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Original article

Percutaneous lung microwave ablation versus lung resection in high-risk patients. A monocentric experience

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Summary. *Background and aim of work:* Lung microwave ablation (MWA) is considered an alternative treatment in high-risk patients, not suitable for surgery. The aim of our study is to compare MWA and pulmonary lobectomy in high-risk, lung cancer patients. *Methods:* This was a single-center, propensity score-weighted cohort study. All adult patients who underwent CT guided MWA for stage I NSCLC between June 2009-October 2014 were included in the study and were compared with a cohort of patients submitted to lung lobectomy in the same period of time. Outcomes were overall survival (OS) and disease-free survival (DFS). *Results:* 32 patients underwent MWA, and 35 high-risk patients submitted to lung lobectomy in the same period were selected. Median follow-up time was 51.1 months (95% CI: 43.8-62.3). Overall survival was 43.8 (95% CI: 26.1-55) and 55.8 months (95% CI: 49.9-76.8) in the MWA group and Lobectomy group, respectively. Negative prognostic factors were MWA procedure (HR:2.25, 95% CI: 1.20-4.21, p= 0.0109) and nodule diameter (HR: 1.04, 95% CI: 1.01-1.07; p= 0.007) for OS, while MWA procedure (HR: 5.2; 95% CI: 2.1-12.8: p < 0.001), ECOG 3 (HR: 5.0; 95% CI: 1.6-15.6; p = 0.006) and nodule diameter (HR: 1.1; 95% CI: 1.0-1.1; p = 0.003) for DFS. *Conclusions:* Our study demonstrated a high percentage of local relapse in the MWA group but a comparable overall survival. Although lung lobectomy remains the gold standard treatment for stage I NSCLC, we can consider the MWA procedure as valid alternative local treatment in high-risk patients for stage I NSCLC. (www.actabiomedica.it)

Key words: Microwave ablation (MWA), lung lobectomy, lung cancer

Background and Aim of Work

Lung cancer continues to be one of the most common types of cancer in the world and the leading cause of cancer-related death.

Early stage (stage I) non-small-cell lung cancer (NSCLC) includes 16% of all lung cancer cases, with 5-year survival rates of 70-90% for small, localized tumours (1).

The treatment of choice for standard-risk operable patients with stage I disease is lobectomy. In selected cases, sub-lobar resection, comprehending both segmentectomy and atypical wedge resections, could be alternative treatments for high-risk operable patients (2).

Different therapeutic alternatives have been introduced for patients who have excessive risk of surgical morbidity and mortality, such as stereotactic radiotherapy and MWA (3).

The use of percutaneous thermal ablation has increased for the treatment of early stage lung cancer, and can be performed by radiofrequency ablation or MWA. The best candidates for percutaneous MWA are patients with stage I NSCLC who present contraindications to surgery or stereotactic radiotherapy due to cardiac and/or respiratory co-morbidities or insufficient vital lung reserve (4). The main advantage of this technique is to destroy a small pathological lung tissue by locally heating, causing minimal damage to the surrounding tissue.

The use of MWA was introduced for the treatment of hepatic tumors. Subsequently, starting in the early 2000s, this technique was widely used for the treatment of primary and secondary lung malignancies (5).

The aim of our study is to compare computed tomography guided percutaneous MWA and pulmonary lobectomy as therapy of NSCLC in high risk patients, in terms of overall survival and relapse of disease.

