

8-2020

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Patel, B., Kalan, M., Khosravian, M., Tolouian, A., Tolouian., R. (2021). Lung cancers and kidney injury, a brief review. *Journal of Nephrothology*, 10(2). <https://doi.org/10.34172/jnp.2021>

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# Journal of Nephropathology



## Lung cancer and kidney injury: an updated review

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### ARTICLE INFO

*Article type:*  
Review

*Article history:*  
Received: 17 June 2020  
Accepted: 9 August 2020  
Published online: 26 August 2020

*Keywords:*  
Cancer, kidney injury, Lung cancer,  
Acute kidney injury, Chronic kidney  
disease, Metastasis, Nephrotic  
syndrome

### ABSTRACT

Lung cancer is the leading cause of cancer deaths worldwide, accounting for an estimated 1.8 million deaths. Lung cancer is also the most common primary cancer leading to soft tissue (ST) metastasis. Renal disease may occur as a direct or indirect consequence of the cancer itself (e.g., post-renal obstruction, compression, or infiltration), its treatment (e.g., radiotherapy or chemotherapy), or its related complications (e.g., opportunistic infection). Existing evidence shows that the most frequent primary solid tumor responsible for renal metastasis is pulmonary carcinoma, followed by gastric, breast, soft tissue, and thyroid carcinomas. Chronic kidney disease is a potential risk factor in the survival of patients with lung cancer. In this review, we will discuss causes of kidney injury in relation to lung cancer, potential mechanisms of kidney injury, and treatment options.

### *Implication for health policy/practice/research/medical education:*

The most common primary solid tumor responsible for renal metastasis is pulmonary carcinoma. In this review, we showed that chronic kidney disease harmfully affects the survival of individuals with pulmonary malignancy.

*Please cite this paper as:* Patel B, Kalan ME, Khosravian M, Tolouian A, Tolouian R, Aboufazel M, et al. Lung cancer and kidney injury: an updated review. J Nephropathol. 2021;10(2):e12. DOI: 10.34172/jnp.2021.12.

### Introduction

Onco-nephrology is concerned with the complex problems associated with cancer and kidney disease (1). The development of renal disease in patients with cancer may lead to increased toxicity of chemotherapeutic agents or decreased distribution of chemotherapeutic agents (2). Kidney disease is usually predictive of a diagnosis of an underlying cancer, simultaneously or through the disease process (3). Therefore, close attention of the oncologists is vital for a quick diagnosis and treatment of renal disease in cancer patients. The incidence and severity of kidney disease differ according to the type and stage of cancer, treatment sequence, and co-morbidities (3). In patients

with active non-renal cancer, diagnostic evaluation of a malignant renal mass could be either an asynchronous primary renal tumor or metastatic disease (4). A study by Humphreys et al indicated recent developments in controlling different types of renal diseases are associated with cancer and its treatment; with specific emphasis on certain conditions such as uric acid nephropathy, drug induced thrombotic microangiopathy, bisphosphonate-induced collapsing glomerulopathy, and hematopoietic cell transplant (HCT)-associated renal failure. Although renal disease in cancer patients is complicated; it is helpful to clinically considering of acute kidney injury as pre-renal, intrinsic, and post-renal causes (5). Another

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common cause of kidney damage in cancer patients is the medications that are prescribed for their existing cancer(s) (6). In a study of Renal Insufficiency and Anticancer Medications (IRMA) among 445 lung cancer patients with renal insufficiency (7), the baseline serum was calculated using KDIGO-KDOQI (Kidney Disease Improving Global Outcome-Kidney Disease Outcome Quality Initiative) definition (7,8). Between the 445 IRMA lung cancer patients, 14.4% had serum creatinine level  $\geq 1.24$  mg/dL (110  $\mu$ mol/L) and 62.1% had abnormal renal function using the formula of Cockcroft–Gault and 55.9% using aMDRD (Abbreviated Modification of Diet in Renal Disease) formula (7).

