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Timing, sites, and correlates of lung cancer recurrence

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Abstract

Introduction: Understanding temporal and anatomic patterns of lung cancer recurrence could guide disease management and monitoring. However, these data are not available in population-based datasets and are not routinely recorded in clinical trials.

Methods: We identified stage 1-3 lung cancer cases diagnosed January 1, 2000, to December 31, 2017, in the tumor registry of a National Cancer Institute-designated comprehensive cancer center. For cases with documented disease recurrence, we recorded anatomic site(s) and timing. We estimated time to recurrence using Kaplan-Meier methods. Associations between case characteristics and recurrence features were assessed using univariable and multivariable logistic regression models and Cox regression models.

Results: 1,619 stage 1-3 lung cancer cases from 1,549 patients were included in the analysis. Of these, 466 patients (30%) developed recurrent lung cancer. The most common type of first recurrence was distant disease, most commonly central nervous system (CNS) (37%). In multivariable analyses, race (P=0.02) and primary treatment modality (P<0.001) correlated with recurrent disease, while tumor histology (P=0.004), and primary treatment modality (P<0.001) were associated specifically with distant recurrence. Patient age (P=0.05) and initial TNM stage (P=0.001) correlated with timing of recurrence.

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The authors have no conflicts of interest to report.

Conclusion: In this single-center series of stage 1-3 lung cancer, recurrent disease was associated with race, histology and treatment modality, and most commonly occurred in the CNS. Modulation of clinical and radiographic disease monitoring according to recurrence risk, timing, and site may offer a means to identify future lung cancer when it remains asymptomatic and highly treatable.

MicroAbstract

Timing and site of lung cancer recurrence are largely unknown. We reviewed 1,619 stage 1-3 lung cancer cases, and analyzed risk, timing, and site of recurrence. We found that distant recurrence occurred earlier than local or regional recurrence, and that the central nervous system was the most common site of recurrence. These findings have implications for disease monitoring and management.

Keywords

latency; metastases; monitoring; surveillance

Introduction

Despite advances in screening, detection, molecular classification, and therapy, lung cancer accounts for almost one-fourth of all cancer-related deaths in the U.S., more than breast, prostate, and colorectal cancer combined.[1,2] Contributing to these poor outcomes is the nature of presentation, with more than 70% diagnosed initially with metastatic disease.[3] Even with aggressive, multi-modality therapy, a substantial proportion of individuals who initially present with localized or locoregional disease eventually succumb to recurrent malignancy.

Given the aging of the U.S. population and the uptake of lung cancer screening, the number of lung cancer cases eligible for and receiving definitive, potentially curative therapy is expected to grow. For this population, which achieves a clinical disease-free state, a thorough understanding of recurrence patterns is essential to optimize post-treatment monitoring. However, to date, obtaining information on patterns of lung cancer recurrence has been hampered by the lack of relevant information in population-based datasets and clinical trials. Surveillance Epidemiology and End Results (SEER), the National Cancer Database (NCDB), and the Veterans Affairs (VA) database do not capture recurrence data such as site or timing. Earlier publications that did characterize disease recurrence focused almost exclusively on stage 1 non-small cell lung cancer (NSCLC),[4–6] which accounts for fewer than 20% of all cases.[7]

Because the nature of disease recurrence has potential relevance to patient management and monitoring, we determined the type and timing of recurrent lung cancer in a diverse population treated at a regional cancer center.

Materials and Methods

Data Extraction

This study was approved by the University of Texas Southwestern Medical Center at Dallas (UT Southwestern) Institutional Review Board (STU 042018-102). Within the UT Southwestern Tumor Registry (which is credentialed by the American College of Surgeons and the American Society of Clinical Oncology), we identified individuals with initial stage 1-3 lung cancer diagnosis between January 1, 2000, and December 31, 2017. We selected this time interval because the relevant clinical data was first consistently collected by the registry in 2000, and because the 2017 cut-off provided at least one-year follow-up for the most recently diagnosed cases. We excluded cases that (1) had incomplete disease information, or (2) never achieved a disease-free state. When necessary, we reviewed individual medical records to clarify registry data abstraction.

