STUDY PROTOCOL

Cost-effectiveness evaluation of robotic surgery, compared to thoracoscopic and open surgery, in the removal of lung lesions based on "real-world" efficacy and cost data from the ATS of Milan

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1. RATIONALE AND INTRODUCTION

Robotic surgery in the pulmonary field: introduction and uses

Robotic surgery is a type of minimally invasive surgery in which the surgeon sits at a console from which, using mechanical arms, he/she controls the instruments inserted into the patient endoscopically [1]. The purpose of this technology is not to replace the surgeon, but to assist him in carrying out increasingly precise operations [2]. Historically, the first uses of robotic surgery date back to the early 1990s and involved abdominal surgery. Currently, in Italy, the greatest use is in the urological sectors, mainly in radical prostatectomy, and in gynecology [3]. However, the use in the thoracic area is spreading rapidly [4]. The use in this area dates back to 2001, when a group from Pisa performed the first lobectomy with the use of the da Vinci® robot. The surgeons completed five robotic lobectomies without mortality [5]. Subsequently, the use of the robotic platform in thoracic surgery expanded and the publication of several studies, including a multicenter one, testifies to its development [6]. With regard to pulmonary pathology, it is used both in benign pathology such as bronchiectasis, granulomas and alveolar echinococcus [7], and in the removal of solitary pulmonary nodules, whose nature is to be determined and whose treatment must be minimally invasive. It is also used in diagnosed small cell lung tumors (SCLC) and not (NSCLC) [8]. Moreover, lung metastases and carcinoid tumors were also removed [9].

Epidemiology of lung cancer and indications for surgical treatment

In Europe, lung cancer remains in second place among the most frequent neoplasms in men with 14.2% in 2020, after prostate cancer, while it is in third place with 9.1% in women, after breast cancer and colorectal cancer. Italy reflects the European trend, with 14.1% in men and 7.3% in women [10]. However, in some countries, such as the United Kingdom and Northern Europe, it is now in second place also in women [11]. As regards mortality, lung cancer causes 20.4% of deaths from cancer, remaining the most frequent cause of death from cancer. In fact, five-year survival for lung cancer is still around 18%, respectively 15% for men and 21% for women; this is also due to the high percentage of advanced stage diagnoses [12]. NSCLC represents 80-90% of cases of lung cancer, while SCLC frequency is around 14% [13,14]. As far as Italy is concerned, in 2020 lung cancer was the first cause of cancer mortality in men (23.9%) and the second in women (12.5%) [10]. In the ATS of Milan area in the three-year period 2016-2018, only 23.4% of lung cancers for all ages were diagnosed in stage I and II, and 76.6% in stage III and IV [15]. When the tumor is resectable, and the patient can undergo surgery, the most indicated treatment for this kind of tumor is surgical removal. The National Institute for Clinical Excellence (NICE) recommends to offer surgical treatment to all patients with NSCLC up to stage IIIB. Furthermore, the NICE guidelines suggest lobectomy as a curative intervention when possible, not specifying a preference between the open and the thoracoscopic approach (NICE Guideline 2019). On the contrary, the European Society of Medical Oncology (ESMO) specifies that VATS is the preferable approach in stage I tumors. However, this recommendation has a level of evidence V (studies without control groups, case reports, and expert opinions) and a rating C (insufficient evidence of efficacy).

Characteristics of robotic surgery

As regards the structural characteristics, the robotic systems developed so far can have two types of design: a single-arm one for single-access surgery and a multi-arm one for procedures with multiple surgical accesses. Important advantages of the multi-arm system are the ability to cover a larger operating field, to insert and maneuver instruments more easily and to allow for better visibility [16]. Among the 22 developed robotic surgery systems: 13 are still to be refined, 7 are commercialized (da Vinci SI®, da Vinci SP®, da Vinci XI®, da Vinci X®, Freehand v1.2, Surgenius Beta and Senhance™ Surgical System), 1 is used only for research, and 1 is dedicated only to the transoral and transanal surgical approach [17]. The seven systems currently on the market are manufactured by four companies. Intuitive Surgical is the American company that produces the da Vinci® robots. It was founded in 1995 and represents the world leader in the sector; it has so far launched four generations of robots, of which three are currently on the market. The da Vinci XI® has four robotic arms and enjoys the most advanced instrumentation, the da Vinci X® has the same architecture as the XI, but uses a more economical technology that allows to reduce costs, the da Vinci SP® instead has a single arm architecture. All Intuitive Surgical systems are CE marked and FDA cleared. Surgica Robotica is an Italian company that currently offers the Surgenius Beta system, and it is developing the Surgenius Gamma. Surgenius Beta has the CE mark. TransEnterix is an American company that manufactures the Senhance™ Surgical System, an FDA-approved and CE-marked three-arm robot. Freehand Ltd is a British company that manufactures Freehand v1.2, a single arm robot with a camera, FDA cleared and CE marked [17].

