Final Report

Topic: Estimation of Accessibility and Benefit of FUS treatment for inoperable Lung Cancer Patients, a retrospective Analysis

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PD Dr. med. Thomas Lesser, CoI

Chief Physician of Thoracic & Vascular Surgery, SRH Wald-Klinikum Gera, Gera Germany

Ph. D. Frank Wolfram, PI

Medical physicists; Thoracic & Vascular Surgery, SRH Wald-Klinikum Gera, Gera Germany

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A. Background & Hypothesis:

Lung cancer (LC) is the mortal leading tumor entity, with increasing incidence in female [1]. Curative treatment is achieved by surgical resection, but 70% of patients are inoperable at diagnosis [2]. HIFU as a non-invasive treatment is not applicable in ventilated lung. By using One Lung Filling (OLF) acoustic access to central tumors can be generated without lung damage [3]. Our work showed the feasibility for FUS ablation using OLF [4] which could lead to a novel, minimal invasive treatment modality for lung cancer (LC). It remains unclear which amount of patients are eligible to OLF and therefore FUS. Therefore a retrospective analysis of inoperable LC cases was performed to identify LC entities preferably fit for OLF and show strength as well as limitations for FUS.

B. Conclusion

The main focus of all milestones was achieved. The majority of Lung Cancer cases are eligible to OLF and therefore FUS. Several factors are limiting the applicability to Lung FUS, so that only 35% of those were eligible to Lung FUS. This rate can be increased up to 56% (35/63) by using vascularity and dense structures (bronchial) sparing FUS technology such as Histotripsy [5]. This would increase particular for SCLC the eligibility to Lung FUS, where a high rate of inoperability and valuable lung function was found.

Most of cases fit for OLF (78%) are diagnosed in advanced stage, where a systemic response of FUS treatment would be highly beneficial. Therefore future trials should be initiated investigating combined FUS immunotherapy as well as histotripsy for lung cancer.

Common abdominal FUS systems already meet the fundamental needs for Lung FUS regarding their ablation speed and focal depth.

C. Status:

What	Database	total cases	Lung Function	CT analysis	Classification Statistics	Reporting & Publication
Not started						
Ongoing						X
Finished	X	X (186/186)	X(110/ min100)	X (63/63)	X	X

D. Progress

During completion of Step 1–3 the database was build and corresponding cases collected. All required Lung Function parameters as well as the radiological tumor features (Fig.2 Lung VCAR) in case of inoperability and functional eligibility to OLF were assessed. During Q4 a few cases were added after transfer of radiological or clinical data from external source, so that in total 186 cases were included (Fig.1). This data pool contained the required minimum of 100 inoperable cases (110).

Fig 1: SPSS Dataset showing 186 cases included

The screenshot shows a SPSS dataset with 186 cases. The variables listed include: Fall, Group, Pat_ID, Sex, DIA_TXT, Histologie, MET, OP, Gross, Gew, Alter, LUFU, VC, TLC, FEV1, FEV1/FVC, FEV1/FVC, DLCO, TLC, COPD, Emp, pulm, Beside, N, maxD, maxD, max, max, Volges, depth, depth, Distast, Sensort, Sens, Beschreib, A, B, R, max, max, max. The data is organized into columns, with some cells highlighted in blue.

Fig. 2 Tumor size, volume and localization determination using LungVCAR (Nexus, GE Healthcare)

E Results:

Rates of Lung Cancer cases were seen in Tab1 regarding inoperability, functional eligibility to OLF and FUS. Inoperability was found in 59,1% (110/186) of cases which is slightly lower than in reported literature (70%). The majority of inoperable Lung Cancer cases 57,3% (63/110) are functional eligible to One Lung Filling (OLF). Out of those, 35% (22/63) had no tumor locations in proximity to sensitive structure and solid tumor tissue so that a fully eligibility to Lung FUS can be assumed. There is no significant difference regarding age, sex or BMI in those groups.

