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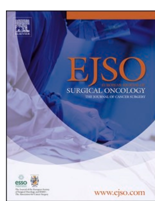

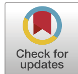

The outcomes of salvage surgery for non-small cell lung cancer after immune checkpoint inhibitor or targeted therapy treatment. A multi-center international real-life study

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ABSTRACT

Objectives: In recent years, targeted therapy and immunotherapy have been demonstrated to improve survival in non-operable, non-small cell lung cancer (NSCLC) patients. The results of salvage lung resection in patients with initially unresectable advanced NSCLC after immune checkpoint inhibitor (ICI) or Target Therapy (TT) treatment remain unclear. This study aimed to define the outcomes of patients undergoing salvage surgery in a multi-center real-life setting.

Methods: An international multicenter retrospective cohort study was conducted. Patients included in the study were judged inoperable, according to a multidisciplinary tumor board decision, before being submitted to ICI or TKI treatment. The rate of complications, the overall survival (OS), and progression-free survival (PFS) were compared. Crude and Multivariable-adjusted analysis were conducted.

Results: Nighty-eight patients affected by NSCLC were included in the study. Most patients were female (N = 50–51 %), and the median age at surgery was 62 years. While ICI was performed in 29 patients (30 %), TT was done in 45 (46 %), and ICI plus chemotherapy in 24 (24 %). The inoperability was determined by metastatic disease in 43 cases (44 %), N2-N3 advanced disease in 18 (18 %), local invasiveness in 10 (10 %), a combination of local invasiveness and N-status in 26 (27 %), and other reasons in 1 case (1 %). Overall, the complication rate was 30 %, the mortality rate was 1 %, and the median LOS was 6 days. No residual lung disease (ypT0) was observed in 30 patients (31 %). The 5-year OS was 74 %, while the 5-year PFS was 44 %. Performing sublobar

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resections was an independent adverse prognostic factor in the multivariable analysis for survival ($P < 0.01$), while the pathological complete response (pCR) was an independent prognostic predictor of improved survival ($P = 0.025$). On multivariable analysis performing a sublobar resection ($P < 0.01$), an increasing ypT stage ($P < 0.01$), and postoperative therapy ($P < 0.01$) were independent prognostic predictors, correlating with impaired disease progression.

Conclusions: Patients selected for Salvage Surgery after ICI or TT have reasonable post-operative and long-term outcomes. In this context, Salvage Surgery could be proposed in selected patients after a careful multidisciplinary evaluation.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and surgical resection remains the gold standard for early stage disease and for selected cases of locally advanced cancers.

Unfortunately, at the time of diagnosis, more than 75 % of NSCLC patients present with an advanced stage or with a metastatic disease, preventing any chance of complete surgical resection [1].

Historically this large group of patients have been treated with platinum-based chemotherapy regimens, with or without radiotherapy, with radical or palliative intent. However outcomes and disease control remained poor and stable for decades, with an overall 5-year survival rate for all stages around 20 % and at the cost of not negligible side effects and impairment of the quality of life [2].

In recent years, the advent of targeted therapy (TT) and immune checkpoint inhibitor treatments (ICI) have radically modified this scenario, making the NSCLC one of the most successful area for precision oncology medicine. This translated into a significant improved survival rates in non-operable NSCLC patients, fewer adverse effects and a better quality of life [3].

The main limitation factor with the modern therapies is still the development of acquired drug resistance that remains unavoidable for the majority of the cases, with patients consequently presenting tumor relapse or progression after a prolonged period of time of disease under adequate control [4].

In this context, it is remarkable a limited subset of the patients who experienced the shift from an oligo-metastatic or locally advanced NSCLC, judged inoperable at the beginning, to a resectable disease, due to a complete or major response to TT or ICI therapy.

In these specific sub-group of patients, who usually present with a tumor spread limited to the chest, salvage surgery could be therapeutic, providing adequate local control and improving survival rate [5,6]. Nevertheless, the topic of “rescue surgery” in patients with initially unresectable advanced NSCLC after ICI or TT is still matter of study.