Recording and Definition of Variables

For each case, we recorded demographics (sex, age, race/ethnicity), primary tumor characteristics (diagnosis date, tumor-nodes-metastasis [TNM] stage, histology), and treatment modality. Race/ethnicity was categorized as Caucasian, African American, and other. Treatment was categorized as local (surgery and/or radiation therapy) or systemic (chemotherapy alone or in combination with surgery and/or radiation therapy). The UT Southwestern Tumor Registry distinguished second and third primary cases from recurrence based on histology, topography and timing in accordance with NCI SEER guidelines.[8] Recurrence was categorized by tumor registrars as local, regional or distant recurrence based on the North American Association of Central Registries (NAACCR), ACoS – Commission on Cancer and SEER/NCI guidelines as outlined in the Standards for Oncology Registry Entry (STORE) Manual.[9] These categories were defined as follows: local, recurrence in initial primary organ; regional, recurrence in adjacent organ or lymph nodes draining the organ; distant, recurrence in a location beyond regional. For cases with subsequent recurrence, we recorded timing, type (local, regional, distant), and anatomic site. We characterized initial site of distant recurrence as lung (if contralateral to the primary tumor), bone, central nervous system, liver, multiple, and other (distant lymph nodes, skin, peritoneum, pleura, generalized not otherwise specified [NOS], and other).

Statistical Analysis

We generated descriptive statistics (medians and means for continuous variables and percentages for discrete variables) for baseline demographic, tumor, and initial treatment characteristics. We categorized tumor histology as adenocarcinoma, squamous cell carcinoma, non-small cell/other, and small cell. We reported summary statistics for patient characteristics using counts and percentages for categorical variables and using medians and interquartile ranges (IQR) for continuous variables. Univariable and multivariable logistic regression models were used to assess the association between recurrence and case characteristics. Variables with a univariable P-value of ≤ 0.2 were entered in a backward selection algorithm to yield the parsimonious multivariable regression model. When we did not identify differences among the four histology categories, we merged them as small cell vs. other to assess statistical relevance. Time to recurrence was estimated using Kaplan-

Meier methods. Median time to recurrence and 95% confidence intervals (CI) were reported. Univariable and multivariable Cox regression models were used to assess the association between time to recurrence and patient characteristics. Odds ratios (OR) with 95% CI and hazard ratios (HR) with 95% CI were reported. Two-sided *P*-values were reported. A *P*-value <0.05 was considered statistically significant. All data analysis was performed using SAS 9.4 (SAS Institute, NC).

Results

Study Cohort

A total of 1,619 stage 1-3 lung cancer cases from 1,549 patients met inclusion for analysis (Figure 1). These included 1,481 primary lung cancer cases, 132 second primary lung cancer cases, and six third primary lung cancer cases. Within the overall cohort, approximately half were female, half age ≤65 years, and half stage 1. Additional case characteristics are listed in Table 1. A total of 130 cases underwent testing for genomic alterations, of which 11 were found to have a driver mutation.

Lung Cancer Recurrence and Timing

Of the 1,619 analyzed cases, 487 (30%) had recurrent lung cancer. In univariate analysis, age at diagnosis, race, tumor stage, histology, and primary treatment modality were significantly associated with development of recurrent disease. Recurrence developed in 35% of individuals age ≤65 years, compared to 26% for age >65 years (*P*<0.001). African American patients had 25% rate of recurrence, compared to 31% for Caucasian, and 38% for other (*P*=0.02). Recurrence developed in 22% of stage 1 cases, 33% of stage 2 cases, and 40% of stage 3 cases (*P*<0.001). By histology, recurrence rates were 30% for non-small cell and 53% for small cell (*P*<0.001). Among cases receiving systemic chemotherapy, 45% had recurrence, compared to 22% for those receiving local therapy alone (*P*<0.001). In multivariable analysis, likelihood of recurrence remained significantly associated with receipt of chemotherapy and race (Table 2). Specifically, African American patients and those patients not administered chemotherapy had lower likelihood of disease recurrence. To determine whether competing causes of mortality accounted for lower recurrence rates among African American patients, we examined vital status of individuals not developing recurrent disease. Notably, mortality rate was lower among African American patients (29%) than among Caucasian patients (39%).

