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Original article

Cost-effectiveness analysis of stereotactic body radiotherapy and surgery for medically operable early stage non small cell lung cancer

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ABSTRACT

Background: Projections estimate an increase of 50% of the incidence of lung cancer by 2030. Early-stage non-small cell lung cancer represented 19% of NSCLC cases diagnosed in the US between 2005 and 2011. There is rising evidence in favour of lung cancer screening, which will reduce the occurrence of later-stage lung cancers while raising the incidence of early-stage NSCLC. Current guidelines state that for early-stage NSCLC, surgical resection should be performed, and stereotactic body radiotherapy (SBRT) is an option for patients who are non-medically operable. In this study, we compared the cost-effectiveness of SBRT with lobectomy in medically operable patients.

Methods: We developed a Markov model based on the survival results of two randomized studies comparing SBRT and video assisted thoracoscopic surgery (VATS) lobectomy in early-stage NSCLC, to describe survival and treatment related complications of patients treated for early-stage NSCLC. This analysis was conducted from the French payer perspective on a lifetime perspective. Utility values, recurrence risks, and costs were adapted from the literature. Deterministic (DSA) and probabilistic (PSA) sensitivity analyses were performed to assess the influence of the assumptions made.

Results: The Markov model developed was consistent with survival data reported in the pool analysis of the randomized studies. SBRT and lobectomy total costs were 9,234.15€ and 10,726.98€, respectively, and the quality-adjusted life expectancies were 16.35 and 15.80 QALYs, respectively. The DSA, run on every assumption made, revealed that the incremental cost-effectiveness ratio was mainly sensitive to the decrement of utility caused by treatment related complications and initial cost of both surgery and SBRT. The PSA showed that SBRT had the highest probability of cost-effectiveness compared to lobectomy.

Conclusions: This is the first medico-economic study evaluating SBRT and lobectomy in stage I NSCLC based on randomized studies, and our analyses suggest that SBRT is dominant over lobectomy in operable early-stage NSCLC treatment. Deterministic and probabilistic sensitivity analyses confirmed that this result was robust and that it was not modified by the assumptions made in the Markov model building.

In 2012, lung cancer occurred in 1.8 million people and caused 1.6 million deaths around the world [1]. In the US, lung cancer incidence was 225,000 new cases in 2017 with a male/female ratio of 1:1, whereas in France, the reported incidence for 2012 was 39,495 with a male/female ratio of 2.5:1 [2,3]. Projections estimate an increase of 50% of the incidence of lung cancer by 2030, for a total of 338,000 new cases per year in the US [4]. Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancers [2]. Moreover, Colonna reported that stage I and II NSCLC represented 19% of NSCLC patients diagnosed in the US between 2005 and 2011 [5]. There is rising evidence in favour of lung cancer screening in smokers and former smokers. The national lung screening trial data demonstrated that a screening by low-dose chest CT scanning reduced the occurrence of later-stage lung cancers and that 70% of the cancers diagnosed were stage I [6]. Current guidelines state that for early-stage NSCLC, surgical resection should be performed and radiotherapy is an option for patients who are non-medically operable [7]. However, due to the projected increase in early-stage NSCLC incidence, the assessment of cost-effectiveness of the therapeutic alternatives is mandatory. Moreover, despite the pool analysis of two randomized phase III studies, STARS and ROSEL reported a significant better overall survival for patients treated with SBRT; however, the hazard ratio confidence interval included 1, and no difference in progression free survival evidence is lacking.

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In this study, we compared the cost-effectiveness of SBRT with lobectomy in medically operable patients.

Methods

We designed a Markov model to simulate the clinical trajectory of a patient with medically operable stage I NSCLC. Markov simulation is a statistical method that allows the simulation of the transition of a hypothetical cohort of patients between different health states in fixed increments of time. The model was created and analysed with the Heemod package for R [8].

Strategies

Two treatment strategies were compared: SBRT and lobectomy. Patients began in the progression free survival (PFS) state, after receiving either SBRT or lobectomy. At each cycle, patients stayed in the PFS state or progressed to a recurrence state, including local recurrence (LR) and regional recurrence (RR), distant recurrence (DR), or death. From the recurrent state, the patient could stay in the same state or progress to death. Cycle length was 1 month.