This study aimed to define the short-term and long-term clinicopathological outcomes of patients undergoing salvage surgery after TT or ICI for initially inoperable NSCLC.

2. Methods

An observational, multicenter, retrospective study was conducted using 12 worldwide institutions’ data (Supplementary Table 1). Patients submitted to salvage surgery in the 2010–2021 period were enrolled. Patients included in the study were initially judged inoperable, according to the Multidisciplinary Tumor Board (MTB) decision, before being submitted to targeted therapy (TT) and immune checkpoint inhibitor therapy (ICI). Sequentially to the treatment, the patients were judged operable with radical intent, according to the MTB decision and after respiratory and cardiac evaluation. Patients submitted for surgical intervention with no radical purpose, such as biopsy, were excluded from the study.

The baseline clinical workup followed international guidelines, including a physical examination, computed tomography (CT) scans, and 18-fluorodeoxyglucose-positron emission (PET) tomography scans. Tissue biopsy was commonly obtained via fibro-bronchoscopy, CT-guided fine needle, or true-cut biopsy [1].

The variables of interest collected were: age (years); sex (female *vs.* male); smoking history (ever *vs.* never); Body Mass Index (BMI); comorbidity (presence to at least one comorbidity *vs.* none); cancer histology (adenocarcinoma *vs.* squamous cell carcinoma); driver gene alterations (e.g. EGFR, ALK, ROS1, RET, KRAS, MET); initial reason of inoperability (locally advanced for invasiveness, locally advanced for N2-N3, locally advanced for both, metastatic disease); pre-treatment cTNM (according to 8th edition of TNM staging system); type of therapy (targeted therapy -TT-, immune checkpoint inhibitor therapy -ICI-, immune checkpoint inhibitor therapy plus chemotherapy-ICI + CT-); radiotherapy (performed in preoperatory setting *vs.* no); ycTNM; radiologic response evaluation criteria in solid tumors (RECIST - v1.1.) (complete response -CR-, partial response -PR-, stable disease -SD-, progression disease -PD-); time between last therapy administration and surgery (weeks); ECOG pre-surgery; surgical approach (open, minimally invasive -VATS/RATS-); type of surgical resection (lobectomy/bilobectomy, pneumonectomy, sublobar resection -wedge/segmentectomy); impossibility to perform complete resection (yes *vs.* no); surgical time (minutes); ypT stage, ypN stage; pathological complete response (pCR); resection status (R0, R1, R2); postoperative therapy (performed *vs.* none).

Data were collected from clinical, pathological, and surgical registries, and follow-up was performed by interviews with physicians of each participating Institution. Data collection for retrospective analysis was approved by the institutional review board of (IRB approval number N. 0012949/22). The STROBE reporting recommendations were used in the reporting of the present study [7].

2.1. Statistical methods

Baseline patient characteristics are summarized and described by their median and interquartile range (IQR) or number and percentages. Shapiro-Wilk Test was used to assess normal distribution for continuous variables.

Overall Survival (OS) and Progression-free survival (PFS) were the primary outcomes analyzed. The secondary outcome assessed was the postoperative complications rate (if at least one complication of any kind was reported in the postoperative period).

The OS and the PFS were estimated by the Kaplan–Meier method [8]. The observation period in the OS was defined as the time from the date of surgery to the date of death by any cause (failure) or until the last follow-up visit (censoring). The observation period in the PFS was defined as the time from the date of surgery to the date of tumor recurrence (failure) or until the last follow-up visit or death by any cause (censoring). A Cox proportional hazard model was employed to estimate the crude and the multivariable-adjusted hazard ratios (HRs) with 95 % confidence intervals (CIs) and evaluate possible OS and PFS predictors. The proportional hazard assumption was also verified by graphical checks and formal tests based on Schoenfeld residuals.