Methods

This was a single-center, propensity score-weighted cohort study of prospectively collected data. The study was conducted at Thoracic Surgery Department of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, an University, considered a third-level Hospital of Milan. All adult patients underwent CT guided MWA for stage I non-small cell lung cancer between June 2009-October 2014 were included and were compared with a cohort of patients submitted to lung lobectomy in the same period of time. Data were downloaded from our Institutional electronic database. All patients were affected by cytological or histological proven Stage I NSCLC. The baseline demographics of patients (age, sex, ECOG performance status) (6), characteristics of tumours (size, location, histological type, 18F-FDG uptake) and treatment details (MWA or surgery) were collected from our database. Histological subtypes were classified as adenocarcinoma and squamous cell carcinoma. Patients submitted to computed tomography guided percutaneous MWA were compared with a cohort of high-risk patients submitted to lung lobectomy. Inclusion criteria used to select patients submitted to surgery were: age >70 year-old, presence of at least one of the following major co-morbidities: COPD Gold 2 or 3 (7); Severe Type II diabetes mellitus, coronary artery disease, severe vascular artery disease. The outcomes of interest in this study included overall survival and relapse (local or distant) of disease. The manuscript was written following STROBE Statement criteria (8).

Microwave ablation technique

The procedure was usually performed under Thorax CT-scan guide. Patients were positioned under CT scan in prone, supine or lateral decubitus position, depending on the side of the target lesion. Local anesthesia and deep sedation was performed, with the assistance of an anesthesiologist. Needle placement was always performed under multi-slice thorax CT guidance. It can show the exact position of the needle as well as the occurrence of pneumothorax or bleeding. This is an extremely important phase of the whole procedure, which depends on the success of the treatment. We used the Emprint™ Ablation System (Medtronic, Minneapolis, MN, USA) for the MWA procedure. Post-procedure monitoring was made by CT scan in the immediate and Chest X-Ray after 1 hour or before (depending on clinical conditions) in order to diagnose eventual lung hemorrhage or pneumothorax. Short term follow up was performed by PET/CT 3 months after MWA procedure. Long term follow up was performed by Thorax CT-scan and PET scan every 6 months. We used RECIST criteria (9) to diagnose local or distant relapse.

Lung lobectomy technique

A pulmonary lobectomy is the removal of a pulmonary lobe, after individual dissection of vein, arteries and bronchus: it is, by definition, an anatomical operation, in which the lobe-specific lymphatic drainage is removed. It is conducted under general anesthesia with a double lumen endotracheal tube, in order to obtain single lung ventilation; recently, some non-intubated thoracic surgery (NITS) procedures have been reported. The surgical approach can be by thoracotomy or by video-assisted thoracoscopic surgery (VATS):

various VATS techniques have been described, which vary in the number of ports and the position of the utility incision (10). Regardless of the type of VATS approach, the most relevant difference from the open surgery is the rib spreading, that is avoided in the VATS technique.

In case of primary lung cancer malignancies, the removal of mediastinal lymph nodes is mandatory, for ensuring a correct N staging. A systematic ipsilateral mediastinal lymphadenectomy is recommended, rather than lymph node sampling, for a more accurate and complete N staging (11).

VATS lobectomy is now considered as a valid alternative to conventional thoracotomy for early-stage primary lung cancer: postoperative pain is significantly reduced, compared to open surgery. Moreover, clinical evidence indicates that VATS lobectomy for early-stage NSCLC is associated with fewer postoperative complications and less negative biological impact than open lobectomy (14). In our Institution, since 2011 we started to treat lung cancer patients with VATS approach. Currently, about 90% of cancer operations are performed with this well defined technique, even the most complex cases. Improvements in camera systems, instruments and stapler technology have facilitated this development.

Statistical analysis

Quantitative parameters were described by median and 95% confidence interval (CI), while qualitative parameters were reported by frequency and percentage. The Kaplan-Meier test was used to describe overall survival and disease-free survival (DFS); the latter was defined as the time between the date of treatment and the date of local or distant recurrence. Overall survival parameter considered death regardless of the cause. We used Cox model to analyze the associations with overall survival and DFS, with multivariate analysis to identify the independent prognostic factors. To compare the adjusted survival for patients treated by MWA or pulmonary lobectomy we used an inverse probability of treatment weighting approach based on propensity scoring with regression adjustment for the following covariates: age, gender, ECOG score, histological finding and diameter of the nodule.

