



Lung cancer surgery in women: focus on gender-related outcomes – a narrative review

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Contributions: (I) Conception and design: CC Zirafa, F Melfi; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: E Sicolo, A Castaldi; (V) Data analysis and interpretation: CC Zirafa, G Romano; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: The cases of lung neoplasm in women have been raised over the years. Genetic, molecular and hormonal factors play an important role and biologically differentiate the disease of female patients from males. Gender differences were also observed in the evaluation of post-operative results of lung cancer patients. Aim of this study is the analysis of gender-related outcomes after surgery for lung cancer, with the individuation of possible factors influencing the natural history of lung cancer disease in women. The authors evaluated literature and their single centre experience in robotic surgery, considering the lack of data in this field.

Methods: Previous published studies were reviewed, selecting the most eminent papers on this topic, in particular referring to international databases. In addition, concerning the single-centre experience, data of 407 patients who underwent pulmonary resection with lymphadenectomy for non-small cell lung cancer by robotic approach were analyzed.

Key Content and Findings: Better post-operative outcomes were described in women than in men, in terms of short-term post-operative results after pulmonary resection for lung cancer, although some studies showed similar results in both sexes. Furthermore, higher survival rate in women than in men was observed, despite a comparable distribution of pathological staging, confirming the influence of the gender in the evolution of lung cancer disease and prognosis.

Conclusions: Several factors influence the history of lung cancer disease in women, so further studies will be necessary to individuate these factors in order to assess targeted therapy to improve the prognosis.

Keywords: Gender differences; women; lung cancer; surgery

Received: 16 May 2022; Accepted: 16 January 2023; Published online: 24 February 2023.

doi: 10.21037/pcm-22-23

View this article at: <https://dx.doi.org/10.21037/pcm-22-23>

Introduction

Lung cancer is the leading cause of cancer death in the world. Over 2,200,000 new diagnosis of lung cancers and about 1,800,000 of death were reported worldwide in 2020 (1). The cases of lung neoplasm in women have been raised over the years, with about 770,000 new diagnoses and 600,000 deaths in 2020 (1). It is estimated that the global incidence and mortality of lung cancer in women

will increase both; the projection for 2040 assumes a 55% increase in cases and a 62% increase in deaths. This incremental trend among women has been described as a “contemporary epidemic” (2).

This increase in incidence of lung cancer in women is mainly associated to a growth in tobacco use (3). However, genetic, molecular and hormonal factors play an important role and biologically differentiate the disease

from male patients. Indeed, pulmonary adenocarcinoma is diagnosed more frequently in women, also in smoker group, in contrast to male smokers which are more likely to develop squamous cell carcinoma (3). The different prevalent histology in female smoker may be related to genetic alteration, involving genes that encode carcinogen metabolizing enzymes implicated in metabolism of carcinogenic polycyclic aromatic hydrocarbons. Increased expression of CYP1A1 gene and GRPR gene are reported in female smokers compared to male. These genetic variations appear to be related to the estrogen induction, that leading to an increased risk due to the oncogenic effects of nicotine (4,5).

Besides, several studies report a higher women's predisposition to develop molecular aberration induced by the carcinogenic effects of cigarette smoke, even when the level of exposure to cigarette smoke was lower than the men's ones (6). The most commonly reported molecular aberrations resulting from effects of tobacco smoke in women concern p53 gene and K-ras oncogene (6,7). Also, among never-smoker patients, women are more likely to be diagnosed with lung cancer than men. As a matter of fact, about 50% of women with lung cancer have never smoked, in comparison with the 15% of never-smoker men (8). Lung cancer in never-smoking women may also be related to second-hand smoke, high-temperature cooking and aerosolization of carcinogens or volatile oils. Indeed, estrogens seem be involved in lung tumorigenesis at several stages: they may active cellular proliferation pathways or, instead, they may provoke metabolic activation, resulting in the production of DNA adducts, causing oxidative damage (9,10). However, the detailed role of estrogens in lung cancer is still to be defined.

Difference between men and women with lung cancer were recorded also in the evaluation of the prognosis, in fact the survival rate is higher in women taking into account the analysis of outcomes of early-stage lung cancer after surgical treatment, while the results in metastatic disease are contradictory. Even in locally advanced non-small cell lung cancer (NSCLC), women achieve significantly higher survival rate than men, regard less age, smoking status and treatment (11).

Recent studies have described better post-operative outcomes in women than in men, both in terms of complications and mortality after surgery. Furthermore, female patients experience a significantly better prognosis after surgical resection, especially in early-stage lung cancer.

The aim of this paper is to review post-operative gender

differences in NSCLC patients and to evaluate the factors influencing the natural history of lung cancer disease in women after surgical lung resection.

