9	.	.				
HTN/CKD ^a														
No	<398	<24.2	343	30.0	44	11.6	<11	<8.9	<0.01	0.06				
Yes	>1248	>75.8	801	70.0	334	88.4	>113	>91.1	.	.				
HLD														
No	550	33.4	451	39.4	78	20.6	21	16.9	<0.01	0.37				
Yes	1096	66.6	693	60.6	300	79.4	103	83.1	.	.				

Abbreviations: NH, non-Hispanic; nD, non-diabetic; DnM, diabetic not taking metformin; D + M diabetic taking metformin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTN, hypertension; CKD, chronic kidney disease; HLD, hyperlipidemia;

^aData coarsened to comply with CMS cell size suppression policy.

Overall Survival.

Table 2

		Kaplan-Meier			Cox UVA			Cox MVA		
		OS2 (%)	95%CI (%)	p	HR	95%CI	p (class)	HR	95%CI	p (class)
Diabetes/Metformin Category	D + M	73.4	64.7–80.3	< 0.01	.	.	.	.	.	0.11
	nD	65.6	62.8–68.3	.	1.37	0.96–1.96	0.08	1.13	0.78–1.65	0.53
Age	DnM	57.7	52.5–62.5	.	1.79	1.23–2.60	< 0.01	1.36	0.92–2.00	0.12
	66–69	72.5	67.8–76.6	< 0.01	.	.	.	.	.	< 0.01
	70–74	73.6	69.3–77.4	.	0.96	0.74–1.24	0.75	1.06	0.82–1.38	0.65
	75+	55.0	51.5–58.4	.	1.87	1.51–2.32	< 0.01	2.06	1.64–2.59	< 0.01
Sex	Male	66.0	62.9–68.9	0.13	.	.	.	.	.	0.43
	Female	62.2	58.4–65.7	.	1.13	0.96–1.33	0.13	1.08	0.90–1.29	0.43
Race/Ethnicity	White Non-Hispanic	65.1	62.5–67.6	0.30	.	.	.	.	.	0.40
	Non-White or Hispanic	61.6	56.1–66.6	.	1.11	0.91–1.35	0.30	0.91	0.73–1.13	0.40
Marital Status	Married	72.7	69.3–75.7	< 0.01	.	.	.	.	.	< 0.01
	Non-Married	57.4	54.1–60.6	.	1.74	1.47–2.06	< 0.01	1.43	1.19–1.72	< 0.01
Geographic Region	West	64.0	60.4–67.4	0.40	.	.	.	.	.	0.48
	East	66.1	60.2–71.3	.	0.94	0.74–1.19	0.63	0.81	0.62–1.07	0.14
	Midwest	68.8	62.0–74.6	.	0.86	0.66–1.13	0.29	0.88	0.64–1.21	0.43
	South	61.9	57.3–66.2	.	1.08	0.89–1.32	0.41	0.88	0.70–1.11	0.28
Population Density	Metropolitan	64.8	62.2–67.4	0.35	.	.	.	.	.	0.67
	Non-Metropolitan	62.8	57.4–67.6	.	1.10	0.90–1.33	0.36	0.95	0.75–1.20	0.67
Year of Diagnosis	2008	62.8	57.8–67.5	0.64	.	.	.	.	.	0.37
	2009	64.0	59.0–68.5	.	0.95	0.75–1.20	0.67	0.94	0.74–1.19	0.60
	2010	63.7	58.7–68.2	.	0.97	0.77–1.22	0.79	1.00	0.79–1.26	0.97
	2011	66.6	62.2–70.6	.	0.87	0.69–1.09	0.23	0.83	0.66–1.05	0.12
Primary Site	Oral Cavity	68.1	64.9–71.2	< 0.01	.	.	.	.	.	0.06
	Oropharynx	62.4	58.3–66.2	.	1.24	1.04–1.49	0.02	0.75	0.60–0.95	0.02
T-Classification	Other	55.8	49.0–61.9	.	1.54	1.23–1.94	< 0.01	0.87	0.67–1.13	0.29
	T0–1	80.3	76.4–83.6	< 0.01	.	.	.	.	.	< 0.01
	T2	64.0	59.6–68.1	.	2.00	1.55–2.57	< 0.01	2.00	1.10–3.64	0.02