Results

In the period of study (June 2009-October 2014), 32 patients were submitted to microwave ablation (MWA group) for Stage I lung cancer. 35 high-risk patients submitted to lung lobectomy in the same period of time have been extracted from our Institutional Database, according to inclusion criteria. The location of the target lesion in MWA group was: left upper lobe (LUL) in 12 patients (37.5%), right lower lobe in 8 patients (25%), right upper lobe (RUL) in 7 patients (21.9%), left lower lobe (LLL) in 4 patients (12.5%) and right middle lobe (RML) in 1 patient (3.1%). Lobectomies performed were as follows: 13 (37.1%) RUL, 4 RLL (11.4%), 2 RML (5.7), 13 LUL (37.1) and 3 LLL (8.6%). Main demographics and clinical data are presented in Table 1. In the current observational study, patients treated with MWA were significantly older and showed worse ECOG performance status than patients who received pulmonary

Table 1. Demographics and clinical data

	MWA group (n=32)	Lobectomy group (n=35)	P value
Male, n (%)	23 (48.9)	24 (51.1)	0.769
Age, years, median, (95% CI)	77 (76.0-79.0)	74 (70.2-75.0)	0.001
Adenocarcinoma	27 (51.9)	25 (48.1)	0.207
Squamous cell carcinoma	5 (33.3)	10 (66.7)	
Tumor size, mm, mean (95% CI)	22.5 (17.0-26.0)	24 (20.0-29.0)	0.399
ECOG score	2 (from 1 to 2)	0 (from 0 to 1)	< 0.001