The platform of the most used robotic system, the da Vinci, consists of several components: the surgeon's console with a three-dimensional vision system and two manipulators, a surgical cart with one or more arms that execute the surgeon's commands, the Endowrist® instrumentation that allows 7 degrees of movement that simulate and amplify the movements of the human hand and wrist, and a visualization system with 3D endoscopes that allows an enlargement of the image in real time. The absence of the tactile function is a significant problem that developers are trying to overcome with the technological innovation of haptic feedback, which allows the surgeon to "feel" the reaction of the tissue or organ to the force exerted [18]. Intuitive surgical, the leading manufacturer of robotic surgery platforms, estimates that over 5 million minimally invasive robotic procedures have been performed since 2000, with nearly 5000 units installed worldwide (https://www.intuitive.com/en-us). After the introduction of the da Vinci platform in Italy in 1999, there were 111 robots active in our county in 2019; of those 22 placed in Lombardy region [19]. To use the robotic platform, specific training is required. Usually. it is provided by the manufacturer and distributor and is addressed to both the surgeon and all operating room personnel, also involving anesthesiologists and sterilization personnel [19]. In the area served by the ATS of Milan, the Training School in Robotic Surgery of the Department of Health Sciences of the State University of Milan was recently established.
The robotic lung-thoracic surgery system comes alongside open surgery and video-assisted thoracoscopy (VATS). VATS is a minimally invasive approach that does not require classic thoracotomy. VATS instrumentation includes optics in addition to classic thoracic or laparoscopic instruments [20]. Minimally invasive surgery (both robotic and VATS) has several benefits over open surgery, such as a lower risk of infection and a lower healing and recovery time, while maintaining overlapping efficacy outcomes [21]. Robotic surgery ensures a greater degree of flexibility compared to the laparoscopic approach, it allows to operate even in hard-to-reach locations, uses instrumentation with greater stability and allows a very precise three-dimensional view [2].
However, the cost of the necessary equipment is relevant; the purchase cost is about 1.7 million euros, while the annual maintenance represents about 10% of this sum. In addition, we have to add the costs

for disposable material and equipment with limited reusability (usually ten procedures). Consequently, the cost of this technology is high and volume dependent [4]. The European Society of Medical Oncology (EMSO) also highlights the fact that the robotic approach can be more expensive than the commonly used VATS [22]. On the other hand, in the robotic approach other costs are reduced, such as those related to hospitalization, the occupation of intensive care units, and the treatment of complications, which are reduced. Furthermore, there are potential advantages such as reduction of blood loss and tissue trauma, and less need for surgery conversion to open surgery compared to VATS. Furthermore, from the patient's point of view, there is an improvement in the quality of life (less pain, faster healing with consequent rapid return to work, less burden on caregivers). Lastly, this method has the advantage of improving ergonomics and reduce the physical effort of the surgeon [23]. Previous studies have attempted to evaluate the cost-effectiveness profile of this method in the thoracic area. Camberlin's study [4] is an HTA report carried out by the Belgian agency KCE, whose economic evaluation consists of a literature review for cost evaluation and a budget impact analysis. This study highlights that the cost structure of the different surgical approaches is very different and difficult to compare and the studies are generally of low quality. However, the analysis of the studies points out that robotic surgery is more expensive than traditional approaches such as thoracotomy and VATS. The systematic review by Turchetti [24] draws the same conclusion, while focusing on further relevant aspects: the facilitation in the execution of complex and advanced operations and the different role of the assistant surgeon during robot-assisted thoracoscopy operations. The organizational aspect most addressed in the literature was instead the training course for the use of the robotic surgical platform [19].

2. OBJECTIVE

2.1. PRIMARY OBJECTIVE

The objective of the analysis is to compare the cost-effectiveness profile of robotic surgery with that of thoracotomy and VATS in the surgical treatment of operable lung cancers in the adult population of the ATS of Milan.