By five years after diagnosis, more than 90% of eventual recurrences had occurred (Figure 2). This time-course differed according to case characteristics. For stage 2 and 3 lung cancer, 80% of eventual recurrences had occurred by two years, whereas only 60% of stage 1 recurrences had occurred by that time-point. More than 90% of small cell recurrences had occurred by two years, compared to approximately 60% of NSCLC recurrences. Interestingly, timing of recurrence was essentially identical between cases treated with and without chemotherapy for the first 18 months, then subsequently separated. When considering all analyzed cases, race (*P*=0.001), TNM stage (*P*=0.03), histology (*P*=0.02), and primary treatment modality (*P*<0.001) significantly correlated with recurrence timing in multivariable analyses (Supplemental Table 1). Analyzing only those cases with disease

recurrence, increasing age at diagnosis (P=0.05) and TNM stage (P=0.001) were significantly associated with timing of cancer recurrence (Supplemental Table 2).

Type and Site of First Recurrence

The most common type of first recurrence was distant disease (56%). Among cases with recurrence, distant disease developed in 79% of small cell cases, compared to 54% of NSCLC cases. Distant disease was also more common in cases receiving systemic chemotherapy (60% of recurrences) than in cases treated with local therapy alone (51% of recurrences). In multivariable analysis, recurrence type remained significantly associated with histology (P=0.004) and primary treatment modality (P<0.001) (Table 3). The most common site of distant disease was central nervous system (37%), followed by other (34%), bone (11%), multiple (8%), lung (contralateral) (5%), and liver (4%) Because small case numbers precluded calculation of odds ratios for several case characteristics, we incorporated liver metastases into the “other” category in our multivariable analysis. In that analysis, specific site of distant recurrence was associated with histology (p=0.004), and primary treatment (p<0.001) (Table 4). Among cases with distant recurrence, 34% were brain metastases for adenocarcinoma histology, versus 16% for squamous histology. Regarding lymph node recurrence, 103 cases were categorized as regional, and six cases were categorized as distant. Supplemental Figure 1 displays the timing of disease recurrence according to type and site. We observed a near-significant trend with regional and distant recurrences developing sooner than local recurrences. Approximately 75% of brain metastatic recurrences developed within two years after diagnosis.

Discussion

While national cancer registries provide detailed data on staging, treatment, and survival of tens of thousands of cancer cases annually, they fail to capture information on the timing, type, and site of disease recurrence. Nor do clinical trials routinely report these data. In the present study, we therefore characterized these disease factors in a diverse lung cancer population treated at a regional cancer center. In this analysis of more than 1,500 stage 1-3 lung cancer cases that achieved a disease-free state after initial therapy, approximately one-third developed recurrent lung cancer. Overall, distant metastases occurred more frequently than local or regional recurrence, with brain metastases the single most common site. Distant metastases also appeared to occur earlier than other recurrence patterns.

There are a number of potential explanations for these findings. It is possible that distant metastases had already occurred prior to local therapy, but were not detected due to inadequate initial staging, consistent with the early dissemination and parallel progression model of cancer growth.[10] Clearly, subclinical microscopic disease represents a reasonable likelihood, as a 1 cm tumor nodule represents approximately 10^9 cancer cells and the result of 40 generational doublings.[11] Thus, even with highly sensitive imaging modalities such as magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT), early tumor deposits remain undetectable. Local or regional subclinical microscopic disease may incidentally receive definitive therapy through inclusion in a resection specimen or radiotherapy port, whereas distant subclinical microscopic disease is

addressed only by systemic therapy (when administered), which may account for timing differences.