Lung cancer is recognized as the second most common malignancy and the leading cause of tumor-related deaths around the globe (9). It is generally divided into two types; small cell lung cancer (SCLC; 15% of the cases) and non-small cell lung cancer (NSCLC; 85% of the cases) (10). Lung cancer is also the most common primary cancer resulting in soft tissue (ST) metastasis. Due to the difficulty of diagnosing NSCLC in its early stages of cancer, more than 30% of NSCLC patients are diagnosed with distant metastasis (11,12). Kidneys receive about 20 to 25% of the cardiac output (about 1.0 to 1.1 L/min) making those susceptible to hematogenous metastasis (13). The renal metastases from NSCLC are diagnosed at autopsy, because renal metastases are often clinically asymptomatic (14). In a study, when the aMDRD formula was used, the incidence of renal insufficiency varied between cancer types, ranging from 50.8% of breast cancer patients to 56.0% of lung cancer patients (6). Kidney metastasis can be detected by magnetic resonance imaging (MRI), ultrasonography, abdominal computerized tomography (CT) scans and positron emission tomography (PET). Kidney metastasis can be categorized as a bilateral, exophytic, small, multiple or wedge-shaped within the renal capsule (15). The most common primary solid tumor that is responsible for renal metastasis is pulmonary carcinoma, followed by thyroid, gastric, soft tissue, and breast carcinomas (16-19). Renal metastatic tumors often occur in the cortical area near the glomerular vasculature (20).

The spectrum of renal disease induced by lung cancer includes acute kidney injury (AKI), chronic kidney disease (CKD), proteinuria, nephrotic syndrome, and electrolyte disorders. In patients with lung cancer, the most common renal complication is AKI.

The manifestations include pre-renal injury due to volume depletion, intra-renal by nephrotoxic chemotherapeutic agents (such as cisplatin-based), tumor lysis syndrome, metastatic kidney infiltrations, or post-renal obstruction (21). Currently, AKI also is reported among hospitalized coronavirus disease 2019

(COVID-19) patients, a critical group to consider among cancer patients who had been infected simultaneously (22-24). CKD is common in patients with lung cancer, especially in the elderly (25). In both, patients with early-stage and advanced lung cancer, CKD affects survival and the treatment regimen (26,27). The incidence of lung cancer induced AKI among males was almost three times higher than females (14). Although the paraneoplastic nephrotic syndrome is not common, it may appear in patients with lung cancer (28). Renal paraneoplastic syndrome symptoms may range from asymptomatic proteinuria to severe nephrotic syndrome. In 1% to 3% of patients with primary lung cancer, nephrotic syndrome caused by membrane glomerulonephritis (MGN) has been reported. There are 49 cases of tumor-related MGN in the literature, including nine cases of SCLC (29). One study reported a case of SCLC without metastases discovered by a paraneoplastic nephrotic syndrome (30). The complete remission of cancer was achieved by chemotherapy and radiotherapy with the resolution of nephrotic syndrome, while tumor progression occurred at the same time with fatal renal failure (30). It was also detected in one case of isolated unilateral renal metastases which was induced by lung cancer (31). Jørgensen et al suggested that the albumin-to-creatinine ratio (ACR) can predict malignancy in certain tissues (32). ACR was assessed in 5425 patients for 10.3 years at the time of the first diagnosis of cancer. They found a significant association between ACR and lung cancer (32). A study investigated patients with newly diagnosed SCLC from 2004 to 2011 in Taiwan. This study showed that SCLC patients with significant proteinuria were associated with poor nutritional status and more severe renal insufficiency (33). In a European case-control study, results of dipstick urinalysis check were collected from 1026 patients with primary lung cancer. Proteinuria was significantly more common in patients with lung cancer as compared to the control group (30.1% versus 8.8%;  $P < 0.05$ ). The incidence of proteinuria was significantly associated with the more progressive disease stage. Additionally, the incidence of proteinuria was significantly higher in patients with SCLC (37.5%) than NSCLC (28%) (34).

### Materials and Methods

Articles related to this topic were searched in Embase, Scopus, Web of Science, PubMed and the directory of open access journals (DOAJ), using specific combination of keywords. The keywords used are; cancer, kidney injury, lung cancer, acute kidney injury, chronic kidney disease, metastasis, nephrotic syndrome, immune checkpoint inhibitors, glomerular damage, epidermal growth factor receptor, renal metastasis and pulmonary carcinoma.

### Mechanism of association of renal disease with lung cancer

Various tumors can cause renal disease through different mechanisms like paraneoplastic effect, obstruction, direct infiltration, distant metastasis from the tumor and secretory diarrhea (caused by hormone secretion). A study by Wen et al suggested that tumor infiltration of the kidneys in patients with SCLC may be considered as a mechanism of AKI (35). Numerous cases of AKI arising from solid tumor infiltration, usually with widespread parenchymal replacement, have been described (36). A case report by Dobkin et al suggested that the lung metastases-induced progressive renal failure occurs mainly by parenchymal distortion and tubular damage by tumor cells. However, the renal injury may be due to sloughed parenchyma or lymphatic obstruction, vascular invasion, thrombosis, and tumor infiltration of the renal parenchyma (37,38).

