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The Influence of Diabetes Mellitus and Metformin on Distant Metastases in Oropharyngeal Cancer: A Multicenter Study

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Abstract

Purpose—Local control in oropharyngeal cancer has improved to unprecedented rates with combined modality therapy, and as a result distant metastases are becoming a principle challenge. We aimed to determine the impact of diabetes mellitus and metformin use on clinical outcomes in a large population of oropharyngeal cancer patients treated in the modern era.

Materials and Methods—We identified 1,745 consecutive patients with oropharyngeal cancer treated at two large cancer centers with external beam radiotherapy from 1998–2011. A total of 184 patients had diabetes mellitus at time of diagnosis, of which 102 were taking metformin. Outcomes assessed included local failure-free survival (LFFS), regional failure-free survival (RFFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Results—Median follow-up was 4.3 years, and the 5-year actuarial rates of DMFS were 89.6% for non-diabetics and 78.7% for diabetic non-metformin users ($p=0.011$), and OS were 83.0% for non-diabetics and 70.7% for diabetic non-metformin users ($p=0.048$). Diabetic metformin users had similar 5-year DMFS (90.1%) and OS (89.6%) to non-diabetics. Multivariate analysis (diabetic non-metformin as reference) demonstrated improved DMFS for non-diabetic patients (0.54 [0.32–0.93], $p=0.03$) and a trend towards improved DMFS with metformin use (Hazard Ratio

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0.46 [95% CI 0.20-1.04], $p=0.06$). LFFS and RFFS were high in all groups and were not significantly different by diabetic status or metformin use.

Conclusions—Diabetic patients not using metformin independently have significantly higher rates of distant metastases than non-diabetic patients, whereas metformin users have similar rates of distant metastases to non-diabetics. Further prospective investigation is warranted to validate metformin's benefit in oropharyngeal cancer.

Keywords

metformin; diabetes; cancer; oropharyngeal cancer; head and neck

Introduction

The epidemiology and management of oropharyngeal squamous cell carcinoma (OPSCC) have dramatically transformed over the last two decades. The epidemic of human papillomavirus (HPV)-positive oropharynx cancer is demonstrated by an estimated 225% increase in prevalence from 1988 to 2004.¹ Simultaneously, the incidence of HPV-negative tumors, often associated with tobacco use, have decreased by 50%. During the same time period, definitive combined modality therapy with concurrent chemotherapy and intensity modulated radiotherapy (IMRT) has emerged as a standard of care for head and neck cancers, including OPSCC.^{2,3} This change in oropharyngeal tumor biology, in combination with improved treatment, has resulted in unprecedented locoregional control (LRC) rates of 80%-90% of HPV-positive OPSCC.⁴⁻⁶ However, despite these improvements, about 35% of these patients experienced progression or death within 8 years of treatment in RTOG 0129.⁴ This is partly attributable to the fact that distant metastasis (DM) rates are not significantly impacted by HPV status. Thus, therapies that prevent DM in OPSCC are being sought, especially in the setting of excellent locoregional control rates.

Although the mechanisms of tumor evolution are complex, the importance of the host microenvironment, including metabolic processes, on survival and metastasis is being increasingly recognized. There is data to suggest that the presence of diabetes mellitus, an aberrant host metabolic state, confers worse oncologic outcomes compared to non-diabetic patients in numerous cancer types.⁷ This is hypothesized to occur due to the increase in multiple growth factors that promote cancer formation and tumor aggressiveness.^{8,9} These findings have sparked interest into pharmacologic methods to inhibit aberrant pathways of metabolism. One promising agent is metformin, an oral anti-hyperglycemic agent that has been shown to possess cytotoxic anti-tumor effects. In preclinical studies, metformin has been shown to decrease proliferation and increase apoptosis of many cancer cells lines, including head and neck squamous cell carcinomas (HNSCC).¹⁰⁻¹⁴ Additionally, metformin has been shown to potentiate the effects of radiotherapy in the presence of a disruptive TP53 mutations, thus making it an attractive agent for combination therapy.¹⁰

Supporting this preclinical data, multiple clinical studies have suggested improved cancer outcomes in diabetic patients taking metformin, primarily in breast and prostate cancer.^{15,16} Although several recent studies have examined the potential clinical impact of metformin use in HNSCC, these studies have had somewhat conflicting results and have been

comprised of heterogeneous patient cohorts with primary tumors from a variety of anatomic sites.^{17,18} Herein, we report the first investigation assessing the impact of diabetes and use of metformin on cancer outcomes in OPSCC. A pooled cohort of 1,745 patients from two large cancer centers in the United States undergoing modern treatment with external beam radiation therapy (EBRT) for OPSCC were identified, and oncologic outcomes are reported and compared between non-diabetic, diabetic non-metformin, and diabetic metformin using patients.