2.2. SECONDARY OBJECTIVES

The secondary objective of the study is to compare the cost-effectiveness profile of robotic surgery versus that of thoracotomy and VATS in the surgical treatment of benign lung lesions in the same population.

3. METHODS

3.1. OVERALL DESIGN AND ORGANIZATION OF THE STUDY

Single multicenter retrospective observational study with Real World Evidence (RWE) approach [25], i.e. an evaluation that uses real-world data (RWD) derived from healthcare flows of the ATS of Milan and data provided by participating centers on the basis of medical records/ clinical databases, both as regards the analysis of efficacy and safety and as regards the economic evaluation of direct costs. For the analysis of quality of life and the calculation of QALYs (quality-adjusted life years), validated questionnaires will be prospectively administered to the participating subjects. The Epidemiology Unit of the ATS of Milan is the study promoter and it will coordinate the collection of data and will carry out the statistical and economic analyses. Other participating centers will be the

thoracic surgeries of the ATS hospitals, which carried out in 2019 (last pre-pandemic COVID-19 year) at least 50 lung operations with the ICD-9-CM codes shown in Table 1.

Table 1

ICD-9-CM code	Description
32.29	Other local excision or destruction of lesion or tissue of lung
32.3	Segmental resection of lung
32.4	Lobectomy of lung
32.5	Pneumonectomy

Both for the evaluation of clinical efficacy and of costs, the study will include all adult subjects (age equal or over 18 years of age at the time of surgery) residents in the ATS of Milan, who were hospitalized between 01/01/2016 and 31/12/2021 for pulmonary surgery (operation codes in any position of the hospital discharge summary form (SDO – Scheda di Dimissione Ospedaliera)) included in Table 1) and whose hospitalization is present in the SDO database of the ATS of Milan in one of the participating centers . For the evaluation of cost-effectiveness in malignant tumors, subjects with metastases at diagnosis will be excluded.

3.2. TECHNICAL CHARACTERISTICS OF ROBOTIC SURGERY, ORGANIZATIONAL AND ETHICAL ASPECTS OF THE TECHNOLOGY

The technical characteristics of the technology under evaluation will be summarized (ie type of device, procedure, etc.). A survey (**Annex 1**) will also be carried out at the participating centers to obtain indications on the temporal phases of acquisition of the technology in its subsequent developments in the territory under study. The organizational aspects will also be described, comparing them with those of the currently most widespread technologies according to the model proposed by Cacciatore et al. [26]. Finally, any problems of an ethical nature posed by the introduction of technology will be highlighted [27].

3.3. CLINICAL EFFECTIVENESS AND SAFETY

Within the evaluation of relative efficacy, we will evaluate clinical efficacy and safety, i.e. undesirable or harmful effects.

3.3.1. Design of the retrospective observational study for efficacy evaluation

For the group of patients who have undergone pulmonary surgery, extracted from the SDOs as described in paragraph 3.1, the surgical modality of each surgery will be identified starting from the administrative databases (ICD-9-CM codes 00.31-00.39 for robotic surgery and 34.21 for VATS in any location, Table 2). Given that preliminary assessments state a low sensitivity of these codes in identifying the surgical approach, this data will be supplemented by information relating to the surgical technique used and not contained in the SDO provided by the participating centers as reported in **Annex 2**.

Table 2 ICD-9-CM codes for the identification of interventions in VATS and robotic surgery

Surgery	Description	Code
VATS	Transpleural thoracoscopy	34.21
Robotics	Computer assisted surgery with CT/CTA	00.31
	Computer assisted surgery with MR/MRA	00.32
	Computer assisted surgery with fluoroscopy	00.33

Imageless computer assisted surgery	00.34
Computer assisted surgery with multiple datasets	00.35
Other computer assisted surgery	00.39

Following preliminary descriptive analyzes on these data, we will evaluate in which types of surgery, among those listed in Table 1, the three surgical methods under analysis are actually used (thoracotomy, video-assisted thoracoscopy (VATS) and robotic surgery). If open surgery is used, the approach will be further evaluated (i.e.posterolateral, muscle-sparing lateral, axillary or anterolateral, thoracosternotomy, or median sternotomy [28]. Instead, in case VATS method is used [29], it will be assessed whether a single surgical access technique (Uniportal VATS) [30], double access (Duke's approach) [31] or triple access (Copenhagen's approach) [32] was used. Furthermore, for ATS residents who underwent surgery a distinction will be made on the operations preceded by histological examination confirmatory of malignancy, comparing the date and the basis of diagnosis of the ATS cancer registry, from those performed for benign tumors and lesions with uncertain malignant potential.