Moreover, considering previous literature studies and their partly contradictory results, our goal is to define, possibly uniquely, the existence of a gender-related difference in the outcomes related to lung cancer surgery.

Besides, focusing on gender differences in NSCLC patients who underwent robotic surgery, no recent and consistent literature data concerning surgical and oncological outcomes are available. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-23/rc>).

Methods

Research methodology

The methodology used to conduct the research of the articles and their review by the authors is illustrated below.

First of all, PubMed was selected as the scientific database for the review. The focus for the article selection concerned: surgical outcomes, overall survival and long term survival in women affected by lung cancer. For this reason, the combination of keywords used to conduct the study were: "Lung cancer", "women", "NSCLC surgery", "outcomes" and "gender".

The use of the aforementioned keywords allowed access to a large number of studies which were further selected by the authors on the basis of the number of patients analyzed and the year of publication. Given the large number of published papers, the authors selected studies with the largest number of patients from 1996 to 2022.

Moreover, the authors considered consistent with the topic of the review, articles that obtained relevant results on gender related overall survival and long term survival. Histology and comorbidities in women were also considered in the choice of the papers.

Furthermore, regarding the analysis of our series, the authors used the computerized health records available at the Institution to obtain data on surgical outcomes, postoperative hospitalization, histology and staging.

As regards the follow-up information, outpatient visits were performed with clinical examination, chest computed tomography (CT) scan and total body fluorodeoxyglucose (FDG)-positron emission tomography (PET) of further radiological investigation, if required.

Table 1 The search strategy summary

Items	Specification
Date of search	2014-1-1/2022-02-28
Databases and other sources searched	PubMed
Search terms used	(“Lung cancer” AND “women”) (“NSCLC surgery” AND “outcomes” AND “gender”) (“NSCLC” AND “women”) (“lung cancer” AND “sex”)
Timeframe	1996–2022
Inclusion and exclusion criteria	Inclusion criteria: original articles and reviews in English about themes like “surgical outcomes and survival in women affected by lung cancer” Exclusion criteria: any paper considered with low reliability
Selection process	CCZ conducted the selection, and authors expressed their opinion regarding the scientific value of the selected article

Quality of life (QoL) analyses was obtained during the follow-up outpatient visit or by telephone interview.

The research strategy is summarized in *Table 1*.

Surgery for lung cancer in women

Outcomes in women after anatomic lung resection

Gender differences are well evident in short-term and oncologic outcomes after surgical treatment for lung cancer (1). Several studies have shown better post-operative results and overall survival rates in women after surgical procedure, specifically in early-stage NSCLC patients (12). The data analysis of 34,188 patients underwent resection for lung cancer, based on the Society of Thoracic Surgeon’s General Thoracic Database, revealed substantial differences in sex comparison, with better results in female group in terms of post-operative complications and mortality (13,14). In addition, recent publications have shown better survival in women in the evaluation of long-term outcomes after pulmonary resection, with a 5-year OS of 60.2% in female and of 48.6% in male patients (15).

Although these positive results, the access to surgical treatment for early-stage lung cancer is un even among the two genders, being less common in female patients than in men (16). Specifically, gender discordance between physicians and patients, in particular in male physician-female patient interaction, is associated with worse clinical pathway (17). This phenomenon seems to be related to

gender differences among physicians in perception of the clinical information and its consequent elaboration for planning therapeutic path. The reasons of this gender bias have not yet been identified and are likely caused by an unconscious mechanism (17,18).

Personal experience

We retrospective analyzed data concerning 407 patients who underwent pulmonary resection with lymphadenectomy for NSCLC by robotic approach, from January 2014 to December 2019.

The sample comprised 236 males (57.99%), with a mean age of 68.4 years [standard deviation (SD) \pm 8.9] and 171 females (42.01%) with a mean age of 67.5 years old (SD \pm 7.44). The group of women included 55 (32%) non-smokers, 73 (43%) former smokers and 43 (25%) current smokers; while the man group consisted of 20 (9%) men have never smoked, 154 (65%) were former smokers and 62 (26%) were current smokers.

Among women, 153 (89.5%) patients underwent robotic lobectomy, 14 segmentectomy (8.2%), 3 (1.7%) pneumonectomy, 1 (0.6%) upper bilobectomy. In male group, robotic lobectomy was performed in 207 (87.7%) cases, segmentectomy in 26 (11.1%) cases, bilobectomy in 2 (0.8%) cases and pneumonectomy in 1 (0.4%) case.