Methods

Study Details

After institutional review board approval, a data transfer agreement was approved by both institutions to conduct the present study. Consecutive patients with non-metastatic oropharyngeal cancer treated with definitive EBRT from 1998 to 2011 at two institutions, XXXX Cancer Center and XXXXX Cancer Center, were identified from a prospectively maintained database or retrospectively by pathology from a tumor registry database, based on the treating institution. Individual patient identifiers were deidentified and then transferred into a centralized database.

All patients had biopsy proven squamous cell carcinoma with pathology reviewed by an expert pathologist at the respective institutions. Patients were required to have definitive EBRT rather than surgery, no prior history of head and neck cancer, and non-metastatic disease at time of treatment assessed by baseline CT, PET/CT, and/or MRI. Additionally, patients that developed diabetes after the diagnosis of their oropharyngeal cancer were removed from all analyses to avoid time-dependent confounding. The remaining 1,745 patients form the study cohort for analysis (998 and 747 patients from the above institutions, respectively). In general, patients were followed every 2-3 months from the time of completion of EBRT for the two years, followed by every 4-6 months thereafter.

Treatment

Treatment was determined by institutional guidelines and multidisciplinary head and neck management teams. The EBRT details of the treating institutions have been previously reported in depth, but generally consisted of approximately 7000 cGy in 33-35 fractions using intensity modulated radiotherapy (IMRT) to the primary tumor (median of 6996 cGy), with tapered doses to the lower risk areas. Chemotherapy was prescribed at the discretion of the treating physician. Definitive surgical resection of the primary tumor was an exclusion criteria, but patients who underwent diagnostic excisional biopsy, tonsillectomy, or neck dissection were included.

Endpoint and Co-variate Definitions

Outcomes were calculated from the end date of radiation therapy. The outcomes measured included local failure-free survival (LFFS), regional failure-free survival (RFFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Diabetes was determined as reported by the patient at time of consultation and was considered a binary variable. Patient who developed diabetes after time of diagnoses were excluded from analysis to avoid need for a time-dependent analysis. The type of diabetic medication patients were on was retrospectively captured from the medical record. Of note, 12 patients had diet controlled diabetes. All patients who were on metformin from time of diagnosis continued for a minimum of 5 years (or death or last follow-up if less than 5 years).

Patients were staged according to the 2010 American Joint Committee on Cancer (AJCC) criteria, for both T and N stage which were analyzed as ordinal variables. Tumors were classified by their site of origin within the oropharynx (tonsil, base of tongue, soft palate, pharyngeal wall, and “other” which includes tumors of uncertain subsite within the oropharynx). Smoking status was categorized as never, former, current, or unknown, and pack-years were calculated for those with a smoking history. HPV and/or p16 data were available in a subset of patients (n=595, 34%) and were dichotomized into positive or negative based on institutional standards. p16 positivity was defined as strong and diffuse immunohistochemical nuclear and cytoplasmic staining in 70% or more of the tumor cells.

Statistical Analysis

To compare baseline characteristics between groups, the chi-square test and fisher-exact test were used for categorical variables, and the Wilcoxon rank-sum test for continuous variables. Actuarial survival-time curves for LFFS, RFFS, DMFS, and OS were calculated using the Kaplan-Meier method, and comparisons were performed using a log-rank test. Time-dependent analyses were not conducted as patients were required to have diabetes at time of diagnosis of their oropharyngeal cancer, patients who developed diabetes post-treatment were excluded, and metformin was continued for a minimum duration of 5-years (approximate median follow-up and time point for reporting of results) or if the duration was unconfirmed, patients were encouraged to continue all diabetes medication during radiotherapy and post-treatment. Univariate hazard ratios (HR) and 95% confidence intervals (CI) were performed using a Cox proportional hazards model, and multivariate analyses were performed using Cox regression. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 21 (SPSS, Inc, USA).