3.3.2. Prospective study design for the evaluation of quality of life and efficacy

All subjects who will undergo lung surgery (Table 1) during 2022 at the participating centers and will give their consent to participate in the study by signing the informed consent form at the pre-hospitalization or at hospitalization before surgery will be eligible to be enrolled. To evaluate the quality of life PROMs related, we will use the generic questionnaire EuroQol-5 Dimension (EQ-5D-5L) and the specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORCT QLQ-LC29), which are available and validated in Italian [33,34]. The pre-intervention questionnaire will be completed on paper during hospitalization before the intervention or at pre-admission and the data will be entered into the web application of the ATS of Milan by dedicated staff. The subsequent questionnaires at day 7 and 30 can be self-completed by patients or electronically, using the dedicated web application of the ATS of Milan or in paper form, by filling in the documents issued on discharge for this purpose. At the first follow-up visit after 30 days, the patient will deliver the completed forms to the Thoracic Surgery department in charge of him. The Thoracic Surgery Department will forward all the documents, including pre-intervention documents, in a single mailing at the end of the study, to the Epidemiology Unit of ATS of Milan. The latter will enter the data and prepare it for subsequent analyses. The choice of how to complete the questionnaire will be left to the participating center. In both cases, when completing the first questionnaire, the study staff will enter the patient's fiscal code (patient identifier) in the application and a unique random ID will be generated which will be issued to the patient on paper so that he can enter it in the two subsequent self-compiled questionnaires. The information necessary for the evaluation of efficacy will be collected with the same modalities of the retrospective study. In addition to the evaluation of the quality of life, a questionnaire for the collection of patient experience (PREMs) will also be administered 30 days after the intervention or at the first follow-up visit [35,36]. The PREMs questionnaire will also be self-completed by patients either electronically, using the dedicated web application of the ATS of Milan, or in paper form, by filling in the document issued during hospitalization, the transmission of which to the Epidemiology Unit will take place with the methods indicated above.

Definition of efficacy outcomes

Efficacy and safety will be evaluated starting from the diagnosis and procedure fields of the SDO, from the life status derived from the ATS patient registry (NAR – Nuova Anagrafe Regionale) and from the data provided by the centers in terms of:

3.3.2.1. Efficacy

The evaluated outcomes will be related to two domains:

-How does technology affect the course of the disease?

Long-term survival

-How technology affects health-related quality of life?

Descriptive analysis of EQ-5D-5L and EORCT QLQ-LC29 questionnaire results by type of approach and surgical procedure

3.3.2.2. Safety

- 30-day mortality
- Reoperation during hospitalization
- Need for conversion to thoracotomy for VATS and robotic surgery
- Major complications by type of surgery (Table 3)

Secondly, differences in terms of duration of operation and hospitalization will be evaluated. This information will be used for the cost-effectiveness assessment.

Table 3 Complications of interest and related ICD-9-CM codes

COMPLICATION	CODE
Iatrogenic cerebrovascular infarction or hemorrhage Central nervous system complication (Brain anoxic damage, Cerebral hypoxia)	997.02 997.01
Cardiac complications, not elsewhere classified (Cardiac: arrest, insufficiency, cardiorespiratory insufficiency, heart failure)	997.1
Post traumatic pulmonary insufficiency	518.5
Urinary complications, not elsewhere classified (Renal: Acute defaillance, acute failure, acute tubular necrosis specified as due to interventions)	997.5
Postoperative infection, not elsewhere classified	998.5x
Hemorrhage or hematoma or seroma complicating a procedure, not elsewhere classified	998.1x
Persistent postoperative fistula	998.6

3.3.3. Collected variables

3.3.3.1. From administrative databases

The staff of the Epidemiology Unit involved in the study will extract the information specified in Table 4 from the current administrative databases of the ATS of Milan. Subsequently, it will perform the deterministic record linkage on a unique key (fiscal code) and will anonymize the dataset for the analysis, removing the tax code, deleting the dates once the time intervals necessary for the analysis have been calculated (age, length of hospitalization, length of post-operative stay, etc.), and assigning a random ID to the patient. Separate copy of correspondence between social security number and random id will be kept in a separate password protected file.