Somewhat surprisingly, recurrence developed less frequently in African American patients. Additionally, African American patients who did develop recurrence did so later than other patients and were significantly less likely to develop distant metastases at multiple sites. Because mortality rates among patients without recurrence were actually lower among African American patients, it seems unlikely that competing causes of death account for these favorable outcomes. These findings run counter to general observations that African American individuals with lung cancer tend to present at later stage and have worse stage-for-stage outcomes.[2,12,13] Multiple factors may contribute to these long-recognized trends, including lower socioeconomic status, reduced access to care, lack of insurance, and lower likelihood of agreeing to undergo aggressive surgical resection when offered. [12–14] However, the present study examines a distinct cohort: those individuals who qualified for, underwent, and benefited from definitive therapy. Furthermore, our patient cohort—drawn from a university-based oncology clinic that provides care to an insured population—represents a socioeconomically similar population. It seems possible that some of the race-linked outcomes reported in other series reflect socioeconomic factors rather than differences in disease biology and response to therapy. Another possible explanation is differences in recurrence *detection*, potentially due to different clinical and radiographic follow-up patterns across races. In the present study, whether African American patients truly fare better—and, if so, reasons for this apparent advantage—requires confirmation in other populations. Alternatively, the relatively small sample size of the current study may have been underpowered to address this question formally. Unfortunately, previously conducted prospective lung cancer clinical trials may not provide sufficient case numbers to address these questions either, given the historically low representation of African American individuals and other minority populations. [12,15]

Not surprisingly, higher-stage primary tumors had greater rates of recurrent disease, and these recurrences occurred sooner. Although women are known to have better prognosis than men with lung cancer,[1,2,7,12] recurrence rates were similar in this study. The observation that those cases treated with systemic therapy had higher rates of recurrence seems most likely to reflect greater inherent risk leading to the decision to administer chemotherapy rather than a detrimental effect of treatment. Nevertheless, this difference persisted in multivariable analyses controlling for initial disease stage, raising the possibility that other unmeasured variables impact treatment and monitoring decisions. For instance, patients not selected for chemotherapy may have been less fit, resulting in decreased frequency and/or duration of post-treatment surveillance, which in turn could reduce detection of recurrent disease.

Currently, recommended post-treatment surveillance for stage 1-3 lung cancer is chest CT with or without intravenous contrast, initially every 6 months, then every 12 months until five years. [16–19] Based on our current findings, this duration of follow-up seems likely to capture the overwhelming majority of disease recurrences. We observed stage 1 and 2 cases having the highest recurrence in the bone, CNS and other, whereas stage 3 had the highest recurrence in CNS and other. The recommended post-treatment surveillance modality of chest CT provides adequate assessment of most sites of recurrent disease, including lung,

thoracic lymph nodes, adrenal glands, much of the liver, and the thoracic spine (the most common site of bone metastases).[20–21] The only common site of metastasis not captured in routine follow-up is the CNS, a noteworthy observation because brain metastases developed in approximately one-third of patients, including stage 1 and 2 cases.

Consistent with general disease patterns of disease dissemination,[22–23] in the present study brain recurrence was more common in non-squamous NSCLC and in small cell lung cancer cases. In small cell lung cancer, the particularly high risk of CNS recurrence has led to recommendations for prophylactic cranial irradiation (PCI) in both limited and extensive stage disease. [24–25] Although trials of PCI for locally advanced NSCLC have not definitely demonstrated a benefit,[26] given the potential for morbidity and clinical decline from symptomatic brain metastases, there may be a role for post-treatment CNS surveillance, particularly in non-squamous cases.

Limitations of this study include a single-center setting and relatively small sample size. Although we had previously incorporated our institution's tumor registry at Parkland Health and Hospital System—the safety-net medical provider for Dallas County and a source of a large population of medically underserved patients to provide socioeconomic and racial diversity—in multiple studies, the Parkland registry has not captured recurrence data. [27–33] Staging and surveillance may not have been implemented consistently across cases. This single-center study lacks sufficient case numbers to evaluate more nuanced considerations, such as recurrence patterns within the widely heterogeneous population of stage 3 lung cancer, which ranges from single-station node-positive disease found at surgery, to non-resectable bulky disease. Additionally, very small numbers of cases with available genomic data preclude analysis of molecular alterations in recurrence patterns. Despite these concerns, because national datasets and registries fail to capture recurrence patterns, the present real-world cohort offers key insights into the growing population of lung cancer patients rendered disease-free after initial definitive therapy. Our study sample also features racial diversity and histologic variation representative of the broader U.S. lung cancer population.