Results

Clinical and treatment characteristics

The median age of the entire cohort was 56 years old (range, 25-91; **Table 1**). Most patients were male (87.1%, n=1520), and had cancers of the tonsil (46.1%, n=805) or base of tongue (48.2%, n=841). Smoking status was known for 99.4% (n=1735) of patients, with 39.7% (n=692) being former smokers, and 18.7% (n=327) were current smokers. The median number of pack-years for all smokers was 17 (IQR 2-38). Sixty-eight percent (n=1185) of patients had T1 or T2 tumors, and 70% (n=1220) had N2 or N3 disease. There were 1561 (89.5%) non-diabetic patients, 82 (4.7%) diabetic patients not on metformin, and 102 (5.8%) diabetics using metformin at time of diagnosis and treatment of their oropharyngeal cancer.

There were no significant differences in baseline characteristics or treatment between groups with the exception of non-diabetics being of younger age ($p=0.001$). Diabetic medication use other than metformin can be found in **Supplementary Table 1**.

HPV or p16 status was known for 595 patients (**Table 1**), and 83.4% of patients with known HPV/p16 status were positive for one of the biomarkers. There were no significant differences across groups (diabetic metformin, non-metformin, and non-diabetic patients) regarding either HPV ($p=0.56$) or p16 ($p=0.16$) status.

Local Failure-Free Survival and Regional Failure-Free Survival

The 5-year actuarial rates of LFFS for diabetic non-metformin, diabetic metformin, and non-diabetic patients were 94.1%, 94.1%, and 93.7%, respectively, and were not significantly different between groups ($p=0.90$ and 0.74 for diabetic non-metformin vs. metformin, and non-metformin vs non-diabetics; **Table 2, Figure 1A**). The 5-year actuarial rates of RFFS for diabetic non-metformin, diabetic metformin, and non-diabetic patients were 93.4%, 93.2%, and 94.4%, respectively, and were not significantly different between groups ($p=0.96$ and 0.74 for diabetic non-metformin vs. metformin, and non-metformin vs non-diabetics; **Figure 1B**).

Distant Metastases-Free Survival

The 5-year actuarial rates of DMFS for diabetic non-metformin, diabetic metformin, and non-diabetic patients were 78.7, 90.1%, and 89.6%, respectively (**Table 2, Figure 2A**). Diabetic non-metformin patients had worse DMFS than non-diabetic patients ($p=0.011$). Diabetic non-metformin users had worse, albeit not statistically significant, DMFS than diabetic metformin users ($p=0.10$). There was no difference in DMFS between non-diabetic patients and diabetic metformin users ($p=0.99$).

On univariate analysis, factors associated with increased distant metastasis rates included age (HR 1.02 [95% CI 1.01-1.04], $p=0.003$), higher T-stage (HR 1.15 [1.06-1.24], $p<0.001$), higher N-stage (HR 1.08 [1.01-1.17], $p=0.04$), and use of definitive intent chemotherapy (HR 1.80 [1.19-2.70], $p=0.01$). Additionally, compared with diabetic non-metformin users, non-diabetic patients had a significantly reduced rate of distant metastases (HR 0.51 [0.29-0.86], $p=0.01$). Metformin users had a similar hazard reduction for distant metastases as non-diabetics in comparison to diabetic patients not using metformin, but this did not reach statistical significance (HR 0.51 [0.22-1.16], $p=0.11$). There was no difference in DMFS between non-diabetic patients and metformin users (HR 0.99 [0.51-1.96], $p=0.99$).

Using multivariate analysis to correct for confounding variables between groups, non-diabetic patients continued to have a significant reduction in distant metastasis rates (adjusted Hazard Ratio (AHR) 0.54 [0.32-0.93], $p=0.03$) compared to diabetic non-metformin patients. Additionally, the use of metformin was associated with a trend toward reduced distant metastases compared with diabetic non-metformin patients (AHR 0.46 [0.20-1.04], $p=0.06$).