Cases	Number	Age (y) mean $\pm$ SD	Sex		Height [cm] mean $\pm$ SD	Weight [kg] mean $\pm$ SD
			M	F		
total	186	68,3 $\pm$ 10,6	137 (74%)	48 (26%)	170,3 $\pm$ 13,5	74,5 $\pm$ 18,6
inoperable	110	68,6 $\pm$ 11	83 (75%)	27 (25%)	168,2 $\pm$ 15	73,0 $\pm$ 18,1
inoperable & fit for OLF	63	67,1 $\pm$ 12,5	50 (79%)	13 (21%)	172,4 $\pm$ 9	77,3 $\pm$ 16,8
inop, fit for OLF & fit for FUS	22	65,1 $\pm$ 7,3	17 (77%)	5 (13%)	172,8 $\pm$ 7	78,8 $\pm$ 14

Cause of inoperability:

Out of 110 inoperable cases, most of those were inoperable due to advanced stage 45% (49/110) and 13% (14/110) due to insufficient lung function only. 29% (32/110) were limited by advanced stage and reduced lung function. In 13% (14/110) unresectable tumor locations were found and only 8% (8/110) of patients refused surgery.

Lung function:

Patients eligible to OLF show a significant ($p < 0,01$) better lung function in all parameters. Severe Chronical Obstructive Pulmonary Disease COPD ($>G2$) is the main cause of exclusion for OLF and therefore Lung FUS. Age is a strong depending factor for eligibility to OLF, where all cases up to 50 a were fit for OLF (100%), with increasing age the rate reduced significant whilst only 40% of patients in the age 80– 90a were fit for OLF.

Group (mean $\pm$ SD)	FEV1 [L]	FEV1 rel [%]	TLCO [%]	FVC [L]	COPD > G2
OLF fit	2,2 $\pm$ 0,7	76,3 $\pm$ 18,9	56,6 $\pm$ 15,7	3,2 $\pm$ 0,9	0%
OLF unfit	1,36 $\pm$ 0,4	49,4 $\pm$ 17,2	30,8 $\pm$ 13,1	2,3 $\pm$ 0,7	55% (26/47)

Histological classification:

Lung Cancer with histological Adenocarcinoma (ADC) and squamous LC (SQC) show similar rates regarding operability (50–60%) as well as eligibility to OLF. Approximately 25% of those entities were without restrictions for OLF and critical tumor locations. Small Cell Lung Cancer (SCLC) were dominantly fit for OLF (62%) but has more frequent critical central tumor locations. Patients with LCLC show unfavorable conditions for Lung FUS, with poor lung function and frequent critical location. Cases with Bronchoalveolar (BAC), Large Cell LC (LCLC) and Neuroendocrine (NET) Lung Cancer could not be classified because of insufficient numbers (less than 4).

Tumor location:

The transcostal depth of tumor tissue location varies over a wide range from 25mm – 176mm depending on location and size. Most (90%) of all tumor tissue were in a maximal depth of 135mm. The difference of minimal to maximal distance (steering range) where for 90% of all cases within 82 mm.

Tumor volume:

The median tumor volume for all OLF fit lung cancers is 11 cc. The variability of volume is larger in male than in female with extreme large outliers up to 550 cc. The lowest median tumor volume showed the Small Cell Lung Cancer (7,5 cc), followed by the Adeno Carcinoma (14 cc) and Squamous LC (24 cc). All lung tumor entities vary over the same range with its volume. Almost all 98% (61/62) tumor manifestations were solitary, just one case showed separation into two nodules.

Location to sensitive structure:

In 54% (34/63) of eligible cases, proximity to sensitive structure was present (<10mm). Out of those, main pulmonary vessels or aorta and pleural cavity are the main critical locations.

Technical requirements for FUS:

- Focal depth for 90% of all tumor tissue are located within 135 mm of transcostal depth (see Tumor Location). Ideally a FUS system should provide a maximal focal range of 160mm and a steering range of 85mm.
- Based on recent experience of a limited OLF time (75 min), a theoretical ablation speed of 0,2cc/min would be required to treat 50% and 3,4cc/min for 90% of cases.

Percentile of % cases	5	10	25	50	75	90	95
required ablation speed [cc/min] to treat	0,03	0,04	0,09	0,20	1,11	3,39	4,23

F. Scientific utilization of program results

A summary of the joint data analysis from Lung Cancer and Lung Metastasis groups was presented at the 6th FUS Symposia in Reston "Towards FUS lung cancer, which patient group of primary and secondary lung cancer is preferably accessible?". These results are considered for submission for publication in the Europ. Journal of Medical Research (EJ Med Res) as an open access journal.

G. Cited Literature

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