The results of the pathological analysis in the female group have documented 112 adenocarcinomas (65.5%), 16

Table 2 Sex differences in surgical outcomes after robotic anatomical lung resection

Clinical and surgical details	Values
Patients	407
Gender	
Male	236 (57.99%)
Female	171 (42.01%)
Surgeries in women	
Lobectomies	153 (89.5%)
Segmentectomies	14 (8.2%)
Bilobectomy	1 (0.6%)
Surgeries in men	
Lobectomies	207 (87.7%)
Segmentectomies	26 (11.1%)
Bilobectomies	2 (0.8%)
Pneumonectomy	1 (0.4%)
Histological findings in women	
Adenocarcinomas	112 (65.5%)
Squamous cell carcinomas	16 (9.3%)
Carcinoids	22 (12.9%)
Other	21 (12.3%)
Histological findings in men	
Adenocarcinomas	137 (58%)
Squamous cell carcinomas	54 (22.9%)
Carcinoids	12 (5.1%)
Other	33 (14%)
Mean P.O. stay in women (days)	6±4
Mean P.O. stay in men (days)	7±4
P.O. complication in women	32 (18.7%)
P.O. complication in men	42 (17.8%)
Follow-up in women	
Alive	68.5%
Died	26.5%
Follow-up in men	
Alive	55%
Died	35.7%

Data are presented as n (%) or mean ± SD. P.O., postoperative; SD, standard deviation.

squamous cell carcinomas (9.3%), 22 (12.9%) carcinoids (3.5% atypical carcinoids and 9.3% typical carcinoids), 21 (12.3%) other histology. Histopathological diagnosis in men showed adenocarcinoma in 137 (58%) patients, squamous cell carcinoma in 54 (22.9%) patients, carcinoid in 12 (5.1%) cases and other histology in 33 (14%) patients. According to Tumor-Node-Metastasis (TNM) staging, 84.9% of early-stage NSCLC was found in male group and 88.1% in female group.

The mean postoperative hospital stay was 6 days (SD ±4) in the female group and 7 days (SD ±4) in the male patient group.

The incidence of major postoperative complications (atrial fibrillation, anemia requiring transfusion, pneumothorax resolved with chest tube placement) was also analyzed and in the female group, complications occurred in 32 (18.7%) patients, whereas in the male group in 42 (17.8%) patients.

Concerning the survival data, at an average follow up of 47.05 months (with SD of 18.5), 68.5% of female patients were alive, 26.5% died, while 4.8% were lost to follow up. Conversely, in the same follow up period, 55% of male patient were alive, 35.7% died and 9.3% were lost to follow-up.

The post-operative quality of life, by using SF-12 questionnaire administration, in 100 consecutive patients underwent lobectomy was evaluated. The interviews were conducted by telephone or during outpatient check-up. The questionnaire was administered at both 15 days and three months after surgery, for short and medium term QoL evaluation. The perception of physical and mental quality of life was summarized with two indexes, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). PCS results turn out to be similar between women and men after surgery, specifically the mean result was 34.7 in female group and 34.9 in male group after 15 days (*vs.* 34.9) and respectively 40.6 and 39.8 after 3 months. Differently, the evaluation of mental score showed lower MCS in women than men after 15 days (35.1 *vs.* 39.4) and after 3 months (39.7 *vs.* 42.0). The pain score was analyzed in both groups at short and medium term after surgery. The index showed similar results in women and men after 15 days (37.1 and 37.7) and a higher score, corresponding to greater pain tolerance, in women after 3 months (46.2 and 42.6).

The analyzed population and the relative findings are summarized in *Table 2*.

Discussion

Female and male patients are characterized by dissimilar incidence and prognosis of lung cancer, due to different exposition to carcinogenic agent added to genetic, hormonal and molecular mechanisms. As a result, different clinic-pathological features are observed in lung cancer among the two genders, with a higher incidence of adenocarcinoma histology in women, characterized by lower grade, frequently in early stages (19).

Fibla and colleagues evaluated data from the Spanish Society of Thoracic Surgeons, including 3,307 patients. They found a higher percentage of adenocarcinoma histology and early stages in female group and at the same time a lower post-operative complication and mortality rate. The authors reported a lower mean age and comorbidity in women than in men, this could at least partly explain the differences in post-operative outcomes among the two groups (20).

This is in line with our results, in fact the mean age and morbidity was similar in both group in our series and significant differences in post-operative complication rate and mortality were not observed. We obtained a higher survival rate in women than in men, despite a comparable distribution of pathological staging and adenocarcinoma histotype in both sexes, confirming the influence of the gender in the evolution of disease and lung cancer prognosis. Other studies have confirmed gender differences in survival rate, with 5-year OS of approximately 55% for men, while of about 70% for women (21-23).