Due to the limited number of patients in each group with HPV/p16 status annotated, this was not included in the MVA. However we sought to determine the impact HPV/p16 status on

DMFS. Actuarial 3-year rates of DMFS for both HPV/p16 positive (91.8%), unknown (90.6%) or negative (85.4%) patients were not significantly different (**Figure 3**, overall log-rank $p=0.23$), consistent with the known literature, nor were there baseline statistically significant differences of HPV/p16 status by group (**Table 1**).

Overall Survival

The 5-year actuarial rates of OS for diabetic non-metformin, diabetic metformin, and non-diabetic patients were 70.7, 82.3%, and 83.0%, respectively (**Table 2, Figure 2B**). Diabetic non-metformin patients had significantly worse OS than non-diabetic patients ($p=0.048$), but not diabetic metformin users ($p=0.31$).

On univariate analysis, factors associated with decreased OS included age (HR 1.05 [1.03-1.06], $p<0.001$), higher T-stage (HR 1.15 [1.09-1.21], $p<0.001$), smoking status (HR 1.39 [1.20-1.61], $p<0.001$), and use of definitive intent chemotherapy (HR 1.58 [1.20-2.09], $p<0.001$). Additionally, compared with diabetic non-metformin users, non-diabetic patients had a significantly reduced rate of death (HR 0.64 [0.42-0.99], $p=0.047$), but diabetic metformin users did not have a significant difference compared to diabetic non-metformin users (HR 0.79 [0.43-1.14], $p=0.44$). On multivariate analysis with diabetic non-metformin group as reference, there were no significant differences compared to non-diabetics (AHR 0.76 [0.49-1.17], $p=0.21$), or metformin users (AHR 0.73 [0.40-1.33], $p=0.30$).

Discussion

The importance of metabolic processes in the pathogenesis of cancer are being increasingly elucidated,^{8,9} and deregulation of energy metabolism was recently classified as an “emerging hallmark” of cancer by Hanahan and Weinberg.¹⁹ This perhaps is not surprising, given that cancer cells require tremendous amounts of metabolic fuel to drive their unregulated growth and proliferation. As early as the 1920's, Otto Warburg described the “Warburg effect”,²⁰ whereby cancer cells preferentially obtain ATP through glycolysis rather than oxidative phosphorylation, even in the presence of oxygen. This observation is the basis for FDG-PET imaging of many types of cancers, including OPSCC. However, it is only recently that alterations in metabolism have been understood as a primary driver mechanism underlying oncogenesis, rather than simply a passenger effect of mutations in oncogenes and tumor suppressors.²¹⁻²³ Thus, given the importance of metabolism in oncogenesis, therapies targeting metabolic pathways may have the potential for significant benefit in cancer outcomes.

Metformin has emerged as a leading candidate drug for the modification of metabolic processes in order to improve cancer specific outcomes. Multiple studies have shown that metformin use is associated with a decreased risk of cancer amongst diabetic patients, including head and neck cancer.^{24,25} Further, several retrospective series have suggested that metformin use is associated with improved outcomes in cancer patients.^{15,16,26,27} In fact, a recent small meta-analysis suggested improved outcomes in head and neck cancer patients using metformin.¹⁸ However, another recent study of 1,151 patients with HNSCC showed no impact on overall or cause specific survival with metformin use after adjusting other factors on multivariate analysis.¹⁷ The latter study did not report locoregional or distant recurrence

outcomes and was comprised of head and neck cancers from a variety of anatomic sites, including only 19 patients with OPSCC treated with metformin. Because of this, the impact of metformin on cancer outcomes in OPSCC has been unclear.

This multi-institutional study, representing to our knowledge the largest investigation to date examining the effect of diabetes and metformin on outcome specifically in OPSCC, contributes to the growing body of literature suggesting the metformin may have beneficial effects on cancer outcome in diabetic patients. We show that for patients with OPSCC undergoing definitive radiotherapy, diabetic patients not taking metformin have significantly worse DMFS in comparison to non-diabetic patients. These results hold even after adjusting for stage, age, smoking, and chemotherapy use in multivariate analyses, with non-diabetic patients not taking metformin having approximately twice the risk of DM as non-diabetic patients. By contrast, diabetic patients taking metformin have the same risk of DM as non-diabetic patients. Neither metformin nor diabetes was associated with risk of local or regional recurrence. This finding may merely be a reflection of the excellent local and regional control, and our lack of power to detect any difference.