Conclusion

In conclusion, the development, type, site, and timing of lung cancer recurrence vary according to patient and disease characteristics. Although lung cancer treatment varies according to factors such as histologic subtype, currently a one-size-fits all approach is applied to post-treatment surveillance. Unfortunately, only a small number of retrospective studies have examined imaging surveillance.[17] The current study suggests that modulation of clinical and radiographic disease monitoring according to recurrence risk, timing, and site may offer a means to identify future lung cancer when it remains asymptomatic and highly treatable. Eventually, detailed molecular and genomic tumor characterization may also predict future recurrence risk and patterns for an individual patient.[34–35] However, until that time, we encourage the collection and analysis of recurrence data in large and diverse populations—as is currently performed to inform lung cancer staging—to advance our understanding of a clinical question that will only grow in importance as the number of earlier-stage lung cancers increases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points:

What is already known about this subject?

A substantial proportion of individuals who initially present with localized or locoregional lung cancer eventually succumb to recurrent malignancy despite aggressive, multi-modality treatment. However, details on the site and timing of recurrence are generally not provided in national datasets or clinical trial reports.

What are the new findings?

We found that risk, timing, and site of recurrent lung cancer varied according to patient and disease characteristics, including age, race, tumor stage, histology, and primary treatment modality. The central nervous system was the most common site of recurrent disease, and distant recurrence occurred earlier than local or regional recurrence. In multivariate analysis, the site and type of recurrence was associated with histology and primary treatment modality.

How might it impact on clinical practice in the forseeable future?

Currently, post-treatment monitoring assumes a one-size-fits-all paradigm. The current study suggests that tailoring disease monitoring according to recurrence risk, timing, and site may offer a means to identify future lung cancer while it remains asymptomatic and treatable.