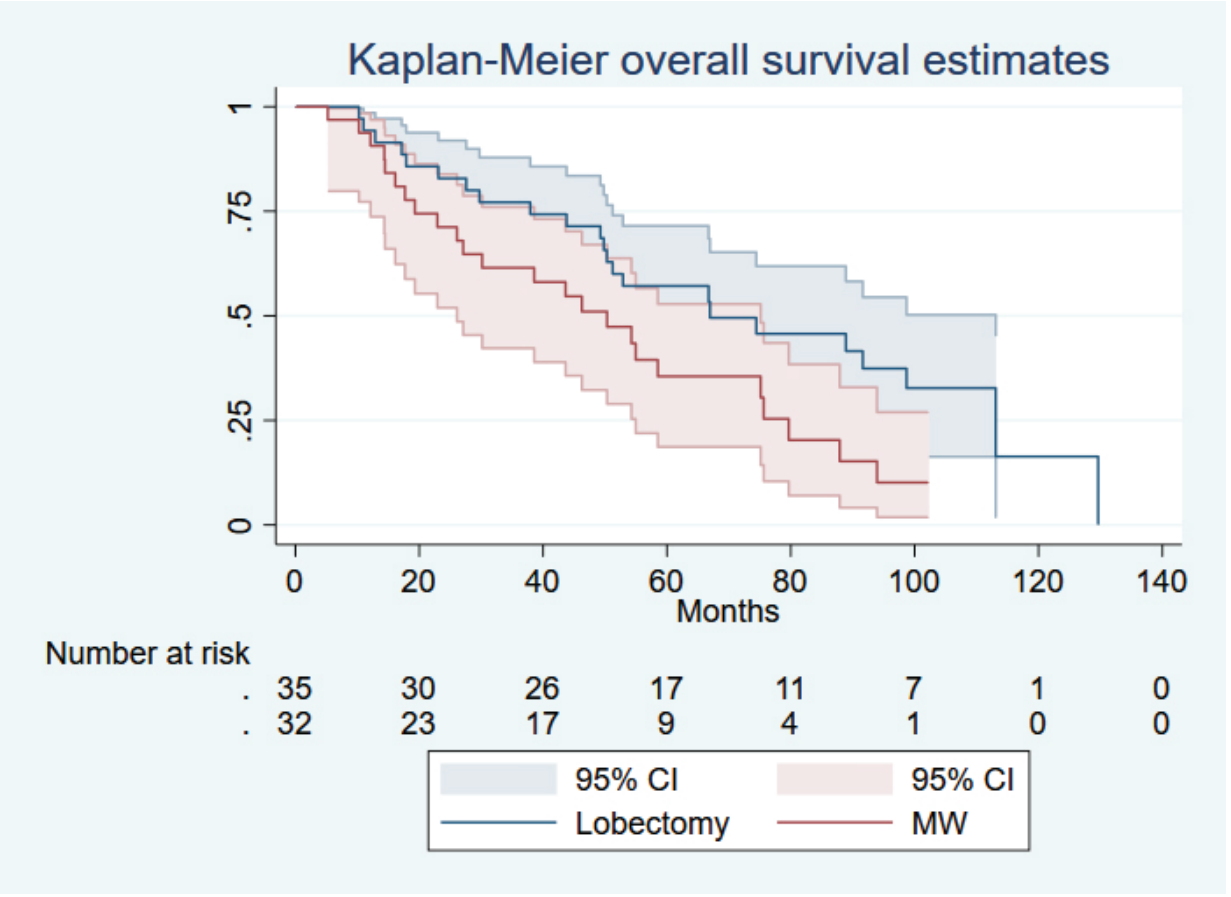

Figure 1

lobectomy. The median follow-up time was 51.1 months (95% CI from 43.8 to 62.3). The MWA group had a median survival of 43.8 months (95% CI from 26.1 to 55.0) while the Lobectomy group had 55.8 months (95% CI from 49.9 to 76.8). The unadjusted overall survival time at three years was 62.5% and 77.1% for the MWA group and Lobectomy group, respectively. Figure 1 shows the Kaplan-Meier curves of unadjusted overall survival as function of treatments (log-rang test, p = 0.041). Negative prognostic factors of overall survival by multivariate Cox proportional hazard regression models with stepwise method were MWA procedure (HR: 2.25, 95% CI from 1.20 to 4.21, p= 0.0109) and nodule diameter (HR: 1.04, 95% CI from 1.01 to 1.07; p= 0.007); conversely, age, gender, ECOG score and histological type were not significant. Using inverse probability of treatment weighting on propensity score, the average treatment effect (ATE) for MWA was estimated at 15.9 months (95% CI from -40.9 to 9.1; p= 0.214) less than pulmonary lobectomy; the latter had estimated potential outcome mean (POM) of 56.4 months (95% CI from 33.3 to 79.5; p< 0.001).

We observed 25 local relapses; twenty-two relapses were in the MWA group and three in the Lobectomy group. Figure 2 shows the Kaplan Meier curves of disease-free survival. Table 2 reports the relapses distribution and time to relapse. Stepwise Cox proportional hazard regression models for DFS (local + distant relapse) identified MWA procedure (HR: 5.2; 95% CI from 2.1 to 12.8: p < 0.001), ECOG performance status 3 (HR: 5.0; 95% CI from 1.6 to 15.6; p = 0.006) and diameter of the nodule in millimeters (HR: 1.1; 95% CI from 1.0 to

