Current status of lung cancer in Spain: a retrospective analysis of patient characteristics, use of healthcare resources and in-hospital mortality

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Abstract

Objective: This study aimed to describe the current status of lung cancer in Spain, including patient characteristics and in-hospital mortality, and to revise disease management and the direct medical costs of secondary care.

Methods: A retrospective observational study was set to analyse anonymised primary and secondary care records of patients admitted with lung cancer in Spain between 2011 and 2016. Data were obtained from the Primary Care Dataset and the Centralised Hospital Discharge Database.

Results: Admissions files from 12,119 primary care and 113,574 secondary care patients were analysed. Only 21% of all patients were females, yet the number of female patients presented an increasing trend over the study period. Non-small-cell lung carcinoma represented 85.29% of all lung malignant neoplasms; metastatic or secondary malignant neoplasms were diagnosed in 76.66% of admissions. Other relevant comorbid conditions registered at the hospital level were hypertension, disorders of lipoid metabolism, diabetes mellitus and a history of tobacco use. In-hospital mortality was 22% over the study period and was associated with respiratory failure. Mean hospitalisation time was 9.57 days and most admissions were due to emergencies. The mean cost of secondary care per patient was €8,475, increasing significantly over the study period. Cost per patient was higher in those diagnosed with a squamous cell carcinoma.

Conclusions: Preventive and early detection measures are recommended, continuing to focus on females. In parallel, a multidisciplinary approach could optimise patient journey considering the presence of disease comorbidities, although its role in lung cancer mortality should be further explored.

Keywords: Lung neoplasms; Retrospective studies; Disease Management; Costs and Cost Analysis; Spain.

Short title: Current status of lung cancer in Spain

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Introduction

Worldwide, lung cancer is the most common cancer type, with an age-standardised incidence rate of 22.5 per 100,000 in 2018 [1]. Prevalence is significantly elevated in North America and Europe, being, in this last case, Hungary the country with the highest incidence rate for both males and females [2]. In Spain, lung cancer incidence rates are 42.1 per 100,000 for males and 14.0 per 100,000 for females; lung cancer incidence has displayed a decreasing trend in males over the past decade, yet it remains as one of the principal causes of disability and mortality [2-4].

The lung cancer age-standardised mortality rate worldwide was 18.6 per 100,000 in 2018, similar to that in Spain, where the 5 year relative survival rate was only 13.5% between 2010 and 2014 [1, 5]. Nevertheless, a decrease in mortality has been observed, presumably promoted by the decreasing smoking prevalence, reversing the increasing trend followed until the mid-nineties; still, for females, lung cancer mortality maintained the growing trend at least until 2012 [6, 7]. The differential incidence and mortality rates observed for females have been primarily related to variations in smoking habits, with studies indicating a higher smoking prevalence among Spanish teenage girls, when compared to boys, up to 2002 [8]. Tobacco smoke remains the principal factor in lung carcinogenesis, followed by indoor radon, a natural radioactive gas found in indoor environments [9, 10]. In addition, polymorphism in several chromosome regions (i.e. the cholinergic nicotine receptor genes) have been associated to lung cancer susceptibility, while less evidence has been found in association with the diet and alcohol consumption [11]. A clear understanding of the effect that these factors may have will be of utmost importance for the implementation of preventive policies.

On the other hand, the development of more efficient diagnostic and treatment models contributes to control cancer incidence and mortality. It has been challenging to advance in this direction due to the complexity of lung carcinoma at the molecular and histological level. In general terms, two main groups have been described based on tumour histology and prognosis: small-cell carcinoma (SCLC) and non-small-cell carcinoma (NSCLC) that represent about 85% and 15% of all lung cancers, respectively [12, 13]. In turn, NSCLCs are classified into adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large-cell carcinoma (LCC). Additionally, distinct genetic variants have influence in disease prognosis, including mutations in the epidermal growth factor receptor (*EGFR*) gene, the Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*) or the B-Raf Proto-Oncogene, Serine/Threonine Kinase (*BRAF*) [13].

These elements, together with other patient characteristics and risk factors are relevant for the revision of preventive and treatment protocols, including the implementation of lung cancer screening programs via low-dose computed tomography (CT), which could provide significant benefits when applied to high-risk populations [14]. International consent in the generalised use of such screenings has not been reached; however, European experts recommend their application, following a risk stratification approach to be based on an accurate description of the population at risk [15]. In addition, the access to real-world evidence that reflects current practice from complementary observational prospective and retrospective studies is considered crucial to revise preventive and treatment protocols, and to develop adequate resource allocation strategies [16, 17].