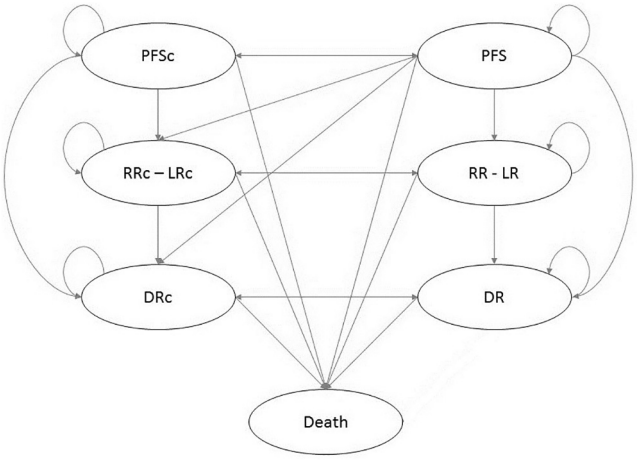

Fig. 1. Schema describing the Markov model build, its health states and the transitions between them. PFS: progression free survival; PFSc: progression free survival with complications of the treatment; RR-LR: regional and local recurrence; RRc-LRc: regional and local recurrence with complications of the treatment; DR: distant recurrence; DRc: distant recurrence with complications of the treatment.

Decision model

We assumed that all patients had no radiological evidence of nodal disease before treatment.

Patients who received SBRT were exposed to a risk of grade 2 and 3 pneumonitis right after the end of the treatment. Grade 2 pneumonitis was treated with a daily administration of prednisone for 3 months, and grade 3 pneumonitis was treated with a daily administration of prednisone and home oxygen for 6 months. Patients who received SBRT were also exposed to chest wall pain 6 months after the end of SBRT and were treated with oxycodone, acetaminophen and lactulose for 6 months [9].

Patients who underwent video assisted thoracoscopic surgery (VATS) lobectomy had an immediate risk of death related to the surgery, a risk of chemotherapy according to nodal pathologic evaluation and a risk of complications [10]. Patients had an immediate risk of infectious pneumopathy and its cost was taken into account in the initial treatment cost. Chemotherapy included 4 rounds of Cisplatin 80 mg/m^2, administered the 1st day, and Vinorelbine 15 mg/m^2, administered the 1st and the 8th days of the cycle. Chemotherapy treatment also included the administration of setron for 1 day, aprepitant for 3 days, prednisone for 4 days and a blood test before every chemotherapy administration. We also considered the implantation of a central venous access system. The probability of undergoing chemotherapy was estimated according to positron emission tomography–computed tomography (PET-CT) sensitivity [11]. Patients were exposed to a risk of atrial fibrillation right after the surgery and treated with daily administration of Vitamin K Antagonist (VKA): fluindione, with a monitoring of the international normalized ratio (INR) every 3 weeks for 3 months. Patients were also exposed to dyspnoea and chest pain right after the surgery and treated as patients in the SBRT arm, for a total duration of 12 months [10,12–14].

The Markov model is represented in Fig. 1.

Disease and treatment assumptions

We derived probabilities of transition from PFS to LR-RR and DR for SBRT and lobectomy from the pooled analysis of STARS and ROSEL, two randomized studies that compared SBRT and lobectomy for operable stage I non-small cell lung cancer [15]. To model the transition probabilities, we retrieved the raw data using the statistical method described by Guyot et al. [16]. Probabilities of transition from LR, RR and DR to death were retrieved using the same method from a study evaluating the survival of 1361 consecutive patients treated by lobectomy, and we assumed that this rate was similar in patients initially treated with SBRT, as it should not depend on the initial treatment modality [17].

We assumed that non-cancer related death rates were similar to the mortality rate published by the World Health Organization (WHO) for the general population [18]. We defined the probability of transition from PFS to death as the mortality probability, according to the age of patients in the general population, as reported by the WHO. For patients undergoing lobectomy, the surgery related mortality probability was retrieved from Falcoz et al. [12].

Utilities

There are very few specific utilities related to health states and complications in patients treated for early-stage NSCLC reported in the literature; hence, we managed to take this uncertainty into account by testing different assumptions in sensitive analyses. We used PFS and recurrence health state utilities as baseline utilities, and we applied utility decrement for complications and chemotherapy. PFS and recurrence health state utilities were retrieved from Doyle et al. [19]. In this study, volunteers from the United Kingdom assessed their preference for each health state in a chained standard gamble interview and on a visual analogue scale rating scale. Health states were defined for advanced NSCLC.

Complications of chemotherapy related utility decrements were retrieved from a literature review and are summarized in Table 1 [20,21].

Costs

Our study was conducted from a French payer perspective, using payment data applicable in public hospitals in 2017.

For treatments delivered at the hospital, the French payer defined diagnosis-related groups called *Groupes Homogènes des Malades* translated in English to "Homogeneous Groups of Patients" (HGPs). HGPs are defined by the major diagnostic category (MDC) and patient's comorbidities; for the same MDC, four HGPs were defined depending on the severity of the patient related to the comorbidities [22]. Each HGP has one or more HGPs corre-

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