		Kaplan-Meier			Cox UVA			Cox MVA		
		OS2 (%)	95%CI (%)	p	HR	95%CI	p (class)	HR	95%CI	p (class)
	T3-4	47.3	42.7-51.8	.	3.48	2.74-4.42	<0.01	5.67	3.21-10.0	<0.01
	Unknown	67.4	60.8-73.2	.	1.88	1.38-2.55	<0.01	4.31	2.22-8.37	<0.01
N-Classification	N0	71.8	68.7-74.6	<0.01	.	.	.	.	.	.
	N1	56.2	50.2-61.8	.	1.72	1.39-2.14	<0.01	1.58	1.24-2.01	<0.01
	N2-3	54.7	50.0-59.2	.	1.80	1.50-2.17	<0.01	1.78	1.42-2.25	<0.01
	0	70.5	67.6-73.2	<0.01	.	.	.	.	.	<0.01
Comorbidity Index		54.0	50.0-57.9	.	1.80	1.53-2.12	<0.01	1.69	1.42-2.01	<0.01
Tract % High School Only	Median	66.8	63.5-69.9	0.02	.	.	.	.	.	0.02
	> Median	62.0	58.6-65.2	.	1.21	1.02-1.42	0.02	1.29	1.05-1.59	0.02
Tract % Below Poverty	Median	68.2	64.9-71.3	<0.01	.	.	.	.	.	0.45
	> Median	60.6	57.2-63.8	.	1.32	1.12-1.55	<0.01	1.08	0.89-1.30	0.45
	No or Unknown	61.1	57.5-64.5	0.01	.	.	.	.	.	0.02
Teaching Hospital		67.1	64.0-70.1	.	0.80	0.68-0.95	0.01	0.81	0.68-0.96	0.02
Surgery	Yes	51.9	48.0-55.6	<0.01	.	.	.	.	.	<0.01
	No	73.1	70.2-75.7	.	0.48	0.40-0.56	<0.01	0.54	0.43-0.67	<0.01
Chemotherapy	No	69.0	65.8-71.9	<0.01	.	.	.	.	.	0.35
	Yes	58.9	55.2-62.3	.	1.40	1.19-1.64	<0.01	0.90	0.72-1.12	0.35
Radiotherapy	No	74.2	70.5-77.6	<0.01	.	.	.	.	.	<0.01
	Yes	59.1	56.1-62.0	.	1.70	1.41-2.04	<0.01	0.43	0.28-0.65	<0.01
ACEi or ARB	No	61.2	58.2-64.0	<0.01	.	.	.	.	.	0.51
	Yes	70.4	66.5-73.9	.	0.73	0.61-0.88	<0.01	1.13	0.78-1.65	0.51
Statin	No	60.3	57.3-63.2	<0.01	.	.	.	.	.	0.01
	Yes	71.8	68.0-75.3	.	0.66	0.55-0.79	<0.01	0.75	0.62-0.93	0.01
HTN/CKD	No	67.8	62.9-72.1	0.07	.	.	.	.	.	0.15
	Yes	63.3	60.6-65.9	.	1.20	0.98-1.46	0.07	1.18	0.94-1.48	0.15
HLD	No	58.7	54.5-62.7	<0.01	.	.	.	.	.	0.05
	Yes	67.2	64.4-69.9	.	0.75	0.63-0.88	<0.01	0.82	0.68-1.00	0.05

Abbreviations: OS2, 2-year overall survival; 95%CI, 95% confidence interval; HR, hazard ratio; UVA, univariate analysis; MVA, multivariate analysis; nD, non-diabetic; DnM, diabetic not taking metformin; D + M diabetic taking metformin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTN, hypertension; CKD, chronic kidney disease; HLD, hyperlipidemia.

Cancer-Specific Survival.