Thus, the aim of this study was to describe the characteristics of patients with lung cancer in Spain and any factors that may play a role in lung cancer mortality, identify any temporal

tendencies and analyse patients' use of medical resources and direct medical costs of secondary care.

Methods

Study setting and design

Healthcare records of patients admitted with lung cancer in primary and specialised healthcare centres in Spain were analysed in a retrospective multicentre observational study. Data was obtained from the Primary Care Dataset and the Centralised Hospital Discharge Database via the Spanish Ministry of Health, two databases that compile data from private and public healthcare centres representative of all Spanish regions [18]. Data is codified at the centre or hospital level by specialised doctors by using the Spanish ICD codification guides made available to health professionals, and centres are responsible for data codification, evaluation and confidentiality. Each database is validated internally and subjected to periodic audits. In this process, errors and unreliable data are eliminated. Data inclusion was established to comprise most recent available data at the moment of the analysis, starting 1 Jan 2011 to 31 Dec 2016.

Data extraction

Records of admissions in which lung cancer was registered as the admission motive were petitioned and identified by means of the International Classification of Primary Care second edition (ICPC-2) and the 9th and 10th revisions of the International Statistical Classification of Diseases and Related Health Problems, clinical modification (ICD-9-CM and ICD-10-CM) codes. The corresponding ICD-9-CM and ICD-10-CM were used to identify lung cancer diagnoses and tumour location, and, when available, the International Classification of diseases for Oncology, third edition (ICD-O-3) was used to categorise tumour morphology (Table 1).

The Spanish Ministry of Health was in charge of data extraction, with any parameters identifying the medical history and health centres previously re-coded to avoid any access to identifying information in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In such cases the Spanish legislation does not require patient consent and ethics committee approval according to the Law 14/2007, 3 July, on biomedical research, Spain [19]. Patients were not directly involved in the research or the study design.

Study variables

Both databases register information about the patient and admission details. Primary care data includes patients' sex, age, income level and employment status, centre location, date of admission and admission motive. The secondary care database registers patients' sex and age, hospital location, date of admission, type of admission, date of discharge, type of discharge (including death), service to discharged the patient, length of stay, readmission rate, admission motive, secondary diagnoses registered during the admission, tumour morphology (codified with the International Classification of diseases for Oncology (ICD-O-3) codes), medical procedures performed and cost of the admission.

Data analysis

Admission motive data was used to identify patients with lung cancer. Primary care records were analysed to determine patient characteristics and socioeconomic profile; all secondary care admission records were used to evaluate patient journey upon hospitalisation: nature of the admission, services to discharge the patient, days of stay and medical procedures. The analysis of patient characteristics via single-patient data was based on the first admission registered per patient due to lung cancer.

Direct medical costs of secondary care were estimated by using the admission cost determined in the database, based on the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health. This calculation included all expenses related treatment (examination, medication and surgery), nutrition, costs associated to personnel, medical equipment and resources.

To describe the patient population patients were grouped according to tumour histology. A descriptive univariate analysis was done. Frequencies and percentages are presented for dichotomous variables and mean and standard deviation or error were calculated for parametric quantitative variables. Odd ratios (OR) with 95% confidence interval (CI) were used to assess the association of secondary conditions with in-hospital mortality, with the group of patients non-deceased during the hospitalisation as the reference group. Two-tailed T-student or one-way analysis of variance were used according to data distribution and two-sample Z tests were used to test for differences in sample proportions, with a $p<0.05$ considered statistically significant in all cases.

Statistical analyses were performed using StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA) and Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

Data obtained from primary care registries corresponded to 26,188 admissions from 12,119 patients with a diagnosis of lung or bronchial cancer between 2011 and 2016. Separately, the database for hospitalisation and specialised care included 173,592 entries with lung or bronchial cancer as the admission motive that corresponded to 113,574 patients (Table 2). Males represented the majority of patients, and were significantly older than female patients in both settings ($p<0.001$).