Despite this, some factors that can constitute a bias in the study of gender related survival after surgery for NSCLC have to be mentioned. Cigarette smoking, for example, is still more widespread in the male population in some regions and this could be associated not only with an increased risk of carcinogenesis, but also with pre-operative poor respiratory function and cardiovascular diseases, with a not negligible impact on post-operative outcomes. Nevertheless, some authors demonstrated that preoperative cardio-respiratory status may influence the long term-survival and female gender have to be considered as an independent favorable factor. Therefore, it remains clear that, despite several confounding factors appear to influence the long term survival after lung resection for NSCLC, there are gender-related hormonal factors involved as well.

Moreover, some *in vitro* trials have shown that NSCLC tumor cells could express estrogen receptors and that some of their metabolites are able to inhibit angiogenesis, confirming

the sex-related difference in tumour biology (22).

Concerning the debated role of hormonal co-factors in lung cancer, a recent meta-analysis have analyzed the role of hormones in lung cancer risk, providing a crucial update on this issue (23). The meta-analysis was conducted by Chung and colleagues and published in 2021. This study aimed at investigate the possible association of early and late menopause with lung cancer risk. Authors reviewed publications through PubMed, EMBASE and Scopus database search up to March 2021. The review has demonstrated an increased risk of developing lung cancer in women who experienced early menopause (≤ 45 years), although this risk is primarily among smokers. A particular finding emerged from the study conducted by Chung is the association between late menopause (≥ 55 years) and lung cancer risk among non-smokers. However, large prospective cohort studies are required to confirm these findings.

An additional recent meta-analysis has demonstrated that a previous breast cancer may dramatically predispose NSCLC in female patients (24).

The review was conducted on 37 previous studies on more than four million of patients by Wang and colleagues. The Chinese group has demonstrated that patients with previous breast cancer are more likely to develop NSCLC than the general population. Furthermore, the risk of developing primary NSCLC after breast cancer is affected by smoking, radiotherapy, chemotherapy, estrogen and progesterone receptor status.

Considering the prognostic factors, in addition, another significant feature analyzed by several authors is the application of the appropriate resection.

Despite positive post-operative results, studies documented that the appropriate lung resection is performed less frequently in women than in men, in terms of the timing and extension of resection, indeed limited resection tends to be preferred in female patients regardless of morbidities or pulmonary function (25,26). Conversely, many authors have found association between female sex and better prognosis regardless of stage or treatment, pointing out the influence of hormonal factors (27).

In the evaluation of post-operative quality of life, similar physical condition was felt in both genders, while a worse mental condition was detected in women. This is consistent with literature, where is reported a lower average score in the emotional domain, that impact on mental status, is typical of female gender (28). Besides, perceived post-operative pain resulted similar in women and men in the short term, with better result in women after 3 months,

suggesting a better pain tolerance in women than men.

Recent studies have highlighted the role of surgeon gender in post-operative results of patients who underwent elective surgery (29). Wallis *et al.* as well showed different post-operative outcomes after surgery linked to surgeon gender, evaluating 1,320,108 patients and 2,937 surgeons. The Authors observed that sex discordances between surgeon and patient were related to a significant increase in the incidence of post-operative complications and deaths. In stratified analyses according to surgeon, patient, surgery and hospital features, gender discordance was confirmed in association with worse outcomes for female patients, but better outcomes were observed for male patients (30).

The eminent scientific value of the mentioned paper is demonstrated by the consistency of the results obtained.

In particular, the studies conducted respectively by Tong (13), Melvan (14) and Fibla (20) analyzed a consistent number of patients, a feature that makes these experiences highly reliable and comparable.

Moreover, our results concerning the gender-related oncologic outcomes are consistent with literature, confirming their objectivity, but the debate is still open.

In conclusion, the female gender appears associated with more positive short-term and oncological outcomes after surgery for lung cancer, in comparison to male gender. Several factors are known to influence the natural history of lung cancer disease in women, such as genetic and hormonal elements, carcinogenic agent, although new factors have recently been identified. Further studies will be necessary to establish the factors that determine the different characteristics and behaviours of lung tumour in the two genders, in order to define targeted therapy to improve the prognosis.

In addition, although our results are consistent with previous studies, the limit of a single center experience must still be considered. Consequently, multicentre experiences with different surgical approaches will be the subject of further studies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Precision Cancer Medicine* for the series “Lung Cancer in Women: From Epidemiology to

Therapy”. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-23/rc>

Peer Review File: Available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-23/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-23/coif>). The series “Lung Cancer in Women: From Epidemiology to Therapy” was commissioned by the editorial office without any funding or sponsorship. FM served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pcm-22-23

Cite this article as: Zirafa CC, Romano G, Sicolo E, Castaldi A, Davini F, Melfi F. Lung cancer surgery in women: focus on gender-related outcomes—a narrative review. *Precis Cancer Med* 2023;6:5.