There are several possible explanations for our data. The first possibility is that metformin itself is an effective anticancer agent, thereby directly helping prevent and eradicate micrometastatic disease in OPSCC and reversing the poor prognosis and aggressive clinical behavior of OPSCC in the setting of diabetes.^{11,13,17,28} Since metformin was (appropriately) not prescribed to non-diabetic patients, it is unclear if non-diabetic patients taking metformin would have an iterative improvement in DMFS and OS, similar to that seen in diabetic patients (metformin vs. non-metformin users). Another hypothesis is that metformin interferes with pathways that are critical to the metastatic phenotype, either by impairing the ability of cells to separate from the primary tumor to extravasate into circulation or by promoting an unfavorable microenvironment at potential host metastatic sites.^{11,13,14} However, given the retrospective nature of this study, an alternative possibility is that the differences in outcome we report between diabetics using or not using metformin are driven by the characteristics of the patients in each subgroup rather than directly by metformin. For example, it is possible that patients with severe diabetes, such as those dependent on insulin, exist in a metabolic state that promotes the formation of distant metastases, and metformin usage is simply a marker for a milder diabetic phenotype that has less effect on the patient's tumor. Additionally, other unmeasured confounding variables may also be driving the differences in DM that we report. Although there is no way to distinguish these hypotheses based on our data, given the wealth of preclinical studies suggesting that metformin has strong antineoplastic activity, we believe that further prospective of the agent even in OPSCC patients with and without diabetes is warranted.

Although the exact mechanism of action of metformin in OPSCC remains unknown, several plausible molecular mechanisms could explain why this agent is deleterious to cancer growth and metastasis. For example, metformin is an activator of AMPK, a kinase that acts as an inhibitor of mTORC1, a critical node of the PI3K-mTOR signaling cascade.²⁹ Supporting this, a recent study demonstrated that metformin does in fact inhibit mTORC1 in OPSCC cell lines, thereby inhibiting cancer cell proliferation *in vitro* and *in vivo*.¹¹ Given that overactivation of the PI3K-mTOR pathway is well established to be a critical driver

oncogenic pathway in HNSCC, evidenced by the fact that over 50% of HPV(+) HNSCCs contain either amplification or mutation of *PIK3CA* in the TCGA dataset,³⁰ mTOR inhibition may be central to metformin's effect on OPSCC. Further pharmacodynamics studies on the impact of metformin use on PI3K signaling in patients would be informative. Additionally, glucose has been shown to a dominant metabolic substrate in HSNCC, and depletion of glucose results in apoptosis in preclinical models of HNSCC.³¹ Thus, metformin may reduce hyperglycemia in diabetic patients, thereby decreasing tumor cells access to this substrate. Other mechanisms, such as promotion of autophagy and down regulation of stem-cell related genes have also been attributed to metformin.^{12,32}

Metformin offers numerous theoretical advantages over standard cancer therapies for OPSCC. First, metformin is a well-tolerated medication, and serious adverse sequelae, such as lactic acidosis, are exceedingly rare.³³ Given that concurrent chemoradiation to the oropharynx and neck is associated with significant acute toxicity,^{34,35} it is important that additional therapies proposed to be used in combination with this regimen do not further exacerbate these side effects; metformin's favorable toxicity profile makes it a very attractive adjunct to chemoradiation in this context. Next, metformin is already an FDA-approved treatment, which will greatly simplify early clinical trial safety studies. Additionally, metformin is an orally available medicine that does not require parenteral administration. Lastly, metformin is a relatively inexpensive medication, an important consideration in an era of exponentially rising health care costs and increasingly limited resources.

The incidence of HPV positivity in OPSCC has increased dramatically in the United States over the past decade,¹ with HPV-positive cancers comprising over 70% of all OPSCC in most modern series, and 83% in the present series. Given that platinum-based chemoradiation has been associated with locoregional control rates in excess of 90% in this cohort,^{5,6} even for patients with locally advanced disease, it is likely that overall prognosis in HPV-positive OPSCC will be increasingly driven by distant recurrence.³⁶ In this context, if metformin was able to reduce DM in diabetic, and perhaps non-diabetic, patients, this could represent a significant adjunctive therapy for this patient population. In fact, metformin is actively being investigated in an ongoing prospective trial in conjunction with chemoradiotherapy for OPSCC (NCT02325401).