Over 73% of the records included a histological description of the tumour. Only 14.71% of the specified diagnoses were of SCLC while 85.29% corresponded to NSCLC (Figure 1A). Overall, adenocarcinoma was the predominant tumour typology, with no differences observed between males and females. Additionally, tumour location was specified in 57.51% of secondary care files. Data suggested a predominance of patients with the tumour located in the upper lobe of the bronchus or lung (Figure 1B).

The temporal analysis revealed a minor increase in the number of patients diagnosed in primary care centres during the study period, from the 1,549 patients attended in 2011 to the 2,087 patients attended in 2016. The percentage of males attended in these centres steadily decreased, while the percentage of females increased ($p<0.001$, 2011 vs. 2016) (Figure 2A). On the contrary, the number of patients attended in secondary care remained stable over the study period; however, a slight decreasing trend was observed among males, compensated by an increase in the percentage of female patients (Figure 2B).

The principal diagnosis upon hospitalisation (admission motive) was in all cases a lung carcinoma, and secondary diagnoses were utilised to perform an analysis of relevant comorbid conditions at the hospital level. Metastatic or secondary malignant neoplasms were registered in 76.66% of patients with a lung carcinoma (Table 3). The second most repeated comorbidity was hypertension, found in 33.57% of patients. A history of tobacco use appeared in 25.29% of patients. Respiratory symptoms were common among these patients, as respiratory failure and bronchitis, likely to be symptoms of the disease. Chronic obstructive pulmonary disease (COPD) was registered in 12.19% of all patients. Other registered comorbidities were disorders of lipoid metabolism and diabetes mellitus, diagnosed in 23.02% and 21.39% of patients respectively.

In-hospital mortality was 22% during the study period. Overall, 82.00% of patients deceased were males, averaging 69.06 (SD=10.88) years. Females represented only 22.66% of deceased patients, and had a mean of 65.69 (SD=13.27) years. Mortality was significantly higher in patients diagnosed with a SCLC, reaching the 29.62% ($p<0.001$).

Metastatic and secondary malignant neoplasms were more commonly diagnosed in this group and the overall number of malignant neoplasms was superior to the number of patients deceased, indicating the presence of multiple tumours per patient. Respiratory failure was associated with death in this population. Overall, the number of patients deceased during hospitalisation remained stable over the study period.

The vast majority of hospitalisation records included in the analysis (98.81%) corresponded to inpatient care, with a predominance of non-scheduled admissions that summed 64.58% vs. 35.42% of scheduled admissions. Only 16% of those were due to readmissions, understood as a second admission within a 30-day period following discharge.

Patients were hospitalised 9.57 days on average, 10.63 days when admissions were due to emergencies and 7.63 days in scheduled admissions. Internal medicine was the service to discharge 25.44% of the patients, 23.78% were attended by oncology services, 21.24% by pneumology and pulmonology services, 18.81% by thoracic surgery services and 4.85% by palliative care services. Altogether, imaging techniques were frequently used to diagnose these patients, as well as biopsies of distinct organs (Table 4). Chemotherapy was administered in 18.21% of all admissions, and lung resection performed in 12.08%.

Socioeconomic data gathered in primary care centres indicated that 70.90% of the patients had an annual rent under the €18,000; 11.81% of the patients were not active or unemployed while 74.14% were pensioners. Finally, a direct cost was associated to each admission in accordance with the nature of the hospitalisation process and medical

procedures utilised. The database registered a direct medical cost of lung cancer that reached the €962.6 million solely considering secondary care.

The mean cost per patient was €8,475, increasing significantly over the study period, from €8,364 per patient the year 2011 to €9,164 per patient the year 2016 ($p<0.001$). Interestingly, within the group of patients with an unspecified tumour type, SCC was responsible for the highest costs per patient, €9,101 on average ($p<0.001$), whereas, when the total costs incurred by these patients was considered, adenocarcinomas were the NSCLC responsible for the largest portion of medical costs ($p<0.001$) (Figure 3).

Discussion

Lung cancer epidemiology has been extensively investigated in Spain, with special emphasis in the trends followed during the eighties and nineties when the first measures to control tobacco consumption in public buildings were implemented. A clear association was observed between these measures and lung cancer incidence, reversing the increasing incidence trend observed until 1994 among males aged 65-74 [7]. A more restrictive legislation was approved the year 2005 and updated in 2011 including the prohibition of smoking in bars and restaurants [20, 21]. This study aimed to analyse tendencies in lung cancer occurrence after 2011, to determine the characteristics of the population at risk and to provide complementary epidemiologic data to on-going observational studies.