The association with postoperative complications was evaluated by the Wilcoxon–Mann–Whitney test or Student’s t-test for continuous variables and the chi-squared test or Fisher’s exact test for categorical variables as appropriate [9]. A multivariable-adjusted logistic regression model was used to estimate the multivariable-adjusted odds ratios (ORs)

with 95%CI and to evaluate possible predictors of postoperative complications.

A stepwise backward selection was used in order to find the best multivariable-adjusted model for each outcome. A listwise deletion approach (i.e., complete case analysis) was used to handle missing data. Multicollinearity among selected covariates in the multivariable analysis was assessed by testing the variance inflation factor.

Statistical analyses were conducted using the SAS software package (SAS Institute Inc., Campus Drive Cary, USA) and Stata software version 17 (Stata- Corp, College Station, Texas).

3. Results

3.1. Patients characteristics

In the period of interest, 98 patients were included in the study. The patients were evenly distributed by gender (female, N = 50–51 %), and the median age at surgery was 62 years (IQR 54–70).

According to the 8th edition of the TNM staging system, at diagnosis, 43 (44 %) patients presented at stage IV, 30 (31 %) at IIIB, 21 (21 %) at IIIA, and 4 (4 %) at IIIC. The initial inoperability was determined by metastatic disease in 43 cases (44 %), N2-N3 advanced disease in 18 (18 %), local invasiveness in 10 (10 %), a combination of local invasiveness and N-status in 26 (27 %), and other reasons in 1 case (1 %). (Table 1).

While immune checkpoint inhibitor therapy (ICI) was performed in 29 patients (30 %), targeted therapy (TT) was done in 45 (46 %), and ICI plus chemotherapy (ICI + CT) in 24 (24 %). The median time from therapy to surgery was 5 weeks (IQR 3–11). The 14 % of the entire cohort (N = 14) and the 19 % of Stage IV patients (N = 8) received radiotherapy. Supplementary material details the distribution of driver gene alterations (Supplementary Table 2) and treatment (Supplementary Table 3).

According to RECIST criteria, a complete radiological response was observed in 12 patients (13 %), while a partial response in 77 (81 %) cases, stable disease in 4 (4 %), and a progression of disease in 2 (2 %). The 86 % of stage IV patients (N = 37) experienced a partial or a complete response. A similar rate of partial or complete response was observed among stage IV patients submitted to radiotherapy (88 %, N = 7).

3.2. Perioperative outcomes

Overall, the complication rate was 30 % (29 cases), the intraoperative complication rate was 4 % (4 patients), and the intraoperative mortality rate was 1 % (1 patient, related to perioperative fibrillation). Supplementary Table 4 details the observed complications. Among the 28 patients (29 %) who underwent minimally invasive surgery, we observed 1 conversion (4 %) due to lymph node fibrosis. The median LOS was 6 days (IQR 5–10), and 30 days mortality rate was 1 % (1 case). No residual lung disease (ypT0) was observed in 30 patients (31 %), but in 2 (7 %) of them, N2 residual disease was observed. An R1 or R2 resection was observed in 7 patients (7 %). The impossibility of resecting the primary tumor was noted in 3 cases (3 %).

No residual lung disease (ypT0) was observed more frequently in ICI (38 %, N = 11) and ICI + TT (N = 11, 46 %) patients than in TT patients (16 %, N = 7).

On univariable analysis, patients with higher ECOG-PS pre-surgery (ECOG = 2, P = 0.03), submitted to extended/complex resection (P = 0.04), and submitted to ICI (P < 0.01) showed a higher incidence of complication. On multivariable analysis, the patients with higher ECOG-PS pre-surgery (ECOG = 2, OR: 33.9; CI95 % 2.75–418.2; P < 0.01), submitted to extended/complex resection (OR: 23.5; CI95 % 1.19–461.4; P = 0.04), and previously submitted to ICI (OR: 26.4; CI95 % 26.4 4.03–173.3; P < 0.01) showed to be independently associated with a higher of incidence complication.