Several limitations of this study should be noted. First, as in any retrospective study, we cannot rule out the possibility that unmeasured confounding variables could be unbalanced between the various subgroups and may have influenced the results. Given the importance of HPV status in the prognosis of OPSCC, another significant limitation is that only 34% of patients had either p16 or HPV ISH testing. However, there was no difference in locoregional control between non-diabetics, diabetic patients on metformin, or non-diabetic patients not on metformin. Given the importance of HPV status on LRC in OPSCC, the equivalent outcomes for these subgroups argues against significant differences in HPV status. Additionally, in the patients with known p16 or HPV ISH status, there were no significant difference in either HPV or p16 status across the subgroups. Further, the risk of DM in HPV-positive and HPV-negative OPSCC is roughly equivalent in our study (**Figure 3**) and multiple previous reports,^{4,6} and therefore differences in HPV status should not significantly alter the fundamental conclusion of this paper. An additional limitation is the

use of metformin and diagnosis of diabetes was based on chart review, and the actual dose received could not be calculated. Furthermore, additional co-morbidities and socioeconomic factors were not accounted for and could have had confounding effects. Lastly, although PET/CT staging is a standard staging exam typically used routinely for all patients undergoing treatment for oropharyngeal cancer at our institutions, data on the frequency of PET/CT use was not available in our database, and therefore we cannot completely rule out stage migration as a possible contributing factor to the results we report.

In summary, this multi-institutional study of the effect of metformin on cancer outcome in OPSCC demonstrated diabetic patients not using metformin had higher distant metastases rates than diabetic patients taking metformin (not statistically significant) or non-diabetic (statistically significant) patients. This data is hypothesis generating, and although our study is limited by its retrospective nature and lack of complete HPV status information, it adds to a growing body of literature suggesting that metformin may be beneficial for certain cancer patients. Whether metformin use is merely an indicator of more mild diabetes, or a beneficial cancer therapy will need further prospective evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Local control in oropharyngeal cancer has improved to unprecedented rates with combined modality therapy, and as a result distant metastases are becoming a principle challenge irrespective of HPV status. Herein, we demonstrate that diabetic oropharyngeal cancer patients not using metformin independently have significantly higher rates of distant metastases than non-diabetic patients, while metformin users have similar rates of distant metastases to non-diabetics.

Figure 1.

Kaplan Meier of actuarial rates for (A) local failure-free survival and (B) regional failure-free survival.

Figure 2. Kaplan Meier of actuarial rates for **(A)** distant metastases-free survival and **(B)** overall survival.

Figure 3.

Kaplan Meier of actuarial rates for distant metastases-free survival by HPV/p16 status.

Table 1

Patient and treatment characteristics

Variable	Diabetes						p-value		
	Total	Yes		No					
		Non-Metformin	Metformin	Non-Diabetic					
	n (1745)	%	n (82)	%	n (102)	%	n (1561)	%	
Age									
	Median (range)	56 (25-91)			62 (39-82)		61 (35-79)	56 (25-91)	
Gender									
	Male	1520	87.1	76	92.7	94	92.2	1353	86.7
	Female	225	12.9	6	7.3	8	7.8	208	13.3
Tumor subsite									
	Tonsil	805	46.1	44	53.7	47	46.1	714	45.7
	Base of tongue	841	48.2	35	42.7	48	47.1	758	48.6
	Soft palate	22	1.3	1	1.2	2	2.0	19	1.2
	Pharyngeal wall	61	3.5	2	2.4	5	4.9	54	3.5
	Other	16	0.9	0	0.0	0	0.0	16	1.0
Smoking									
	Never	716	41.0	27	32.9	36	35.3	653	41.8
	Former	692	39.7	39	47.6	48	47.1	605	38.8
	Current	327	18.7	15	18.3	18	17.6	294	18.8
	Unknown	10	0.6	1	1.2	0	0.0	9	0.6
Pack years									
	Median (IQR)	17 (2-38)		15 (3-40)		22 (4-50)		16 (2-35)	
T stage									
	T1	484	27.7	13	15.9	26	25.5	445	28.5
	T2	701	40.2	37	45.1	38	37.3	626	40.1
	T3	296	17.0	19	23.2	19	18.6	258	16.5
	T4	216	12.4	11	13.4	18	17.6	187	12.0
	Tx or unknown	48	2.8	2	2.4	1	1.0	45	2.9