The number of new lung cancer cases slightly increased in primary care while it remained stable in secondary care between 2011 and 2016. The portion of females increased in both cases. In addition, females diagnosed with a lung carcinoma were significantly younger than males. Previous data gathered between 1996 and 2002 indicates the higher smoking prevalence in Spanish girls aged 15–17 years old, accompanied with heavier smoking habits [22]; however, it is not clear whether enough time has elapsed to extract definitive

conclusions. Likewise, the expected differential incidence of SCLC and NSCLC in males and females was not observed herein [9]. The differential trends in incidence in males and females have been previously observed, however, geographic and socioeconomic differences play an important role [23, 24]. The proportion of SCLC and NSCLC, 15% vs. 85% was consistent with previous descriptions, as it was the greater prevalence of adenocarcinoma [25].

Hospitalisation records showed the importance of internal medicine services in the treatment of lung cancer, together with oncology and pulmonology services, supporting the need of establishing protocols that facilitate a multidisciplinary care of the disease, called to improve patients' prognosis [26]. Consequently, the great number of emergency admissions found in this patient population could be reduced.

Regarding patient survival, the database does not permit an analysis of lung cancer mortality due to the lack of data on deaths occurred outside of healthcare centres. In-hospital mortality was 22% over the study period, reaching the 29.62% in patients with SCLC, and remained stable between 2011 and 2016. Data gathered in Spain between 1975 and 1989 showed relative increments in mortality, especially among males, that contrasted with the decreasing trends measured in countries as England and Switzerland [27]. In general terms, global data indicates a decrease in lung cancer mortality over the past years, resulting from the decreasing mortality among males [28].

The segregate analysis of patients that died during the hospitalisation provided interesting data. Previous studies associated the presence of comorbid conditions in lung cancer directly to survival [29]. Herein, several differences appeared between the patients that died and the total patient population. The presence of metastatic and secondary malignant neoplasms appeared determinant in this pool of patients. On the other hand, the registration

of other comorbidities as tobacco smoking appeared low at the hospital level. Preliminary results obtained from an observational cohort study taking place in Spain, indicated that up to 86% of patients hospitalised due to lung malignant neoplasms could be current or ex-smokers, which could indicate an incomplete registry of such factors in Spanish hospitals [30]. Alcohol consumption has been previously appointed as a factor in lung cancer carcinogenesis, however, evidence in never smokers is contradictory [31, 32]. Similarly, the diagnosis of diabetes has been previously associated to a worsened prognosis in lung cancer patients, an affect that was not observed in this database [33, 34]. Nonetheless, it must be taken into account that data registered upon admission may be incomplete.

In terms of medical costs, evaluations made in the United States measured a mean direct medical cost per NSCLC treatment of around €14,000 per patient, with strong variations depending on cancer stage [35]. Similarly, calculations in Australia show mean annual costs of cancer care of around €2,800 per patient that increase to €31,000 the last year of life [36]. Data obtained in different countries by distinct methods is hardly comparable, although in all cases delayed diagnoses suppose an important increase in costs. The present study shows a small increasing trend in the cost per patient over time that could be compensated by the implementation of prevention and early screening measures.

It is plausible that a number of limitations may have influenced the results of this study. The database providing secondary care data is codified with ICD-9 and ICD-10 codes, thus, data reliability is subjected to the accuracy of codification achieved at the hospital level. In addition, the shift from ICD-9 to ICD-10 between the years 2015 and 2016 should be taken into account to interpret quantitative data. The analysis of secondary conditions was limited to those registered upon admission and to secondary care and may not represent disease comorbidity. Finally, the analysis of direct medical costs was restricted to

secondary care settings and pharmaceutical were not quantifiable via this database. Further research should consider all medical costs to increase comparability.

Conclusions

Overall lung cancer incidence appeared stable in secondary care centres, yet, given the relative increase of female patients, preventive or early detection measures are recommended to reverse this trend, which is likely to have an influence in disease costs. In addition, a multidisciplinary approach is called to optimise patient journey. The potential roles of disease comorbidities in lung cancer prognosis should be further explored.

List of abbreviations

ADC: Adenocarcinoma.