Table 1
Baseline Characteristics in the overall population.

Factor	All n = 98
Age *(years), Median (IQR)*	62 (54–70)
Sex *(Female), n (%)*	50 (51)
Smoking History *(Ever), n (%)*	69 (70)
BMI, *Median (IQR)*	26 (23–28)
Comorbidity, *n (%)*	57 (58)
Histology, *n (%)*	
Adenocarcinoma	78 (80)
Squamous cell carcinoma	19 (20)
Type of Therapy, *n (%)*	
Targeted therapy	45 (46)
Immune checkpoint inhibitor therapy	29 (30)
Immune checkpoint inhibitor therapy plus chemotherapy	24 (24)
Reason of Inoperability, *n (%)*	
Locally advanced for invasiveness	10 (10)
Locally advanced for N2-N3	18 (18)
Locally advanced for N + Invasiveness	26 (27)
Metastatic disease	43 (44)
Radiotherapy *(Yes), n (%)*	14 (14)
Radiological RECIST, *n (%)*	
CR	12 (13)
PR	77 (81)
SD	4 (4)
PD	2 (2)
Time between last therapy subministration and surgery (*week*), *Median (IQR)*	5 (1–10)
ECOG Pre-Surgery, *n (%)*	
0	56 (57)
1	35 (36)
2	7 (7)
Surgical Approach, *n (%)*	
Open	70 (71)
Minimally invasive (RATS/VATS)	28 (29)
Type of Surgical Resection, *n (%)*	
Lobectomy/Bilobectomy	77 (79)
Pneumonectomy	12 (12)
Sublobar (segmentectomy/wedge)	9 (9)
Surgical Time *(min), Median (IQR)*	181 (145–220)
Impossibility to resect *(Yes), n (%)*	3 (3 %)
ypT, *n (%)*	
ypT0	30 (31)
ypT1	26 (27)
ypT2	28 (29)
ypT3	10 (10)
ypT4	4 (4)
ypN, *n (%)*	
ypN0	59 (60)
ypN1	14 (14)
ypN2	25 (26)
Pathological resection status, *n (%)*	
R0	91 (93)
R1	4 (4)
R2	3 (3)
Postoperative Therapy, *n (%)*	56 (59)

3.3. Survival and progression-free survival analysis

The median follow-up was 27 months (CI 95 % 19–38). A total of 18 (19 %) deaths of any cause and 29 (30 %) patients experienced a disease recurrence. The recurrence sites distribution showed that the brain was the most frequent site (14 cases - 35.9 %), followed by local recurrence (lymph nodes 7 cases −17.9%- and lung 7 cases −17.9%-), bone 4 cases (10.3 %), pleura 4 (10.3 %), adrenal gland 2 cases (5.1 %), and the liver 1 case (2.6 %).

The 3-year and 5-year OS were 79 % and 74 %, respectively. (Fig. 1). On univariable analysis, ypT4 NSCLC (HR: 14.9; CI95 %: 2.32–95.4; P < 0.01 - Supplementary Fig. 1), positive resection margins (HR: 32.9; CI95 %: 5.36–201.9; P < 0.01 - Supplementary Fig. 2), and patients submitted to segmentectomy or wedge resection (HR: 6.48; CI95 %: 2.14–19.6; P < 0.01 - Supplementary Fig. 3) showed a significantly worse survival.