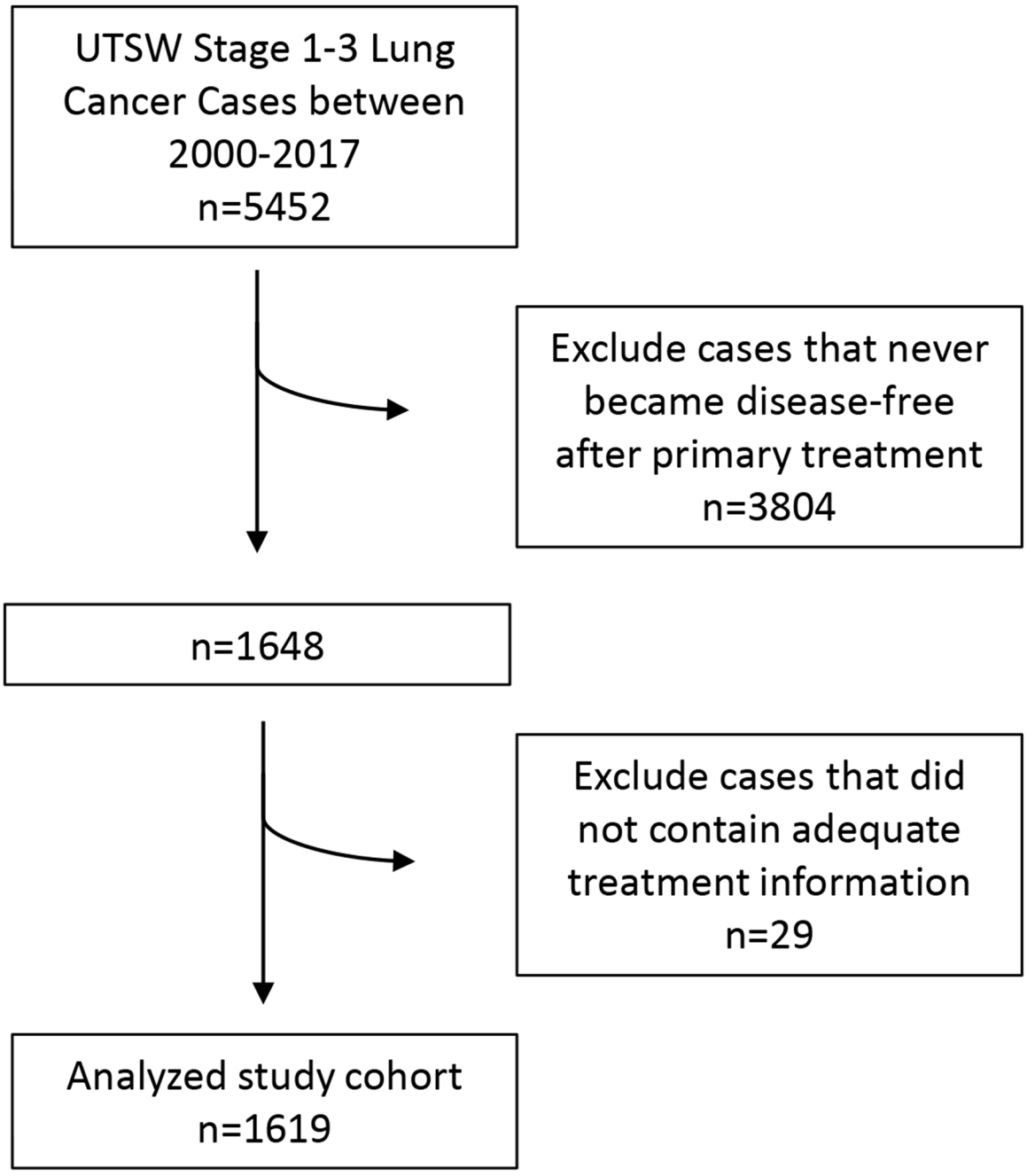

Figure 1.
CONSORT diagram

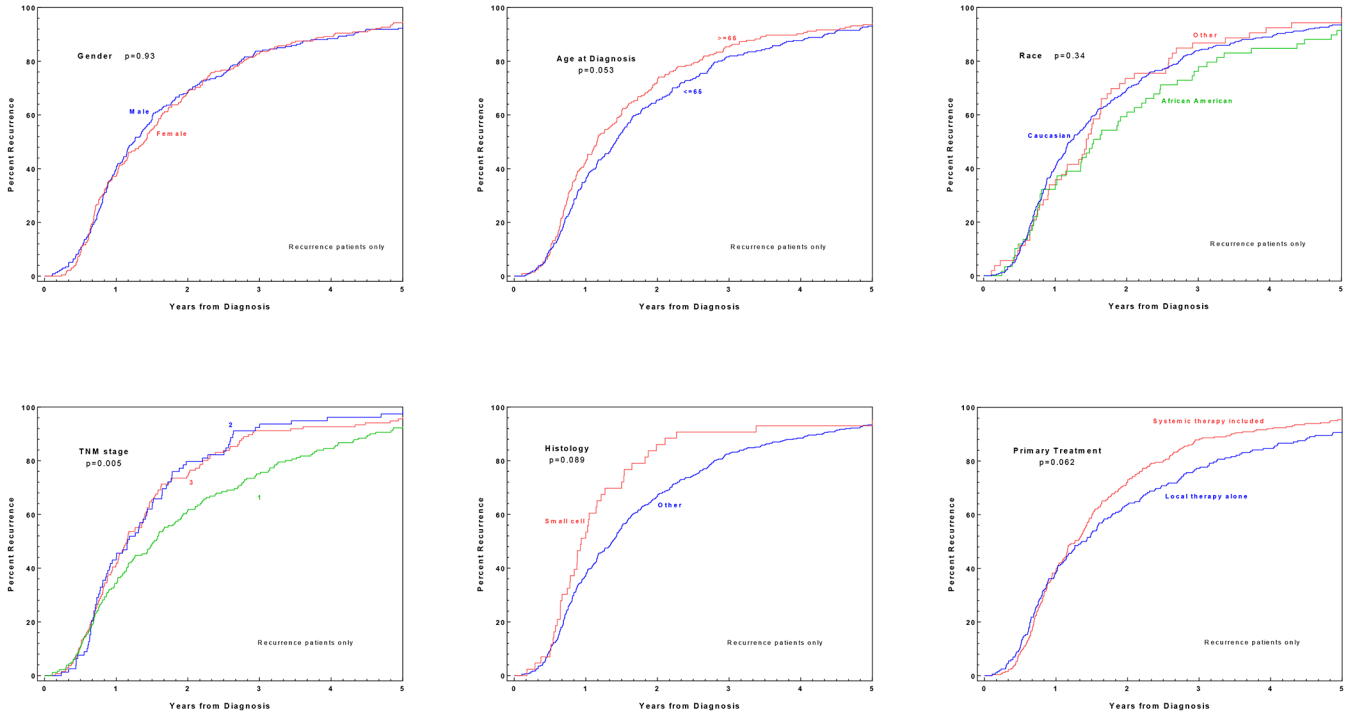

Figure 2.

Time to recurrence according to case characteristics (among cases with eventual recurrence)

Table 1.

Case characteristics.

Characteristic		N (%)
Primary Cancer	1	1481 (92)
	2	132 (8)
	3	6 (0)
Gender	Male	798 (49)
	Female	821 (51)
Age at Dx	<= 65	780 (48)
	>= 65	829 (52)
Race	Caucasian	1213 (75)
	African American	250 (15)
	Other	156 (10)
TNM stage	1	856 (53)
	2	255 (16)
	3	367 (23)
	Missing	141 (8)
Histology	Adenocarcinoma	838 (52)
	Squamous	361 (22)
	Small cell	88 (5)
	Non-small cell, other	332 (21)
Primary treatment	Local only	980 (61)
	Local + systemic	639(39)
Recurrence	Yes	487 (30)
	No	1086 (67)
	Unknown	46 (3)
Type of first recurrence	No recurrence	1086 (67)
	Local	108 (7)
	Regional	103 (6)
	Distant	273 (17)
	Unknown	49 (3)
Site of first distant recurrence	Bone	31 (11)
	CNS	102 (37)
	Liver	12 (4)
	Lung	14 (5)
	Other	93 (34)
	Multiple	21 (8)

Table 2.

Univariable and multivariable analyses of disease recurrence. Recurrence (Yes/No) by all patients.

	# Recurrence		UVA			MVA with all variables			MVA after model selection		
	No	**Yes**	**OR (95% CI)**	***p***	**Overall *p***	**OR (95% CI)**	***p***	**Overall *p***	**OR (95% CI)**	***p***	**Overall *p***
