

Survival and metastasis in muscle-invasive bladder cancer patients who present with indeterminate pulmonary nodules before treatment

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BACKGROUND: Indeterminate pulmonary nodules (IPNs) are common during initial evaluation of bladder cancer patients. Their significance is still unknown.

OBJECTIVE: Determine the significance of indeterminate pulmonary nodules, including their size and number, in muscle-invasive bladder cancer patients before definitive local therapy by surgery or chemoradiotherapy.

DESIGN: Retrospective review, single-center descriptive study.

SETTINGS: A tertiary cancer center.

PATIENTS AND METHODS: We performed a retrospective review of patients who underwent definitive local therapy of bladder cancer by either radical cystectomy and lymph node dissection or with chemoradiotherapy between January 1997 and December 2015. We identified patients with baseline CT scans done during staging work-up prior to definitive treatment. Patients with proven clinical metastasis at presentation were excluded, while patients who had IPNs without features suggesting metastasis were included.

MAIN OUTCOME MEASURES: Disease-free survival and overall survival.

SAMPLE SIZE: 168 patients.

RESULTS: The median age of patients at diagnosis was 66 years; 92% were males and 56% were smokers. IPNs (3 cm or less) were present in 74 patients (44.0%). Median follow-up was 24 months. IPNs were associated with decreased disease-free survival while IPNs did not affect the overall survival (HR=1.9; 95% CI: 1.1-3.4); $P=.01$ and HR=1.5; 95% CI: 1.0-2.5); $P=.07$, respectively. In addition, nodules >1 cm had reduced disease-free survival (HR=2.5; 95% CI: 1.1-5.9); $P=.04$. In the surgery group ($n=126$), the median number of lymph nodes excised was 14, with no association between lymph nodes status and the presence of IPNs ($P=.08$).

CONCLUSION: The presence of IPNs, especially nodules >1 cm had a negative effect on disease-free survival. Tailored postoperative follow-up of these patients may impact disease outcomes.

LIMITATIONS: The retrospective nature, the lack of standardized preoperative imaging protocols, the lack of a central radiology review and the small number of patients.

CONFLICT OF INTEREST: None.

Bladder cancer represents about 4% of newly diagnosed malignancies in adults and 3% of cancer-related deaths in both sexes.¹ At initial diagnosis, up to 30% of bladder cancers are muscle-invasive and can be fatal if untreated, with <15% 2-year survival.² Open radical cystectomy and pelvic lymph node dissection is the treatment of choice for patients with muscle-invasive or high-risk superficial bladder cancer, resulting in durable cancer-specific survival. Pathological tumor stage, the status of lymph nodes, excised lymph nodes number, lymphovascular invasion and surgical margins are established factors controlling oncologic outcomes after open radical cystectomy. Metastasis develops in 38% of patients over the disease course, with the lung being the second most common site for distant metastasis. Furthermore, 22% of patients who underwent radical cystectomy for localized disease developed metastasis on follow-up.^{3,4}

Indeterminate pulmonary nodules (IPNs) are round opacities at least moderately well marginated with a maximum diameter not greater than 3 cm that are determined radiologically.⁵ The national comprehensive cancer network guidelines recommend an imaging follow-up after radical cystectomy for the chest, abdomen and pelvis every 3-6 months for 2 years. After that, the frequency of imaging depends on the clinical status of the patient,⁶ but there are no recommendations addressing IPNs. Because it is not uncommon to have a preoperative image showing an IPN in patients with bladder cancer, it is of paramount importance to know how to correctly evaluate them and consequently, how to manage the patient appropriately.

In our study, we evaluated the association of IPNs, including their size and number, with disease-free survival (DFS) and overall survival (OS) in patients with locally confined disease at presentation who underwent definitive local therapy by surgery or chemo-radiotherapy.

PATIENTS AND METHODS

After the approval of the institutional review board, we retrospectively reviewed records of bladder cancer patients who underwent definitive local therapy by either radical cystectomy and lymph node dissection or by chemo-radiotherapy during the period between January 1997 and December 2015. We identified patients who had baseline computed tomography scans within 3 months prior to their definitive treatment. Patients with proven clinical metastasis at presentation were excluded (CTs, bone scans or PET scans showing lesions suspicious of metastatic disease to extrapulmonary regions), while patients who had IPNs without features suggesting metastasis were included.