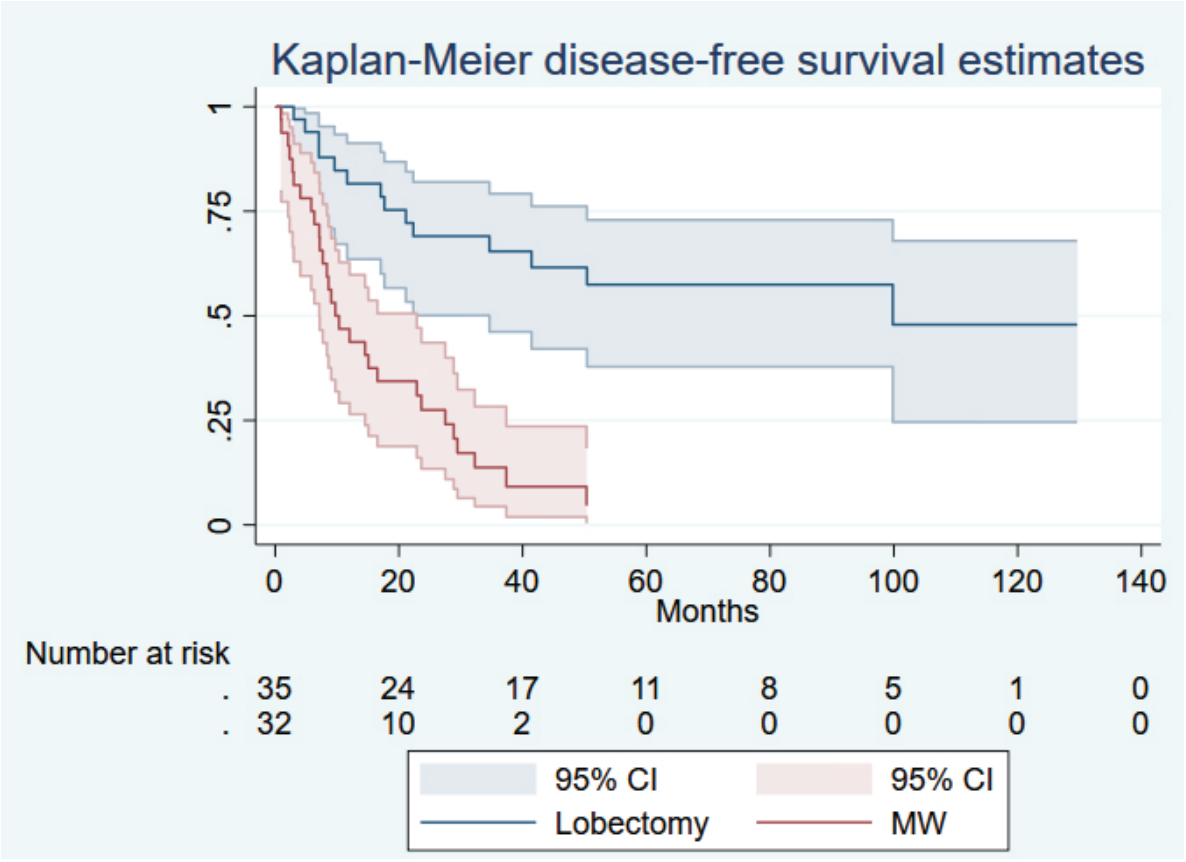

Figure 2

1.1; p = 0.003) as negative prognostic covariates. On the contrary this regression model did not include age, gender, histological type and local recurrence because considered not significant. Using inverse probability of treatment weighting on propensity score for DFS, the ATE for MWA was estimated at 32.8 months (95% CI from -46.6 to -19.3; p < 0.001) less than pulmonary lobectomy; the latter had estimated POM of 48.2 months (95% CI from 34.6 to 61.8; p< 0.001).

Table 2. Outcome variables

Outcome variable	MW group (n=32)	Lobectomy group (n=35)	P value
Overall survival, months, median (95% CI)	43.8 (26.1-55.0)	55.8 (49.9-76.8)	
3-year survival rate	62.5%	71.1%	
Local relapse, n (%)	22 (68.7%)	3 (8.6%)	<0.001
Time to local relapse, months, median (95% CI)	9 (6-16)	50.4	0.185
Distant relapse, n (%)	18 (56.2)	13 (37.1)	0.119
Time to distant relapse (95% CI), months	17.3 (7.3-28.1)	17.1 (7.1-28.1)	0.904
Recurrence (Distant + Local relapses), n (%)	28 (90.6)	14 (40.0)	<0.001
Time to recurrence, months, median (95% CI)	10.0 (7.2-17.7)	37.9 (21.4-55.3)	<0.001

Conclusions

Microwave ablation as a treatment for lung cancer has been shown to be safe in high risk patients (5). This technique has not yet been widely adopted and in stereotaxic radiation therapy continues to be used as the first choice treatment for inoperable patients in many centers.