Table 4 Variables collected from administrative databases

Data flow	Data relating to	Variables
Hospital Discharge Summary (SDO)	Patient	Civil status, study level
	Hospital admission	Admission date, intervention date, discharge date, type of discharge, within hospital transfers
	Diagnoses and complications	All ICD-9-CM diagnosis codes present in a SDO
	Procedures	DRGs, ICD-9-CM procedure codes, procedure date
Patient registry	Patient	Sex, birth date, city of residence, vital status at 2022/12/31
SDO, outpatient services, pharmaceuticals, exemptions	Patient comorbidities	Charlson comorbidity index calculated through the algorithm in use at the Epidemiology Unit
Cancer registry	Cancer	Histology (morphological code ICDO3, margins of resection, number of mediastinal lymph nodes removed, number of positive mediastinal lymph nodes, stage at diagnosis)

3.3.3.2. From the data provided by the centers through a dedicated platform made available by the ATS of Milan

The Epidemiology Unit of the ATS of Milan has an IT platform, which can display the list of their patients included in the study only to clinicians who have or have had the patient in treatment. The same platform allows the clinicians in charge to view the information relating to the patient and pertinent to the study in question. Information can be derived from the administrative databases and from the internal databases of the center. The platform will also allow to fill in an ad hoc questionnaire, which will be piloted on 2 patients per center, for the collection of additional data necessary for the study. The information collected will form a database that will be linked via fiscal code to that derived from administrative flows passing through the third table of correspondence between random id and fiscal code. The questionnaire will collect the following information (details in the data collection form, **Annex 2**). Part of the information necessary for the study will be acquired by the Epidemiology Unit of the ATS of Milan directly from available internal information flows of the participating Centers. Specifically, this is information collected by the participating Centers in the context of collaboration with important projects for the construction of European and Italian registries (such as those of the ESTS (European Society of Thoracic Surgeons) and the Study Group and Italian Register of VATS Lobectomy) or which can be extracted by participating centers from computerized medical records. The participating centers will select the subjects included in this study and the variables included in the CRF of the same.

Table 5 Variables collected at participating thoracic surgery centers

Data relating to:	Variables
Intervention	Surgical approach - Open - VATS • Need for conversion to thoracotomy

	• Equipment used (brand and model) - Computer-assisted • Need for conversion to thoracotomy • Equipment used (brand and model)
Patient	Smoking habit Performance status
Complications	See Table 3

3.3.3.3. Quality of life questionnaires: PROMs and PREMs

Through the dedicated ATS application, the answers to the EQ-5D-5L and EORCT QLQ-LC29 questionnaires and to the PREMs questionnaire (**Annex 3**) will be collected in an electronic database. This database will have a unique ID code for the 4 questionnaires relating to each patient (generated at first administration and entered by the patient in the two subsequent self-administrations of the other three questionnaires). The database will be subject to record linkage with the administrative databases for data collection of the variables in Table 4. Furthermore, the variables in Table 5 will be collected by the referring clinicians. The collection methods will be the same used in the retrospective study.

3.3.4. Data analysis

3.3.4.1. Power of the study

To study the efficacy, data from the retrospective and prospective study will be analyzed jointly. For the retrospective part, approximately 5,000 patients operated on for lung cancer in the participating centers from 01/01/2016 to 12/31/2021 will be included. Based on the average of approximately 450 subjects operated on in the participating centers over 6 months during the years 2019-2021, a sample of 400 subjects eligible for enrollment in 6 months during 2022 was considered in the prospective observational study. As regards the statistical power in the analysis of the primary efficacy outcome, i.e. long-term survival, the calculation was based on an assumption of non-inferiority. The following formula was used to calculate potency in survival studies which is based on the hazard ratio [37].

$$1-\beta=\Phi(z-z_{1-\alpha}),\quad z=(\ln(\theta)-\ln(\theta_0))\sqrt{np_Ap_Bp_E}$$

Where:

θ_0 = hazard ratio under the null hypothesis, set equal to 1
θ = observed hazard ratio
pE = probability of event, i.e. death, set equal to 0.8 on the basis of epidemiological data from the ATS cancer registry
pA = proportion of treated by robotic surgery equal to 0.12 on the basis of the data present in the SDOs for the year 2019 and of the preliminary information provided by the participating centers
pB = 1-pA
n = sample size, equal to 5400
Φ = distribution function of the standard normal
A = I-type error, set equal to 0
$1-\beta$ = statistical power

By varying the observed HR of VATS death versus the observed control group between 1.08 and 1.15, the statistical power ranged from 0.5 to 0.91. The power calculation was performed using R (v4.1.2, R Core Team 2021, Vienna, Austria.)