Data collected included demographics (age, gender), preoperative disease characteristics and interventions (clinical staging, chemotherapy and radiotherapy), pathologic variables (tumor stage, lymph nodes yield and positivity) and postoperative oncologic outcomes (OS and DFS). Pathological staging of bladder tumors and their associated lymph nodes was performed according to the 7th edition of 2010 TNM classification.⁷ An indeterminate pulmonary nodule was defined according to Fleischner Society recommendations as a round opacity, at least moderately well marginated with a maximum diameter no greater than 3 cm. The nodule was deemed indeterminate if a biopsy was not performed at the time to characterize its nature. We used a pre-specified threshold for size (>1 cm vs ≤ 1 cm) and number (<2 vs ≥2) to describe them. The time period from diagnosis to the last documented follow-up was reported. Also, the time period from diagnosis to the first documented metastasis or death was calculated. Univariate and multivariate analyses were done using Cox proportional hazards models. The effect of IPNs on patient survival, measured by DFS and OS, was evaluated using Kaplan-Meier curves and analyzed by the log-rank test. The effect of their presence, their size and their number was taken into consideration. A significance criterion of $P \leq .05$ was used in the analysis. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of the 168 bladder cancer patients, 74 (44%) had IPNs identified on imaging reports; 154 (92%) were males. The median age of patients was 66 years and 94 (56%) were smokers. Seventy-seven patients (46%) were staged as T2 or more. On preoperative imaging, 74 patients (44%) had IPNs. The median follow up time was 24 months (**Table 1**). Surgery was performed on 126 patients (75%) with an average lymph node yield of 14 and with 25% of the lymph nodes being positive for metastasis. No association was found between lymph nodes status and the presence of IPNs ($P = .08$). On follow-up, 57 of 168 patients (33.9%) developed distant metastasis, with some patients developing metastasis to more than one site. Sites of metastasis were bone (36 patients, 42%), lung (27 patients, 31%), liver (11 patients, 13%) and others (12 patients, 14%).

Multivariate analysis revealed that patients with IPNs were at higher risk of developing metastasis (especially the risk of developing lung metastasis when compared to other sites) and showed a decreased disease-free survival (HR=1.9; 95% CI: 1.1-3.4); $P = .01$ (**Figure 1A**, **Table 2**). IPN size of more than 1 cm was associated

with an increased risk of metastasis (HR=2.5; 95% CI: 1.06 (5.9); $P=.04$) (**Figure 1B**). In addition, tumor stage (HR=2; 95% CI: 1.07 (3.7); $P=.03$) was associated with an increased risk of metastasis. On the other hand, surgery was associated with a decreased risk of metastasis (HR=0.3; 95% CI: 0.2 (0.6); $P=.0002$) when compared to chemo-radiotherapy. However, It is noteworthy that neither the presence of IPNs, nor their number and size had an affect on OS (HR=1.5; 95% CI: 0.96 (2.5); $P=.07$) (**Figure 2A, 2B**), while surgery was significantly associated with a better OS (HR=0.6; 95% CI: 0.3 (0.9); $P=.02$) (**Table 3**).

DISCUSSION

In addition to the radiological definition of IPNs (as described by the Fleischner Society as mentioned above),⁶ the American College of Chest Physicians defines a pulmonary nodule as indeterminate if it is not calcified in a benign pattern and has not been shown to be stable after 2 years of follow-up.⁸ Both guidelines recommend management in high- and low-risk patients. However, for patients with extra-pulmonary malignancy, these guidelines are not applicable. The Fleischner Society suggests that frequent follow-up CT may be indicated without specifying an interval.

Non-calcified pulmonary nodules represent metastasis in about 19% of patients with cancer.⁶ Bladder cancer metastasis to the lungs may present in various patterns, including multiple nodules, a single nodule and micro-nodules.^{8,9} In this study, we examined patients who had IPNs lacking features suggestive of metastasis for which close follow-up was recommended since targeted biopsies are difficult to obtain and are associated with increased morbidity. Furthermore, several studies demonstrated the limited value of a PET scan in bladder cancer patients, resulting in a more challenging decision-making process in such cases.¹⁰

Many researchers have studied pulmonary nodules in cancer patients. One of the earliest studies was done by Cahan et al prior to routine CT scan use, where they studied biopsy results from thoracotomies in 800 patients; 500 of which were found to have non-small cell lung cancers, and 196 cases were actually metastasis. Bladder cancer cases in this series were mostly associated with non-small cell lung cancers rather than metastasis.¹¹

In a study by Khokhar et al, 42% of IPNs in various types of cancer patients were malignant. Of 12 bladder cancer cases studied in this series, 4 (33%) were malignant IPNs; all were primary lung cancers and none represented metastasis.⁹

Many researchers have also studied the significance

Table 1. Patient demographics (n=168).