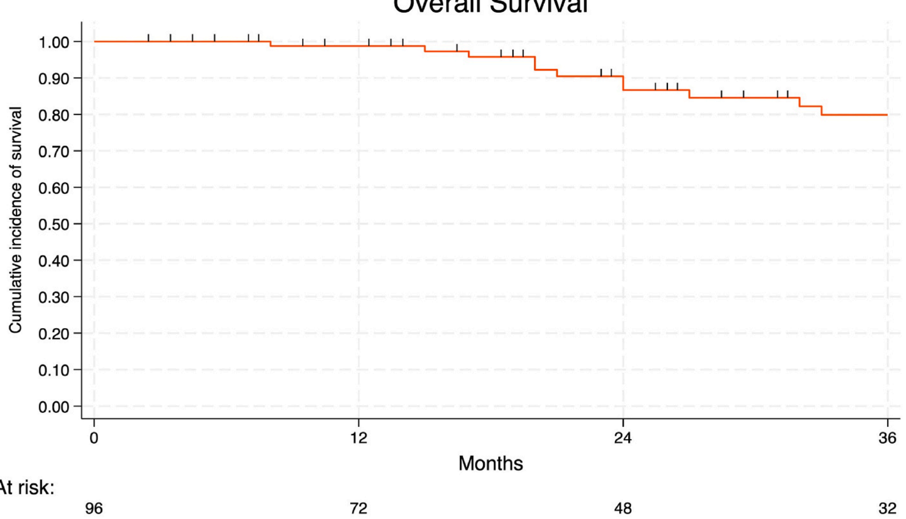

Fig. 1. Kaplan-meier curve for overall survival.

The type of pre-Salvage Surgery therapy (i.e., ICI vs. ICI + CT vs. TT) did not significantly affect the prognosis (P > 0.05). On the multivariable-adjusted model, performing sublobar resection was an independent prognostic predictor, correlating with poor survival (HR: 31.1; CI95 %: 3.92–247.01; P < 0.01), while a pCR was an independent prognostic predictor, correlating with improved survival (HR:0.056; CI95 %: 0.0045–0.70, P = 0.025).

The 3-year and 5-year PFS were 60 % and 44 %, respectively. (Fig. 2). On univariable analysis, ypT4 NSCLC (HR: 9.34; CI95 %: 2.21–39.4; P < 0.01) and positive resection margins (HR: 6.12; CI 95 %: 1.37–27.2; P = 0.02) showed a significant association with disease progression; while patients submitted to sublobar resection showed a trend towards a worse prognosis (HR: 2.48; CI95 %: 0.91–6.75; P = 0.07). The type of pre-Salvage Surgery therapy (i.e., ICI vs. ICI + CT vs. TT) did not significantly affect the disease progression (P > 0.05). On multivariable analysis performing a sublobar resection (HR: 7.66; CI95 %: 1.86–31.6; P < 0.01), an increasing ypT stage (ypT2 HR: 6.89, CI95 %: 1.8–26.4; ypT3 HR: 11-9, CI95 %: 2.1–67.6; ypT4 HR: 72.4, CI95 %: 11.2–465.6;- P < 0.01), and postoperative therapy (HR: 4.59; CI95 % 1.49,14.1; P < 0.01) were independent prognostic predictors, correlating with impaired disease progression.

4. Discussion

In patients with non-small cell lung cancer, salvage surgery could represent an available treatment option following downstaging or an excellent response to definitive chemotherapy and/or radiation therapy [10]. In addition, the established and ongoing trials (e.g., Keynote-001, NADIM 1 and 2, Checkmate 816, Keynote 671, Aegean, ADAURA, ALNEO, NeoADAURA, IMpower010), as well as real-life studies results, widely support the use of immune checkpoint inhibitor therapy (ICI) or Target Therapy (TT) in neoadjuvant and adjuvant settings, in addition to unresectable disease setting [2,11–17]. Consequently, salvage surgery is a reasonable option in patients with NSCLC who became resectable after immune checkpoint inhibitor therapy or target therapy.