Table 3

		Kaplan-Meier			Cox UVA			Cox MVA		
		CSS2 (%)	95%CI (%)	p	HR	95%CI	p (class)	HR	95%CI	p (class)
Diabetes/Metformin Category	D + M	88.8	79.2–94.1	<0.01	.	.	.	.	.	<0.01
	nD	73.7	70.3–76.8	.	2.54	1.30–4.95	0.01	2.33	1.16–4.65	0.02
Age	DnM	66.1	59.6–71.8	.	3.50	1.76–6.97	<0.01	3.03	1.49–6.16	<0.01
	66–69	77.6	71.9–82.2	<0.01	.	.	.	.	.	<0.01
	70–74	78.0	72.8–82.3	.	0.99	0.70–1.40	0.95	1.04	0.73–1.50	0.82
	75+	67.7	63.2–71.7	.	1.56	1.16–2.10	<0.01	1.77	1.29–2.44	<0.01
Sex	Male	76.6	72.9–79.9	0.01	.	.	.	.	.	<0.01
	Female	68.6	64.0–72.7	.	1.38	1.09–1.74	0.01	1.55	1.19–2.02	<0.01
Race/Ethnicity	White Non-Hispanic	74.8	71.7–77.7	0.04	.	.	.	.	.	0.77
	Non-White or Hispanic	66.1	59.0–72.4	.	1.33	1.01–1.74	0.04	1.05	0.77–1.42	0.77
Marital Status	Married	79.8	75.8–83.1	<0.01	.	.	.	.	.	0.12
	Non-Married	67.5	63.3–71.3	.	1.70	1.33–2.17	<0.01	1.24	0.95–1.63	0.12
Geographic Region	West	70.7	66.2–74.7	0.08	.	.	.	.	.	0.12
	East	75.6	68.6–81.3	.	0.81	0.58–1.14	0.22	0.68	0.46–1.02	0.06
	Midwest	82.6	74.6–88.2	.	0.60	0.38–0.94	0.02	0.60	0.36–1.00	0.05
	South	71.4	65.7–76.4	.	1.02	0.77–1.34	0.92	0.77	0.55–1.08	0.12
Population Density	Metropolitan	73.5	70.3–76.4	0.41	.	.	.	.	.	0.78
	Non-Metropolitan	71.7	65.1–77.2	.	1.12	0.85–1.49	0.42	0.95	0.68–1.34	0.78
Year of Diagnosis	2008	73.8	68.9–78.1	0.87	.	.	.	.	.	0.90
	2009	72.3	67.4–76.5	.	1.07	0.81–1.42	0.61	1.06	0.80–1.42	0.68
	2010	73.8	67.5–79.1	.	1.02	0.76–1.37	0.92	1.06	0.78–1.44	0.70
Primary Site	Oral Cavity	77.0	73.1–80.4	<0.01	.	.	.	.	.	0.01
	Oropharynx	70.5	65.4–75.0	.	1.40	1.08–1.82	0.01	0.62	0.45–0.85	<0.01
T-Classification	Other	65.5	57.2–72.5	.	1.68	1.22–2.32	<0.01	0.71	0.49–1.02	0.06
	T0–1	89.1	85.1–92.1	<0.01	.	.	.	.	.	<0.01
	T2	69.8	63.9–74.9	.	2.98	2.01–4.42	<0.01	1.95	0.77–4.92	0.16
	T3–4	56.7	50.6–62.3	.	5.36	3.68–7.80	<0.01	7.62	3.17–18.3	<0.01

	Kaplan-Meier			Cox UVA			Cox MVA		
	CSS2 (%)	95%CI (%)	p	HR	95%CI	p (class)	HR	95%CI	p (class)
N-Classification	Unknown	74.6	66.5–81.1	.	2.74	1.73–4.36	5.20	1.91–14.2	< 0.01
	N0	80.9	77.5–83.9	<0.01	.	.	.	.	.
	N1	63.7	55.8–70.6	.	2.14	1.57–2.91	1.63	1.15–2.31	0.01
	N2–3	62.6	56.6–68.0	.	2.21	1.69–2.88	1.80	1.30–2.49	< 0.01
Comorbidity Index	0	76.1	72.6–79.2	<0.01	.	.	.	.	0.04
	1+	67.8	62.7–72.5	.	1.47	1.16–1.86	1.31	1.02–1.69	0.04
Tract % High School Only	Median	76.0	75.0–79.6	0.01	.	.	.	.	< 0.01
	> Median	70.2	66.1–73.9	.	1.39	1.10–1.76	1.56	1.15–2.11	< 0.01
Tract % Below Poverty	Median	78.6	74.7–81.9	<0.01	.	.	.	.	0.24
	> Median	67.7	63.5–71.6	.	1.66	1.30–2.10	1.19	0.89–1.58	0.24
Teaching Hospital	No or Unknown	69.4	65.0–73.3	0.01	.	.	.	.	0.13
	Yes	76.3	72.5–79.7	.	0.72	0.57–0.91	0.82	0.64–1.06	0.13
Surgery	No	58.6	53.6–63.2	<0.01	.	.	.	.	< 0.01
	Yes	83.0	79.8–85.8	.	0.34	0.26–0.43	0.42	0.30–0.58	< 0.01
Chemotherapy	No	80.4	76.8–83.4	<0.01	.	.	.	.	0.74
	Yes	64.5	59.9–68.7	.	1.92	1.51–2.44	1.06	0.77–1.44	0.74
Radiotherapy	No	85.4	81.3–88.6	<0.01	.	.	.	.	0.05
	Yes	66.3	62.5–69.8	.	2.50	1.86–3.36	0.53	0.28–1.01	0.05
ACEi or ARB	No	71.0	67.3–74.3	0.04	.	.	.	.	0.52
	Yes	77.0	72.3–81.0	.	0.77	0.60–0.99	0.91	0.69–1.21	0.52
Statin	No	69.2	65.5–72.6	<0.01	.	.	.	.	0.09
	Yes	80.1	75.6–83.8	.	0.61	0.47–0.80	0.77	0.57–1.04	0.09
HTN/CKD	No	75.7	69.9–80.5	0.29	.	.	.	.	0.21
	Yes	72.3	68.9–75.3	.	1.16	0.88–1.54	1.23	0.89–1.71	0.21
HLD	No	69.1	63.9–73.7	0.03	.	.	.	.	0.21
	Yes	75.2	71.7–78.2	.	0.77	0.60–0.97	0.83	0.63–1.11	0.21