	Value	Numbers (%)
Gender	F	14 (8)
	M	154 (92)
Mean age (years)	66	
Smoking	Yes	94 (56)
	No	74 (44)
Clinical stage	T0	1 (0.6)
	T1	39 (23)
	T2	105 (63)
	T3	16 (10)
	T4	7 (4)
Type of definitive treatment		
Chemo-radiotherapy		42 (25)
Surgery		126 (75)
Neoadjuvant Chemotherapy	No	116 (69)
	Yes	52 (31)
Adjuvant Chemotherapy	No	127 (76)
	Yes	41 (24)
Metastasis	No	111 (66)
	Yes	57 (34)
Dead	No	96 (57.1)
	Yes	72 (42.9)
Follow-up (mean) (months)	43	
Lung nodule (n=74)	No	94 (56)
	Yes	74 (44)
Number	<2	18 (24.3)
	≥2	56 (75.7)
Size	≤1 cm	60 (81.1)
	>1 cm	14 (18.9)
Lymph node metastasis (surgery n=126)	N/A	7 (5)
	Negative	74 (59)
	No data	8 (6)
	Positive	37 (29)
Lymph nodes removed (median)		14

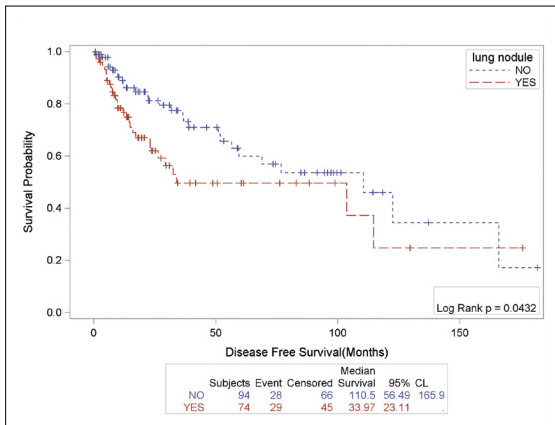


Figure 1A. Disease-free survival by presence of lung nodule.

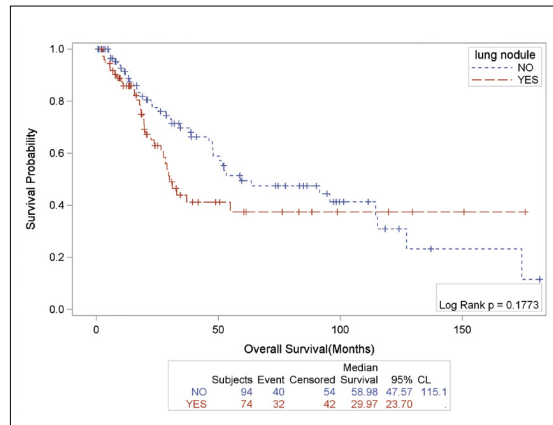


Figure 2A. Overall survival by presence of lung nodule.

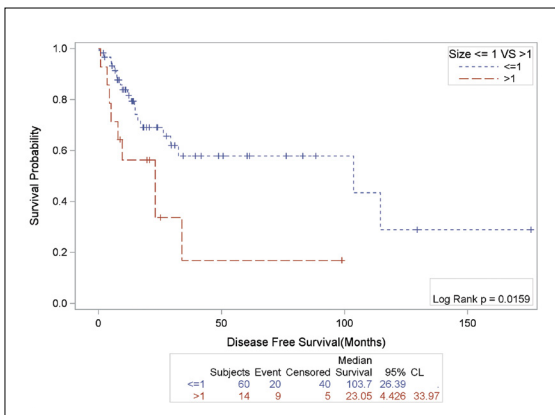


Figure 1B. Disease-free survival by size of lung nodule (≤ 1 cm or >1 cm).

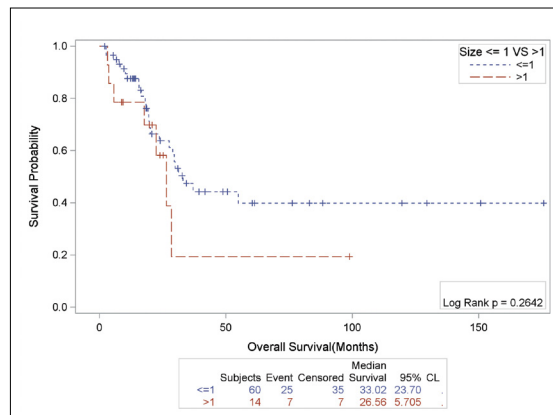


Figure 2B. Overall survival by size of lung nodule (≤ 1 cm or >1 cm).