### Lung cancer drugs

Cisplatin, a commonly used chemotherapeutic agent for lung cancer, is found to be nephrotoxic (39). Almost 20% of patients with high-dose cisplatin therapy developed AKI (40). Pemetrexed, a folate metabolism blockade, is currently used in combination with cisplatin for metastatic NSCLC and malignant mesothelioma (41). A study reported a patient with metastatic NSCLC who developed renal failure and tubular cell apoptosis accompanied with nephrogenic diabetes insipidus and distal renal tubular acidosis after consecutive treatment with pemetrexed (42). Therefore, it is necessary to adjust the dosage of anticancer drugs, such as platinum salts, and dose according to the level of renal function and by suitable, validated methods to prevent drug accumulation and decrease associated adverse events. For this purpose, several guidelines, publications, and handbooks are available for clinicians for dosage adjustment of anticancer drugs in patients with renal failure (43). However, some important anticancer drugs, such as gemcitabine, are not nephrotoxic, therefore, it is not necessary to reduce the dosages (7).

The spectrum of cancer-associated renal diseases has changed over the past 20 years due to the use of newer chemotherapeutic regimens including immune checkpoint inhibitors (ICPIs) and epidermal growth factor receptor (5). Immune checkpoint inhibitors target the programmed death 1 (PD-1) signaling pathway and have recently been approved for use in progressive pretreated NSCLC and melanoma. Evidence suggests that immune checkpoint inhibitors are associated with increased risk of AKI, glomerular damage, and electrolyte disturbances (44). A study reported six cases of AKI in patients with lung cancer treated with ICPIs, with each case showing evidence of acute interstitial nephritis on kidney biopsy (45,46). By analyzing randomized clinical trials (RCT)

data from 3695 patients, Cortazar et al reported an overall incidence of almost 2.2% for ICPI-associated AKI (47). In 2018, a meta-analysis of 48 RCTs including 11 845 patients treated with immune checkpoint inhibitors had a 4.2-fold higher risk of AKI against controls taking non-nephrotoxic agents (48). A study examined cancer patients treated with immune checkpoint inhibitors from 2008 to 2018 who then underwent a kidney biopsy with reported nephrotoxicity associated with ICPIs incidence as low as 2% when nivolumab was used alone; in contrast to 4.5% when nivolumab and ipilimumab were used as a combination.

In other studies, immune checkpoint inhibitors were shown to cause acute tubulointerstitial nephritis, thrombotic microangiopathy, nephrotic syndrome (focal segmental glomerulosclerosis, minimal-change disease (MCD), membranous nephropathy, pauci-immune glomerulonephritis, and immunoglobulin A (IgA) nephropathy (49). Proposed mechanisms include direct lymphocytic cellular infiltration of the renal interstitium, immune complex-mediated renal injury, vasculopathy, and release of cytokines causing podocyte foot process effacement (49).

Anticancer therapeutics targeted against epidermal growth factor receptor includes gefitinib and erlotinib for lung cancer. Gefitinib was used in the treatment of pulmonary malignancies associated with MCD in a single case report (50). Another case report study showed an individual with anaplastic lymphoma kinase-positive advanced non-small cell pulmonary carcinoma who detected complex kidney cyst during crizotinib therapy. (51). Epidermal growth factor receptor can be bound by ligands that regulate renal inflammation, cell growth, and fibrosis, potentially leading to kidney damage, as summarized by Rayego-Mateos et al (52).

### Chronic kidney disease (CKD) and dialysis

It is well-known that CKD has a relative prevalence in cancer patients, unrelated to the malignancy type (3). The causes of CKD in cancer consist of the effects of nephrotoxicity of some anticancer drugs and the glomerular diseases associated with the cancer (53).

While there are a few reports (54,55) regarding patients with CKD following treatment of pulmonary malignancy, chronic renal failure may harmfully impact the survival rate of patients with pulmonary malignancy. After adjusting for numerous contradictory factors, Wei et al revealed that CKD increases the risk of mortality and is a potential risk factor for lung cancer patients (56).