CT: Computed tomography.

ICD-O-3: International Classification of diseases for Oncology, third edition.

ICD-9-CM: 9th revision of the International Statistical Classification of Diseases and Related Health Problems, clinical modification.

ICD-10-CM: 10th revision of the International Statistical Classification of Diseases and Related Health Problems, clinical modification.

ICPC-2: International Classification of Primary Care, second edition.

LCC: Large-cell carcinoma.

NSCLC: Non-small-cell carcinoma.

SCC: Squamous cell carcinoma.

SCLC: Small-cell carcinoma.

SD: Standard deviation.

Transparency section

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Declaration of financial and other interests

The authors have declared that no competing interests exist.

Authors' contributions

JD contributed to the investigation by analysing and interpreting the economic situation of lung cancer in Spain and was a major contribution in the intellectual content revision. AM analysed the evolution of lung cancer management over the study period and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Parameters identifying the medical history and health centres were re-coded prior to extraction to avoid any access to identifying information in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In such cases the Spanish legislation does not require patient consent and ethics committee approval according to the Law 14/2007, 3 July, on biomedical research, Spain. Patients were not directly involved in the research or the study design.

Availability of data and materials

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm

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Tables

Table 1. ICD-9-CM, ICD-10-CM and ICD-O-3 codes used to identify lung cancer diagnoses and classify tumours.

Setting and coding system	Years	Codes	Description
Diagnoses and tumour location	-	-	-
Primary care (ICPC-2)	2011-2015	R84	Malignant neoplasm of bronchus/lung
Secondary care (ICD-9-CM; ICD-O-3)	2011-2015	162.2–162.9; 209.21	Malignant neoplasm of bronchus and lung
Secondary care (ICD-10-CM; ICD-O-3)	2016	C34.0–C34.92	Malignant neoplasm of bronchus and lung
Tumour type	-	-	-
Secondary care (ICD-O-3)	2011-2015	8012; 8041–8043; 8070–8076; 8140–8141	Large cell carcinoma; Small cell carcinoma; Squamous cell carcinoma; Adenocarcinoma

Table 2. Patient descriptive parameters and tumour classification according to ICD-9-CM and ICD-10-CM.

Setting	N	% of patients	Age (SD)
Primary care centres	12,119	-	68.04 (12.34)
Males	9,360	77.23	68.97 (11.52)
Females	2,759	22.77	64.89 (14.35)
Secondary care centres	113,574	-	67.44 (11.25)
Males	90,389	79.59	68.16 (10.71)
Females	23,181	20.41	64.63 (12.77)

Table 3. Secondary conditions registered in more than 10% of all patients and of deceased patients.

Secondary diagnoses	% of all patients	% of deceased patients	Odds ratio, 95% CI
Secondary or metastatic malignant neoplasm	76.66	104.25	2.02 (1.98-2.06)
Malignant neoplasm of bone	16.50	28.20	2.12 (2.06-2.19)
Malignant neoplasm of respiratory system	15.55	24.14	1.80 (1.74-1.85)
Malignant neoplasm of the liver	12.46	22.61	2.39 (2.31-2.47)
Unspecified essential hypertension	33.57	24.90	0.86 (0.84-0.89)
History or current tobacco use	25.29	18.17	0.83 (0.81-0.85)
Disorder of lipoid metabolism	23.02	15.91	0.75 (0.73-0.78)
Respiratory failure	15.21	20.29	3.52 (3.41-3.64)
Diabetes mellitus	21.39	48.95	0.99 (0.96-1.02)
Bronchitis	10.05	10.50	1.06 (1.02-1.11)
Chronic obstructive pulmonary disease	12.19	9.11	0.87 (0.84-0.91)
History or current alcohol dependency	11.06	22.47	0.87 (0.84-0.91)

Table 4. Medical procedures registered in patients with lung cancer.

Medical procedures	% of admissions
Imaging	-
Thorax tomography	38.95
Abdomen tomography	18.51
Thorax radiography	21.69
Biopsy	39.77
Lung and bronchus	12.52
Lymph nodes	3.98
Chemotherapy	18.21
Radiotherapy	3.15
Surgery	-
Lung resection or excision	12.08
Respiratory therapy	22.96
Oxygen enrichment	10.61
Mechanical ventilation	1.62
Medication via nebulizer	4.28

Figures

Figure 1. Percentage of patients per tumour typology (A) and location (B).