The results of our study suggest that salvage surgery after inhibitor therapy (ICI) or Targeted Therapy (TT) could be performed with a reasonable incidence of perioperative complications, more frequently associated with higher ECOG-PS, extended/complex resections, and submitted to ICI. Moreover, patients submitted to salvage surgery presented good survival and progression-free survival, influenced mainly by the type of surgical resection performed (worse in the case of sublobar resection) and the ypT stage. Finally, even if a considerable rate of complete response was observed in the primitive tumor, a non-

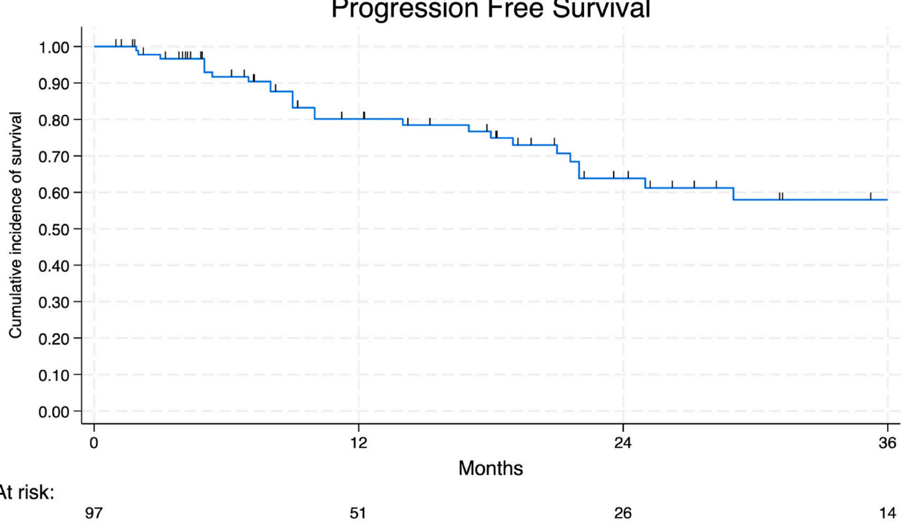

Fig. 2. Kaplan-Meier curve for Progression-Free Survival.

negligible rate of persistent N2 disease was observed, highlighting the importance of lymph nodal dissection and staging.

Although the perioperative outcomes of salvage surgery after chemotherapy or chemoradiotherapy are established, the safety and feasibility of salvage surgery after definitive treatment with an ICI and TT, alone or in combination with chemotherapy (CT) and/or radiotherapy (RT), is rarely explored and often only in limited series [18–22]. In real-life studies, perioperative morbidity of salvage surgery usually ranges from 25 % to 50 % for ICI and from 10 % to 35 % for TT. Likewise, Video-assisted Thoracic Surgery (VATS) and Complex procedures (ex. Bronchial or Arterial Sleeve resection) are described as feasible after ICI and TT, with an acceptable percentage of complications [18–22]. Similarly, in their randomized clinical trial, Forde and associates documented a morbidity incidence of 41.6 % of the patients submitted to neoadjuvant nivolumab-plus-chemotherapy and a rate of 11.4 % of grade 3 or 4 surgery-related adverse events. Moreover, in the neoadjuvant nivolumab plus chemotherapy arm VATS approach was commonly performed (30 %), the conversion rate was acceptable (11 %), and sleeve lobectomy was often performed (1.3 %) [23]. The results of our analysis, conducted in a multi-institutional international setting, support the safety of salvage surgery and the feasibility of complex and extended procedures, as well as minimally invasive procedures.

Recent clinical trials revolutionized the treatment paradigm of NSCLC in perioperative settings [2,24]. Nevertheless, real-life data on OS and PFS of salvage surgery are relatively scarce. Ohtaki et al. reported a 3-year OS and RFS of salvage surgery after TT of 75.1 % and 22.2 % [21]. Similarly, in a similar setting, Li and colleagues observed a median PFS of Salvage surgery post-TT at 23.4 months (improved compared to TT alone) [25]. Comparably, Song et al. described a median event-free survival of 14 months and a median postoperative survival of 17 months in a cohort of advanced NSCLC patients submitted to salvage surgery after targeted therapy [26]. In salvage surgery post-ICI setting, Bertolaccini et al. observed that two out of eight patients died after recurrence/progression of the disease after 6 and 32 months, respectively [20]. The long-term result of our survival analysis documented a 5-year OS of 74 % and a 5-year PFS of 44 %, corroborating the correctness of surgical indication in this particular setting. Moreover, the multivariable-adjusted analysis pointed out the importance of performing a complete anatomic resection in order to achieve the optimal oncological outcome and the best survival results.