Gender											
Male	527	247	Reference		0.42	Reference		0.71	not used in MVA		
Female	559	240	0.92 (0.74 - 1.13)	0.420		0.96 (0.75 - 1.21)	0.71				
Age											
<= 65	495	268	1.51 (1.22 - 1.88)	<0.001	<0.001	1.21 (0.95 - 1.55)	0.13	0.13	removed in model selection		
>= 65	589	211	Reference			Reference					
Race											
Caucasian	810	370	Reference		0.02	Reference		0.03	Reference		0.02
African American	182	60	0.72 (0.53 - 0.99)	0.044		0.67 (0.47 - 0.95)	0.02		0.68 (0.49 - 0.94)	0.020	
Other	94	57	1.33 (0.93 - 1.89)	0.114		1.28 (0.87 - 1.88)	0.22		1.24 (0.86 - 1.79)	0.240	
TNM Staging											
1	651	186	Reference		<0.001	Reference		0.60	removed in model selection		
2	168	81	1.69 (1.24 - 2.30)	0.001		1.10 (0.77 - 1.56)	0.61				
3	214	140	2.29 (1.75 - 2.99)	<0.001		1.20 (0.85 - 1.69)	0.31				
Histology											
Small cell	39	44	2.67 (1.71 - 4.16)	<0.001	<0.001	1.428 (0.819 - 2.490)	0.21	0.21	removed in model selection		
Other	1047	443	Reference			Reference					
Primary Treatment											
Local therapy alone	742	211	0.35 (0.28 - 0.44)	<0.001	<0.001	0.42 (0.31 - 0.58)	<0.001	<0.001	0.35 (0.28 - 0.44)	<0.001	<0.001
Systemic therapy included	344	276	Reference			Reference			Reference		

Table 3.