As regards the analysis of quality of life, the prospective study will take into consideration patients undergoing three types of surgery: robot-assisted, VATS, and open surgery. Specifically, the number of groups enrolled is assumed starting from the average of interventions carried out in the period 2016-2021. Therefore, for the prospective study, we estimated 48 subjects operated with robotic surgery, 94 with VATS, and 258 with open surgery. Literature relating to the comparison of the quality of life in patients operated with VATS and open surgery [38] illustrates the analysis of the EQ-5D questionnaire at different post-intervention time points. The data of our interest relate to the mean and standard deviation of the Visual Analogue Score of the EQ-5D questionnaire administered 4 weeks after the intervention; respectively: VATS 78.1, Open 73.5. The one-way analysis of variance methodology was used to study the power. For robotic surgery, since the necessary data in the literature are not available, we assumed an average of the Visual Analogue Score EQ-5D ranging from 80 to 83, which allowed the calculation of the estimated power illustrated in the table below. A standard deviation of 17.2 was assumed for all three groups based on literature data [38]. For the analysis of statistical power, we used the PROC POWER procedure, statement ONEWAYANOVA of the SAS software (v. 9.4, SAS Institute Inc., Cary, NC, USA).

Mean Visual Analogue Score EQ-5D	Power
80	0.669
81	0.790
82	0.880
83	0.939

3.3.4.2. Efficacy study

Since this is an observational study, all analyses must take confounding into account. For each outcome, a Direct Acyclic Graph (DAG) will be prepared, discussed by surgeons and epidemiologists, i.e. a graph that allows hypothesizing the causal relationship between intervention and outcome taking into account potential confounding factors, measurable or not. On the basis of this graph, which underlies a causal model, the variables to be included in the multinomial regression model will be selected for estimating the probability of being treated with each surgical modality as a function of potential confounders (known as propensity score). Among the variables that will be considered to define the DAGs are age, gender, performance status, treatment center and tumor characteristics. The inverse of this estimated probability will be used as weight in the regression models (inverse probability weighted, IPW) which will have the outcome as the dependent variable and the treatment modality as the independent variable: robotics, VATS and thoracotomy (reference). Differences in the duration of surgery and hospitalization will be analysed using an IPW generalized linear regression model. The 30-day odds ratio (OR) of death for VATS and robotic surgery versus thoracotomy will be estimated by means of an IPW logistic regression model. Relative survival will be evaluated using a Cox IPW model and expressed both in terms of hazard ratio (HR) and as one and 5 year survival. For inpatient reoperation, the need for conversion to thoracotomy for VATS vs. robotic surgery and major complications by type of surgery,

which are expected to be rare events, a we will consider a IPW zero-inflated (Poisson or negative binomial) approach. All estimates will be presented together with 95% confidence intervals obtained from a robust standard error [39]. The same analyses, if allowed by the study number, will be repeated in the three surgical subgroups (atypical and segmental resection, lobectomy, pneumonectomy), in subjects aged less than or equal to 65 years vs. superior, in patients with performance status of 0 vs. 1 vs. 2. Sensitivity analyses will be carried out using alternative models for the probability of estimating the type of intervention.

3.3.4.3. Quality of life and patient experience

Descriptive analyses will be carried out, also using bar graphs, of the items of the EQ-5D-5L and EORCT QLQ-LC29 questionnaires, comparing the pre- and post-operative values for each surgical approach. Starting from the results of the EQ-5D, the utility index associated with the health-related quality of life (HRQoL) will be calculated, and will be summarized through appropriate measures of position and variability for the three surgical approaches. Differences between surgical approach in terms of utility index will be estimated using a model for longitudinal data weighted by the inverse of the probability of surgical approach, similarly to what is described in the previous paragraph. As regards the PREMs questionnaires, descriptive analyses of the individual items will be carried out globally and by type of treatment.

3.4. COSTS AND ECONOMIC EVALUATION

This is a *de novo* economic evaluation. The target population is the adult population undergoing lung surgery (atypical resection, segmentectomy, lobectomy, pneumonectomy) for benign or malignant pathology in the ATS of Milan, the intervention is the robotic surgical approach or computer-assisted surgery. This approach will be compared with both open surgery and VATS. The cost-effectiveness evaluation will be conducted according to the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) guidelines [40].