Variable	Diabetes						p-value	
	Total	Yes		No				
		Non-Metformin	Metformin	Non-Diabetic				
	n (1745)	%	n (82)	%	n (102)	%	n (1561)	%
N stage								0.18
N0	305	17.5	18	22.0	11	10.8	276	17.7
N1	120	6.9	6	7.3	7	6.9	107	6.9
N2a	124	7.1	10	12.2	6	5.9	108	6.9
N2b	380	21.8	15	18.3	23	22.5	342	21.9
N2c	533	30.5	25	30.5	38	37.3	470	30.1
N3	183	10.5	6	7.3	12	11.8	165	10.6
Nx or unknown	100	5.7	2	2.4	5	4.9	93	6.0
HPV								0.56
Positive	371	21.3	13	15.9	28	27.5	330	21.1
Negative	139	8.0	4	4.9	7	6.9	128	8.2
Unknown	1235	70.8	65	79.3	67	65.7	1103	70.7
p16								0.16
Positive	366	21.0	12	14.6	30	29.4	324	20.8
Negative	39	2.2	2	2.4	0	0.0	37	2.4
Unknown	1340	76.8	68	82.9	72	70.6	1200	76.9
Dose (Gy)								0.11
Median (IQR)	6996 (6600-7000)		7000 (6848-7125)		6996 (6600-7000)		6820 (6600-7000)	
Chemotherapy								
Yes	1357	77.8	67	81.7	88	86.3	1202	77.0
No	388	22.2	15	18.3	14	13.7	359	23.0
Induction	333	19.1	19	23.2	22	21.6	292	18.7
Concurrent	1089	62.4	57	69.5	69	67.6	1541	98.7

Abbreviations: HPV, Human papilloma virus; IQR, inter-quartile range

Abbreviations: HPV, Human papilloma virus; IQR, inter-quartile range

Table 2

5-year actuarial outcomes

	Diabetic Non-Metformin			Diabetic On Metformin			Non-Diabetic		
	5-year Rate	95% CI		5-year Rate	95% CI		5-year Rate	95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper
LFFS	94.1	88.4	99.8	94.1	89.0	99.2	93.7	92.3	95.1
RFFS	93.4	87.9	98.9	93.2	87.9	98.5	94.4	93.2	95.6
DMFS	78.7	68.9	88.5	90.1	84.0	96.2	89.6	88.0	91.2
OS	70.7	59.7	81.7	82.3	73.7	90.9	83.0	80.8	85.2

Abbreviations: LFFS, local failure-free survival; RFFS, regional failure-free survival; DMFS, distant metastases-free survival; OS, overall survival.

Table 3

Uni- and multivariate analyses for distant metastases

		UVA			MVA		
		HR	95% CI	P-value	AHR	95% CI	P-value
Metformin use	(categorical) Diabetic, Non-metformin	Reference			Reference		
	Metformin	0.51	0.22-1.16	0.11	0.46	0.20-1.04	0.06
	Non-diabetic	0.51	0.29-0.86	0.01	0.54	0.32-0.93	0.03
Age	(continuous)	1.02	1.01-1.04	0.003	1.02	1.00-1.04	0.01
T stage	(ordinal)	1.15	1.06-1.24	<0.001	1.15	1.05-1.25	<0.001
N-stage	(ordinal)	1.08	1.01-1.17	0.04	1.13	1.03-1.24	0.01
Smoking		0.83	0.69-1.01	0.06	0.86	0.71-1.04	0.12
Chemotherapy use	(categorical) None	Reference			Reference		
	Concurrent	1.80	1.19- 2.70	0.01	1.59	1.04- 2.41	0.03
	Induction	0.87	0.41-1.84	0.71	0.73	0.34-1.58	0.42
	Other *	0.98	0.38-2.54	0.96	0.54	0.19-1.56	0.26

Abbreviations: HR, hazard ratio; MVA, multivariate analysis; UVA, univariate analysis

* Adjuvant, or Concurrent plus adjuvant, or induction plus concurrent