Yamamoto et al retrospectively analyzed data of patients who suffered surgery for NSCLC between 2007 and 2014, of the 671 patients, 55 had CKD (57). Furthermore, among patients who underwent pulmonary tumor

surgery, chronic renal failure was accompanied with poor overall survival (57). Squamous cell carcinoma was more frequently diagnosed in patients with CKD as compared to patients without it. The 5-year disease-free and 5-year overall survival rates in patients with CKD were 60.0% and 68.9%, respectively, and for patients without CKD were 69.7% and 80.0%, respectively. While CKD patients have restriction in their choice of systemic treatment, surgery remains the main support for the treatment of pulmonary tumor in this group (57). As CKD individuals tend to have a poor respiratory function, cardiothoracic surgeons should cautiously choose the type of resection to attain equilibrium between the therapeutic benefit and harm in lung cancer patients. Few studies are available on the perioperative morbidity of lung surgery in lung cancer patients on dialysis (58,59). For instance, a retrospective review of seven patients on dialysis undergoing lung surgery was performed. In these patients, there was a high occurrence of respiratory problems as well as hyperkalemia, hemodynamic instability, and a tendency for postoperative bleeding (60).

#### **Risk of lung cancer in patients with CKD or renal cancer**

Reduced kidney function may be an independent risk factor for cancer in older men and this risk increases when glomerular filtration rate falls to approximately 40 ml/min, as well as in patients on dialysis or transplant recipients (61). Therefore, CKD prevention may be a new and valuable approach for decreasing cancer risk in the general population (61).

The detection of primary lung cancer is difficult when kidney cancer spreads primarily to the lungs. Bowman and colleagues identified 151 patients undergoing systemic targeted therapy for metastatic renal cell carcinoma (RCC) from 2006 to 2013, and reported the proportion and incidence rate for developing NSCLC with previous metastatic RCC (62). The incidence rate for the progress of NSCLC in patients with metastatic RCC was 0.87 per 100 person-years (62). Lung cancer is more prevalent after kidney transplant (63). Therefore, vigilant attention should be paid to transplant candidates noting; age, smoking and medical history of cancers- especially lung cancer (64).

#### **Treatment of renal metastasis**

Renal biopsy is an essential diagnostic technique in diagnosing kidney disease in individuals with confirmed malignant disease (35). The techniques to treat metastatic kidney disease are broad, especially based on the type of metastatic renal disease. A study of two cases with paraneoplastic nephrotic syndrome induced by advanced SCLC concluded that if the primary tumor is unresectable,

irradiation can be the first choice in the treatment of nephrotic syndrome (28). Verma et al reported 4 cases of solitary kidney metastasis in individuals with pulmonary malignancy that experienced stereotactic body radiation therapy (SBRT) and concluded that SBRT for mitigation of renal metastases from NSCLC is a safe and effective treatment (65). Nephrectomy may also be a beneficial choice in the treatment of solitary kidney metastasis in individuals with NSCLC (66). In this regard, Adamy et al examined the effect of nephrectomy in patients with solitary renal metastatic tumors and suggested that surgical resection may be an appropriate approach with a positive effect on the patients' survival rate (67). In highly selected cases, patients with metastatic NSCLC, have surgical resection of extrathoracic metastasis to reduce symptoms and increase disease-free time (68). In addition, a case report by Degen et al examined whether the minimally invasive procedure of cryoablation was a possible treatment in the control of solitary kidney metastasis from pulmonary malignancy (69). While this treatment is not the standard of care, this case report revealed the ongoing and new advancements in onco-nephrology and therapy of metastatic lung cancer to the kidneys.

#### **Conclusion**

Lung cancer is recognized as the second most common cancer and the leading cause of cancer-related deaths worldwide. Lung cancer is also the most common primary cancer leading to recognized soft tissue metastasis. Kidneys receive about 25% of the cardiac output making them susceptible to hematogenous metastasis. The most common primary solid tumor responsible for renal metastasis is pulmonary carcinoma. In this review, we found that CKD harmfully affects the survival of individuals with pulmonary malignancy and the reduced kidney function may be a potential risk factor for cancer. Additionally, we found that the renal disease has arisen from lung cancer or its treatments such as immune checkpoint inhibitors. Future observational and RCT studies are warranted to comprehensively investigate the impacts of lung cancer on renal function and structure to better guide the clinicians in treating patients and saving lives.

#### **Authors' contribution**

Primary draft by AHA and MA<sub>s</sub>. MEK, BP, RT and AT completed and extended the manuscript. MK and MA<sub>b</sub> edited the paper. RT and AHA finalized the paper. All authors read and signed the final manuscript.

#### **Conflicts of interest**

The authors declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data accuracy, duplicate publication) have been ultimately obeyed by the authors.

### Funding/Support

None.

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