3.4.1. Economic evaluation outcomes

The results of the cost estimates for each surgical approach will be summarized in tables and presented graphically. The outcome of the cost-effectiveness (CEA) and cost-utility (CUA) analysis will be the incremental cost-effectiveness ratio (ICER); in terms of cost per year of life gained for the first case and in terms of cost per QALYs earned for the second. The ICER of robotic surgery and VATS versus open surgery and the ICER of robotic surgery versus VATS will be calculated. A cost-effectiveness plan will also be constructed for these comparisons. Since the ICER alone cannot answer the question of whether a technology is cost-effective per se, it will be compared with a value in euros that society is willing to pay for an additional QALY earned ("societal willingness-to -pay"). Since there are no Italian regulatory references for willingness-to-pay, the references of NICE (£20-30,000), those of the Italian Association of Health Economics (€25-40,000) and the ICER calculated for dialysis (€50,000) will be used. Lastly, if the technology is cost-effective in at least one subgroup, a budget impact analysis will be carried out.

3.4.2. Point of view, time horizon

The point of view of both the cost-effectiveness and cost-utility evaluation is twofold. Initially, the point of view of the hospital structures will be adopted, therefore the direct health costs will be estimated, i.e. those relating to surgery, diagnostics, length of stay, health personnel, and drugs. These costs will be compared with the rate reimbursed for the DRG. Subsequently, the analysis will be extended to the point of view of society, considering indirect healthcare costs and non-healthcare costs, direct and indirect and intangible costs, evaluating the VAS and the utility index of the EQ-5D. The time horizon of the evaluation will be limited to 5 years from the intervention and the purchase of the technology. The tangible investments will be discounted according to the net present value method (marginal cost 5%/year and payment period of 5 years).

3.4.3. Model, clinical and cost input parameters

A decision tree model will be applied to summarize the consequences of the different interventions with regards to their clinical outcomes and costs incurred.
The input parameters for efficacy will be derived from the retrospective and prospective observational study. If further information becomes necessary, once the decision tree has been built, it will be calculated if possible by the court of the efficacy study. Otherwise, it will be derived from the literature. For the calculation of the QALYs, the utility values will be obtained starting from the results of the EQ-5D questionnaires prospectively administered to the patients, as described in paragraph 3.3.2., using the score function of van Hout et al. [41] and the Italian values of reference by Scalone et al [42].
For the input parameters of the costs, the identification of the resources will take place through a panel of expert thoracic surgeons and epidemiologists participating in the study. The quantification of resource consumption will take place using the administrative databases of the ATS with regard to pre-operative examinations, length of stay, follow-up visits, drugs and other identified direct health costs, using the same court identified for the efficacy study. To estimate the indirect health costs (patient travel, domestic assistance) the distance between the residence and the intervention hospital will be calculated for each patient. We will also use the estimate of the accesses number to the healthcare facility by surgical modality in the 30 days preceding and in the 6 months following the operation, using the administrative databases. For direct and indirect non-healthcare costs, such as the patient's lost days of work and lost productivity or early retirement, the *human capital approach* will be used.
For the allocation of costs strictly related to the surgical intervention with the three access modalities (purchase and maintenance of the instrumentation, duration of the intervention, personnel, etc.) a literature review will be performed. They will be compared with the rate reimbursed by the SNR per DRG. The determination of the unit cost for all other direct health costs (exams, visits, drugs) will be equal to the rate reimbursed by the regional health system, using the rates of the Lombardy region for hospital assistance, outpatient services and the prices of drugs agreed between AIFA and producer and published in the Italian Official Gazette. All costs will be expressed in euros.

3.4.4. Sensitivity analysis

Since the costs are volume-dependent, the effect of a different number of cases on the costs and therefore on the cost-effectiveness with respect to the measured volumes will be evaluated. Furthermore, to evaluate the robustness of the model, deterministic sensitivity analyzes will be performed to evaluate the fluctuation of the results as the parameter values vary with respect to the

minimum and maximum of the confidence interval. Univariate analysis will be presented by tornado-plot.