Abbreviations: CSS2, 2-year cancer-specific survival; 95%CI, 95% confidence interval; HR, hazard ratio; UVA, univariate analysis; MVA, multivariate analysis; nD, non-diabetic; DnM, diabetic not taking metformin; D + M diabetic taking metformin; NH, non-Hispanic; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HTN, hypertension; CKD, chronic kidney disease; HLD, hyperlipidemia.

Toxicity Incidence.

Table 4

	All Patients			nD			DnM			D + M			<i>p</i> (D + M v nD)			<i>p</i> (D + M v DnM)		
	N	%	n	N	%	n	N	%	n	N	%	n						
All Patients	–	1646	100.0	1144	100.0	378	100.0	124	100.0									
Weight Loss	No	1078	65.5	764	66.8	233	61.6	81	65.3				0.74			0.46		
	Yes	568	34.5	380	33.2	145	38.4	43	34.7									
Antiemetic Prescription	No	875	53.2	603	52.7	209	55.3	63	50.8				0.69			0.38		
	Yes	771	46.8	541	47.3	169	44.7	61	49.2									
ED Visit	No	1161	70.5	818	71.5	262	69.3	81	65.3				0.15			0.41		
	Yes	485	29.5	326	28.5	116	30.7	43	34.7									
Hospital/ED Visit w/Nausea/Emesis	No	1360	82.6	944	82.5	312	82.5	104	83.9				0.71			0.73		
	Yes	286	17.4	200	17.5	66	17.5	20	16.1									
Hospital/ED Visit w/Dehydration	No	1201	73.0	834	72.9	277	73.3	90	72.6				0.94			0.88		
	Yes	445	27.0	310	27.1	101	26.7	34	27.4									
Hospital/ED Visit w/Malnutrition	No	1225	74.4	857	74.9	275	72.8	93	75.0				0.98			0.62		
	Yes	421	25.6	287	25.1	103	27.3	31	25.0									
Gastrostomy or Feeding Tube	No	1015	61.7	718	62.8	224	59.3	73	58.9				0.40			0.94		
	Yes	631	38.3	426	37.2	154	40.7	51	41.1									
Dysphagia	No	866	52.6	618	54.0	187	49.5	61	49.2				0.31			0.96		
	Yes	780	47.4	526	46.0	191	50.5	63	50.8									
Tracheostomy or Airway Obstruction	No	1225	74.4	852	74.5	274	72.5	99	79.8				0.19			0.10		
	Yes	421	25.6	292	25.5	104	27.5	25	20.2									
Speech Pathology	No	1343	81.6	937	81.9	305	80.7	101	81.5				0.90			0.85		
	Yes	303	18.4	207	18.1	73	19.3	23	18.6									

Abbreviations: ED, emergency department; nD, non-diabetic; DnM, diabetic not taking metformin; D + M diabetic taking metformin.