of IPN in patients with various cancer types. Similar to our results, Xu et al evaluated a cohort of 240 kidney cancer patients who underwent either chest X-ray or CT prior to surgery and found that IPNs were associated with decreased DFS in patients with renal cell carcinoma (HR=1.9; 95% CI: 1.04 (3.5); $P=.04$), while OS was not influenced. In addition, the number and size of nodules did not affect survival.¹² A similar study performed by Mano et al showed that nodules greater than 1 cm were associated with lung metastasis, distant metastasis and mortality from renal cell carcinoma. A pre-specified threshold of 1 cm was used to define pulmonary nodules as large (>1 cm) or small (≤ 1 cm) with IPNs defined as ≤ 2 cm.¹³

Other studies also investigated the importance of IPNs in colon cancer patients. Brent et al found that only a minority of patients with IPNs in colon cancers did actually develop metastasis, and this occurred only in patients with positive nodes (N1 or N2 disease).¹⁴ In contrast, Quyn et al showed that about 20% of colon

cancer patients with IPNs had progressed, with no association between size of nodules and lung metastasis, but an association was found with the number of nodules; as around half of cases with 4 or more nodules had progressed on serial CT imaging suggesting pulmonary metastasis ($P\leq.01$).¹⁵ According to our study, the presence of pulmonary nodules and a nodule size of more than 1 cm were associated with decreased DFS, but not a decrease in OS. Moreover, the presence of lymph nodes metastasis did not increase the risk of metastasis for patients with IPNs.

In addition, our study showed that 56% of all patients with bladder cancer were smokers, a value close to that found in a pooled analysis by Brennan et al where 66% of cases were attributed to smoking.¹⁶ Despite the fact that smoking is an established risk factor for primary lung cancer and that a significant proportion of IPNs may actually represent primary lung neoplasms rather than metastasis,¹⁶ none of the patients in our cohort had been diagnosed with lung cancer on follow-up.

Table 2. Factors associated with disease-free survival with lung nodules (n=74).

		P value	Hazard ratio	95% hazard ratio confidence limits	
Disease-free survival					
Clinical stage	T2 vs. T1	.0292	2.002	1.073	3.736
Type of definitive treatment	Surgery vs. Other	.0002	0.341	0.194	0.599
Lung nodules	Yes vs. No	.0153	1.952	1.137	3.352
Smoking	Yes vs. No	.4654	0.815	0.472	1.410
Age		.0416	0.971	0.944	0.999
Disease-free survival by size and number of lung nodules					
Size	>1cm vs. ≤1cm	.0358	2.506	1.063	5.910
Number	≥2 vs. <2	.6787	1.229	0.463	3.264
Smoking	Yes vs. No	.1363	0.550	0.250	1.208
Age		.0757	0.965	0.928	1.004

Multivariate Cox regression analysis.

Table 3. Factors associated with overall survival with lung nodules (n=74).

		P value	Hazard ratio	95% hazard ratio confidence limits	
Overall survival					
Clinical stage	T2 vs. T1	.2423	1.519	0.754	3.064
Type of definitive treatment	Surgery vs. Other	.0200	0.551	0.333	0.910
Lung nodules	Yes vs. No	.0709	1.559	0.963	2.525
Smoking	Yes vs. No	.7606	0.928	0.576	1.497
Age		.2205	1.016	0.990	1.043
Overall survival by size and number of lung nodules					
Size	>1cm vs. ≤1cm	.2341	1.734	0.700	4.295
Number	≥2 vs. <2	.5498	0.767	0.322	1.827
Smoking	Yes vs. No	.6464	1.188	0.569	2.484
Age		.1899	1.027	0.987	1.068

Multivariate Cox regression analysis.

To the best of our knowledge, there is only one study (Cahn et al, 2017) that attempted to find the significance of IPNs in bladder cancer patients, and their effect on overall survival. They limited their study to patients who underwent radical cystectomy for urothelial carcinoma of the bladder and to those who had one or more identifiable pulmonary lesions on preopera-

tive staging imaging measuring <2 cm in any axis. They concluded that the majority of IPNs in their patients were stable on follow-up and that they rarely represent a malignancy.¹⁷

The limitations of this study are that it was retrospective with a small number of patients in a single institution. Other limitations are the lack of baseline

preoperative imaging protocols and the lack of central a radiology review. These facts may have affected the true prevalence of IPNs. In addition, we have not evaluated the histopathologic nature of the IPNs. On the other hand, despite our short follow-up, the 24-month survival data included in this study allows for clinically meaningful interpretation because of the relatively short time (a median of 7-18 months) required for initial

bladder cancer recurrence after radical cystectomy.^{2,3,18} We conclude that the presence of IPNs, especially nodules with a size more than 1 cm, have a negative impact on DFS. Therefore, we recommend tailored postoperative follow-up of these patients to improve their disease outcome. Besides, the data presented suggests a more aggressive tissue diagnosis for the larger than 1 cm nodule with possible early chemotherapy.

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