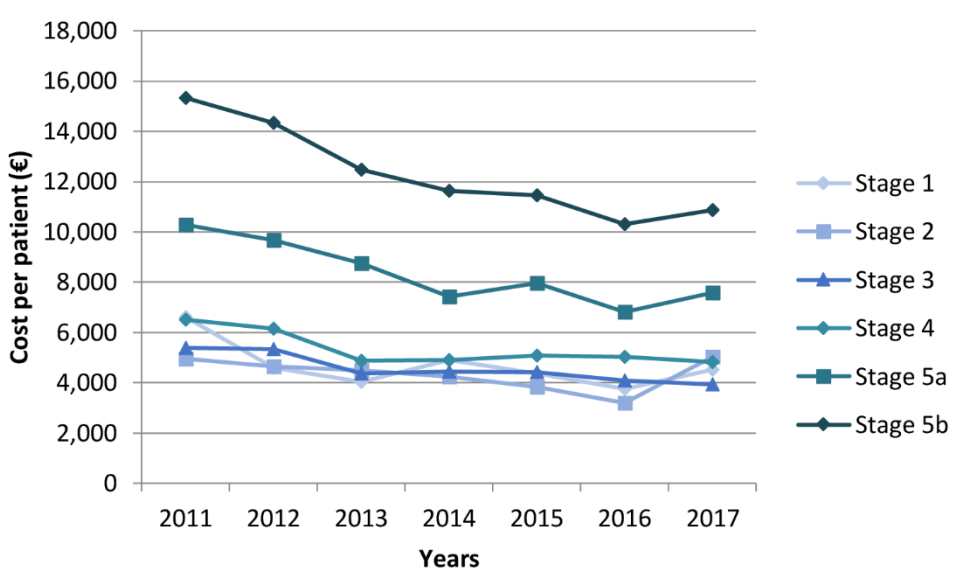

Figure 2. Percentage of male and female patients admitted with lung cancer in primary (A) and secondary care centres (B).

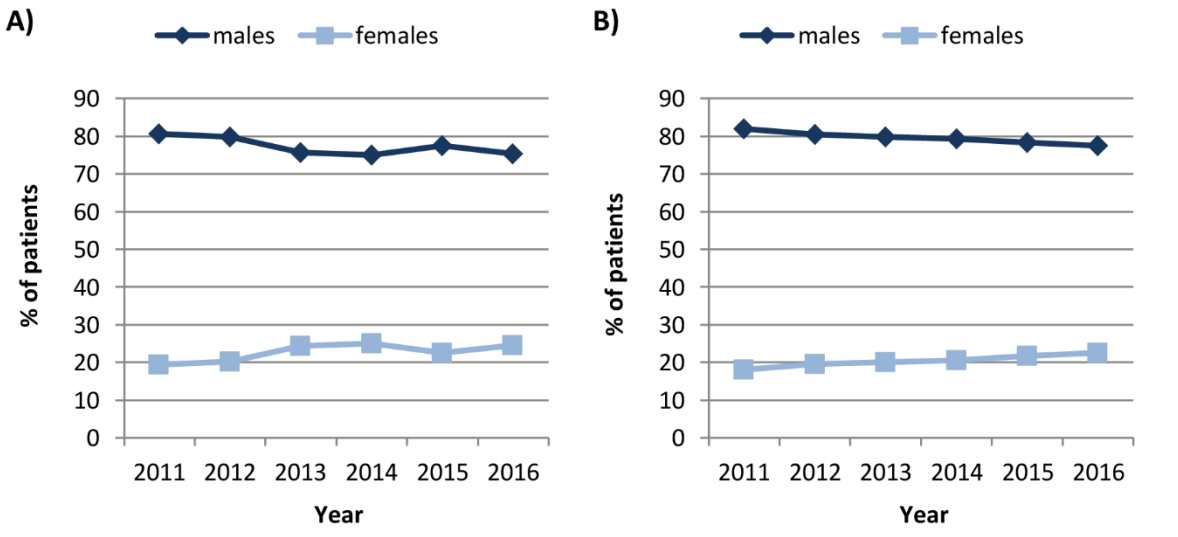

Figure 3. Annual direct medical cost estimated for the group of patients with a specified tumour.