The pathological complete response and the impossibility of resecting the primitive lung neoplasm are both well-known usual findings after neoadjuvant or definitive systemic treatment with ICI and TT. In the CheckMate 816 trial, a complete pathologic response was observed in 30.5 %. Likewise, in their meta-analysis of 548 patients who underwent preoperative ICI, Cao and colleagues reported that 24 % of patients with pCR to the primary lesion and 20 % with both the primary lesion and sampled lymph nodes' complete response [24]. Similarly, Lococo et al. reported a 50 % complete pathologic response in patients submitted to Salvage Surgery after Alectinib, while Li and colleagues 11 % after Gefitinib or Crizotinib [12,25]. In our series of patients submitted to definitive ICI or TT, salvage surgery reveals no evidence of viable tumor tissue in 30 % of cases. Notably, in 7 % of them, N2 residual disease was observed, underlining the importance of mediastinal lymph node sampling and/or dissection as the standard of care in this setting.

Our analysis presents some limitations, principally associated with a multi-institutional dataset setting, with the lack of a control group, and with the retrospective design. In particular, the contribution of cases is understandably not homogeneous among participating institutions, and selection bias is unavoidable. However, the indication of treatment was established by the Multidisciplinary tumor board (MTB) in each case, and the patients were all recruited in High-volume Institutions and Tertiary Centers.

5. Conclusions

Systemic therapy based on immune checkpoint inhibitor therapy (ICI) and target therapy (TT) represents a game-changer in NSCLC management. Our study showed that patients selected for Salvage Surgery after ICI or TT have reasonable post-operative and long-term outcomes. In this context, Salvage Surgery could be proposed in selected patients after a careful MTB evaluation.

Collaborators

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CRediT authorship contribution statement

Francesco Guerrera: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Filippo Lococo:** Data Collection, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Ludovic Fournel:** Data Collection, Writing – review & editing. **Domenico Viggiano:** Data Collection, Writing – review & editing. **Giuseppe Mangiameli:** Validation, Data curation, Writing – review & editing. **Maria Giovanna Mastromarino:** Data Collection, Writing – review & editing. **Gianluca Guggino:** Validation, Supervision, Writing – review & editing. **Joseph Seitlinger:** Investigation, Data Collection, Methodology, Writing – review & editing. **Pietro Bertoglio:** Data Collection, Methodology, Writing – review & editing. **Luca Luzzi:** Data Collection, Supervision, Writing – review & editing. **Paolo Albino Ferrari:** Data Collection, Writing – review & editing. **Claudia Filippini:** Methodology, Formal analysis, Writing – review & editing. **Marco Alifano:** Supervision, Validation, Writing – review & editing. **Stefano Margaritora:** Supervision, Validation, Writing – review & editing. **Luca Voltolini:** Supervision, Validation, Writing – review & editing. **Emanuele Voulaz:** Data Collection, Writing – review & editing. **Marco Lucchi:** Project Supervision, Writing – review & editing. **Francesco Jacopo Romano:** Data Collection, Writing – review & editing. **Piergiorgio Solli:** Supervision, Validation, Writing – review & editing. **Sara Najmeh:** Supervision, Validation, Writing – review & editing. **Annamaria Carta:** Data Collection, Writing – review & editing. **Enrico Ruffini:** Conceptualization, Supervision, Writing – review & editing.

Ethics statement

The present study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. Approval was granted by the Institutional Review Board (N. 0012949/22 del 13.04.22). Individual informed consent was necessarily waived due to the retrospective nature of this study and to the anonymity of patients enrolled.

Data availability statement

The anonymized data are not available to the GDPR legislation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.109592.

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