Type of first recurrence.

	# Cases				MVA after model selection						
					Local		Regional		Distant		Overall *p*
	Local	Regional	Distant	No Rec.	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	
Gender											
Male	52	56	136	527	not used in MVA						
Female	56	47	137	559							
Age at Dx											
<= 65	55	57	157	495	removed in model selection						
>= 66	52	44	111	589							
Race											
Caucasian	83	83	202	810							
African American	12	12	35	182	removed in model selection						
Other	13	8	36	94							
TNM stage											
1	50	43	90	651							
2	14	23	44	168	removed in model selection						
3	27	27	86	214							
Histology											
Small cell	7	2	34	39	1.21 (0.51 - 2.836)	0.67	0.33 (0.08 - 1.39)	0.13	2.17 (1.31 - 3.58)	0.003	0.004
Other	101	101	239	1047	Reference		Reference		Reference		
Primary treatment											
Local therapy alone	53	50	108	742	0.46 (0.30 - 0.66)	<0.001	0.41 (0.27 - 0.62)	<0.001	0.34 (0.25 - 0.45)	<0.001	<0.001
Systemic therapy included	55	53	165	344	Reference		Reference		Reference		

Table 4.

Site of first distant metastasis.

	# Cases					MVA after model selection								
						Bone		CNS		Lung		Multiple		Overall *p*
	Bone	CNS	Lung	Multiple	Other	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	
Gender														
Male	18	42	6	11	59	removed in model selection								
Female	13	60	8	10	46									
Age at Dx														
<= 65	12	66	9	11	59	removed in model selection								
>= 66	19	33	5	10	44									
Race														
Caucasian	26	78	9	12	77	Reference		Reference				Reference		
African American	2	12	3	1	17	0.15 (0.02 - 1.20)	0.074	0.71 (0.28 - 1.84)	0.487	1.36 (0.31 - 6.03)	0.683	0.52 (0.058 - 4.67)	0.562	0.024
Other	3	12	2	8	11	1.31 (0.29 - 5.94)	0.728	1.84 (0.65 - 5.22)	0.249	2.86 (0.47 - 17.38)	0.254	10.73 (2.71 - 42.52)	0.001	
TNM stage														
1,2	26	39	12	13	44	Reference		Reference				Reference		
3	2	37	2	3	42	0.08 (0.02 - 0.38)	0.001	0.95 (0.49 - 1.85)	0.874	0.18 (0.04 - 0.87)	0.033	0.20 (0.05 - 0.81)	0.025	0.001
Histology														
Adenocarcinoma	20	43	7	8	49	Reference		Reference				Reference		
Squamous	6	7	6	4	22	0.85 (0.27 - 2.66)	0.776	0.391 (0.140 - 1.089)	0.073	2.52 (0.70 - 9.07)	0.158	1.86 (0.44 - 7.95)	0.402	
Small cell	1	17	0	1	15	0.47 (0.050 - 4.48)	0.511	1.217 (0.433 - 3.418)	0.708	####	####	0.64 (0.06 - 7.17)	0.721	####
Non-small cell, other	4	35	1	8	19	1.02 (0.27 - 3.85)	0.975	2.955 (1.269 - 6.876)	0.012	0.72 (0.08 - 6.62)	0.769	3.29 (0.74 - 14.66)	0.118	
Primary treatment														
Local therapy alone	18	30	9	12	39	removed in model selection								

	# Cases					MVA after model selection							
						Bone		CNS		Lung		Multiple	
	Bone	CNS	Lung	Multiple	Other	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Systemic therapy included	13	72	5	9	66								Overall *p*