Many studies published consider heterogeneous patients with different stages of NSCLC. Analyzing the long-term outcomes of patients treated with thermal ablation for stage I NSCLC would help physicians choose the best treatment for high risk patients. Our report compares patients submitted to computed tomography guided percutaneous MWA with a cohort of patients submitted to lung lobectomy in the same period of time, downloaded from our Institutional database. Overall survival was comparable in both groups. Zachary and colleagues reported a review of long-term results, which included 108 patients, all-cause survival at 1, 2, and 3 years was 83%, 59%, and 43%, respectively (13). Narsule et al. had performed 21 radiofrequency ablation and 4 MWA for a total of 25 ablations. Stage I disease was present in 21 patients. Mean follow-up was 42 months, median survival was 39 months, and overall survival at three years was 52% (14). Palussiere et al. examined eighty-two patients that were treated with RFA electrodes and five with MWA. Overall survival (OS) and disease-free survival (DFS) were 58,1% and 27,9%, respectively (15).

In our study, local progression occurred in twenty-two relapses in the MWA group and three in the Lobectomy group. Narsule et al. observed that local progression occurred in 10 patients (47,6%) and the median time to that was 35 months (14). Dupuy et al. published the results of the American College of Surgeons Oncology Group Z4033 (Alliance) Trial which showed similar local control rates after radiofrequency ablation of stage IA NSCLC of 68.9% at 1 year and 59.8% at 2 years (16). Palussiere et al. observed a 21,1% rate of local progression at 3 years post-ablation. In univariate analysis, increasing tumor size (P = 0.003) was the only predictive factor related to risk of local tumor progression (15). This data was confirmed by our study, which demonstrate a high percentage of local relapse in the MWA group but a comparable overall survival. Although lung lobectomy remains the gold standard treatment for stage I NSCLC, looking at our results we can consider the MWA procedure as a valid alternative local treatment in high-risk patients not suitable for surgery for stage I NSCLC. Furthermore, lung MWA treatment can be repeated overtime, in case of local relapse, in addition to conventional radiotherapy.

We highlighted the extremely similar "time to distant relapse" between MWA group and Lobectomy group in our study. On the other hand, looking at the percentage of local relapse, it is worth noticing that in the MWA group there is a sub-optimal local cancer control. Notwithstanding the weighted overall survival was not different in two groups.

Even though the lobectomy group cohort was selected according to severity criteria and major comorbidities, it resulted statistically younger and with lower ECOG score, compared to MWA group; this is to consider as an unavoidable selection bias, due to the non-randomized nature of the study. A randomized trial between MWA and surgery it is, in fact, extremely difficult and unethical.

Strengths and limitations of the study

To the authors' knowledge, this is the first report of propensity score weighted comparison between lung MWA and surgery for lung cancer with therapeutic purpose. The study has some limitations: firstly it is a retrospective study and is lacking the power of a prospective, randomized study. This is justified by the impossibility to propose an alternative local treatment in patients that are suitable for surgery, which remains the gold standard for treatment of stage I lung cancer. Another limitation is the monocentric nature of the study, that is a limit for its clinical applicability. Furthermore, the relatively small sample size does not allow to make firm conclusions.

To conclude, although lung lobectomy remains the gold standard treatment for stage I NSCLC, looking at our results we can consider the MWA procedure as a valid alternative local treatment in high-risk patients not suitable for surgery for stage I NSCLC.

Furthermore, lung MWA treatment can be repeated overtime, in case of local relapse, in addition to conventional radiotherapy.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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