4. DATA COLLECTION AND STORAGE METHODS

The study will be conducted in accordance with EU regulation 2016/679, EU directive 2016/680 and its amendment. In particular, the data of the patients enrolled during the course will be kept, archived and processed in full compliance with the privacy regulations pursuant to art. 13 of Regulation no. 2016/679/EU and the national privacy legislation in force and the Code of Ethics regarding data processing for statistical-scientific purposes. To guarantee the confidentiality of the data, the cloud computing service system will be used, supplied to the ATS by third parties, equipped with high security standards, where there are the administrative data necessary for the study and where the variables extracted from them will be kept and all the data will be analysed. The managers of the participating centers will exchange data with ATS via a web platform, published on hosting compliant with the GDPR, subjected to the control of appropriate perimeter protections, and created ad hoc with technologies and methods previously submitted to the analysis of the Data Protection Officer (DPO) for the verification of the standards of safety. For the definition of ownership of the data, specific agreements will be signed between the entities. The results of the analyses will be disseminated only in aggregate form through the publication of an HTA report and through articles in a scientific journal. If some analysis subgroups consisted of three subjects or less, the related data will not be published.

5. CHARACTERISTICS OF THE STUDY AND INFORMED CONSENT

As for the retrospective observational part, it provides for the analysis of administrative databases of the ATS of Milan managed by the staff of the Epidemiology Unit during their normal activity. The data sources are those normally used by the Epidemiology Unit, i.e. the pathological anatomy reports, the hospital discharge forms, the flow of outpatient services, territorial pharmaceuticals and the "file F" relating to the assisted residents of the ATS of Milan. To complete the collection of data necessary for the efficacy analysis, additional information is requested from the clinicians who treat or have treated the patient and who participate in the study via the web platform created ad hoc by the Epidemiology Unit of the ATS. This retrospective study will be carried out in compliance with the Provision no. 146 of 5 June 2019 – Provision containing the provisions relating to the processing of particular categories of data, pursuant to art. 21, paragraph 1 of Legislative Decree 10 August 2018, n. 101 (Published in the Official Gazette n. 176 of 29 July 2019) which recalls the previous Authorization n. 9/2016 - General authorization for the processing of personal data carried out for scientific research purposes - 15 December 2016 (Published in the Official Gazette No. 303 of 29 December 2016), which allows the processing of data suitable for revealing the state of health even in absence of the consent of the interested parties, for scientific research purposes in the medical, biomedical or epidemiological fields in compliance with the limits and conditions set out in the Authorization itself.

For the prospective part of the study, informed consent will be requested from the patient (**Annex 4**) at the time of pre-admission or surgical admission before surgery. It is the responsibility of the investigator to provide each patient with complete and adequate verbal and written information regarding the study objective and procedures and the possible risks involved. The patient must be informed of his right to withdraw from the study at any time. Written information that will be given to the patient must be approved by the EC and must be provided to each patient prior to any study-related procedure. A copy

of the signed and dated informed consent form (IC) must be issued to the patient, the other, signed in original, must be archived.

6. FINANCIAL ASPECTS

As this is an observational study, there are no additional costs related to patient management for the prospective part. The costs related to the implementation of the information network, being an activity of institutional interest of the ATS of Milan, will be borne by the same through the use of internal personnel resources. No funds are foreseen for the conduct of the study, for the participating centers, nor for the sending notices to the doctors participating in the study. Participation will be on a voluntary basis.

7. EXPECTED RESULTS

The expected result is the evaluation of the cost-effectiveness profile of robotic surgery for the treatment of lung malignant lesions based on the evaluation of both the effectiveness and the costs measured in patients treated in the area of the ATS of Milan in recent years. This information will make it possible to determine whether the technology is cost-effective in the specific healthcare context and what would be the impact on the budget of a greater diffusion of the technology in the coming years.

8. PUBLICATION PLAN

The results of the cost-effectiveness analysis are expected to be published in Italian on the ATS website and in international scientific journals in the sector. In addition to the staff of the Epidemiology Unit of the ATS directly involved in the study and in the analyses, the heads of the participating centers will be included among the authors. A working group will then be defined in which all the collaborators who have directly participated in the study for each center will be present, defined at the beginning of the study itself.

9. ANNEXES LIST

Annex 1 Initial questionnaire for participating centers

Annex 2 Electronic data collection form for retrospective and prospective study (effectiveness analysis)

Annex 3 Electronic data collection form for prospective study (quality of life, PROMs, PREMs)

Annex 4 Informed consent for prospective study

Annex 5 Information for the attending physician

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