Assessment of concentration and penetration depth of cisplatin in human lung tissue after decortication and hyperthermic exposure

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Background: Hyperthermic perfusion of the pleural cavity with cisplatin after pleurectomy/decortication is an additional therapeutic option to reduce local relapse of malignant pleural tumours. Although there are data on the clinical effect, only little is known about the local impact on human lung tissue by cisplatin. The objective of this experimental study is to evaluate both the concentration and the penetration depth of cisplatin in human lung tissue after normothermic and hyperthermic exposure under ex-vivo-in-vitro conditions.

Methods: This study was approved by the local ethics committee. In total, 46 patients underwent elective lobectomy and wedge resections were taken from the resected lobes. A decortication of the visceral pleura was performed under ex-vivo conditions, and the tissue samples were incubated with cisplatin (c =0.05 mg/mL) at 37, 42 or 45 ℃ for 60 minutes. Then the mass concentration of platinum was measured with flameless atomic absorption spectroscopy and then converted into cisplatin concentration. In addition, the current data were compared with previous data of our working group (42 ℃, without decortication).

Results: The overall maximum penetration depth was 7.5 mm due to limitations of our methods. The functional maximum penetration depth did not vary with temperature (P=0.243) but by decortication (P<0.001). The cisplatin concentration decreased with increasing penetration depth (P<0.001). An increase of temperature showed no effect on the cisplatin concentration in decorticated tissue samples (P=0.985). However, decortication at 42 ℃ significantly increased the cisplatin concentration in comparison to not decorticated tissue samples (P=0.005).

Conclusions: Decortication of the visceral pleura increases the cisplatin concentration in the lung tissue. Therefore, it possibly reduces the likelihood of a local relapse. An increase of temperature did not show any effect.

Keywords: Hyperthermic perfusion; chemotherapy perfusion; penetration depth; cisplatin

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Introduction

One of the biggest challenges in thoracic oncology is the treatment of malignant pleural mesothelioma (MPM), a rare tumor entity mainly caused by exposition to asbestos with a latency period of 30 years (1) and reaching its peak of incidence at about 2020 (2). Conventional chemotherapy alone only shows a median survival of less than one year (3). Due to its diffuse growth, only a macroscopic resection is achievable, preferring lung tissue conserving techniques as pleurectomy/decortication (P/D) or extended (e)P/D (4,5). In consequence, unclear resection margins as well as metastatic extrapleural nodes show a worse outcome (6). As a result, concepts of additional intracavitary chemotherapy were developed to improve local tumor control within a multimodal treatment regime. Today the additional HITOC (hyperthermic intrathoracic chemotherapy) is the most commonly used method, with reliable data on pharmacokinetics (7,8), clinical safety (9-11) and potential benefit in survival (12-14).

However, there is only little known about the local effects of the administered drugs (mostly a combination with cisplatin) on the lung tissue, including maximum depth of penetration and whether therapeutically effective doses are applied. A previous *ex-vivo*-study of our working group showed that the penetration depth of cisplatin in not decorticated human lung tissue was approximately 3–4 mm at 42 ℃ (15). Another *ex-vivo*-study emphasizes the importance of dose, combination of cytostatic drugs and temperature on the survival of MPM-cell lines, whereas the time of treatment was not decisive (16). Further data are inconsistent in whether MPM-cells are sensitive or rather resistant to commonly applied concentrations of cisplatin (17,18).

The objective of this experimental study was to evaluate both the concentration and the penetration depth of cisplatin in human lung tissue after decortication and hyperthermic exposure under *ex-vivo-in-vitro* conditions.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6307).

Methods

Patients and study design

This experimental study was approved by the local Ethical Committee of the University of Regensburg (reference number: 19-1379-101). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients signed an informed consent before participating in the study. Patients were included between March 2019 and March 2020. Criteria for inclusion were an age older than 18 years, elective anatomical lung resection (lobectomy) and no obtained neoadjuvant therapy like previous radiochemotherapy. Neither randomisation nor blinding was conducted. Participating hospitals were the departments of thoracic surgery of the University Medical Center Regensburg and of the Hospital Barmherzige Brüder Regensburg. The experimental investigations took place in the laboratory of the Department of Thoracic Surgery at the University Medical Center Regensburg. The analyses of the specimens were performed in the Institute of Pharmacy of the University of Greifswald. In total, 55 patients underwent elective lobectomy due to tumor diseases and wedge resections with stapler devices were taken from the resected lobes under ex-vivo conditions. Eight tissue samples were rejected due to small diameter and one sample was used as blank sample, resulting in 46 included tissue samples.

Experimental setting and pharmacokinetic analysis

The tissue samples were transported into the laboratory without embedding in any fluid. A decortication of the visceral pleura was performed and the tissue samples (about 3–10 cm^3) were incubated with cisplatin (c =0.05 mg/mL) at 37, 42 or 45 ℃ for 60 minutes. The tissue samples were frozen in liquid nitrogen and subsequent slices of 50 µm were prepared with a cryomicrotome (Leica CM1900). In each case, ten slices were put together in a 1.5 mL Eppendorf cup and incubated in a 0.9% NaCl and 65% nitric acid solution (each 200 µL per 100 mg wet weight tissue) followed by a homogenisation (MP Biomedicals FastPrep-24) for one minute. We incubated the cups in a water bath at 80 ℃ for 24 hours or until there was a clear solution. 30 µL of the content from each cup were diluted with 970 µl of water (dilution of 1:33). Then the mass concentration of platinum was measured with graphite furnace atomic absorption spectroscopy (AAS) at the University of Greifswald. Every sample was analysed in triplicate with a relative standard deviation of 5% or less. For each measurement series, a calibration with eight standards between 14.5 and 162 µg/L of platinum was performed by using a quadradic function; correlation coefficients (r) for the calibration curves were >0.997. Afterwards, the penetration of cisplatin was related to

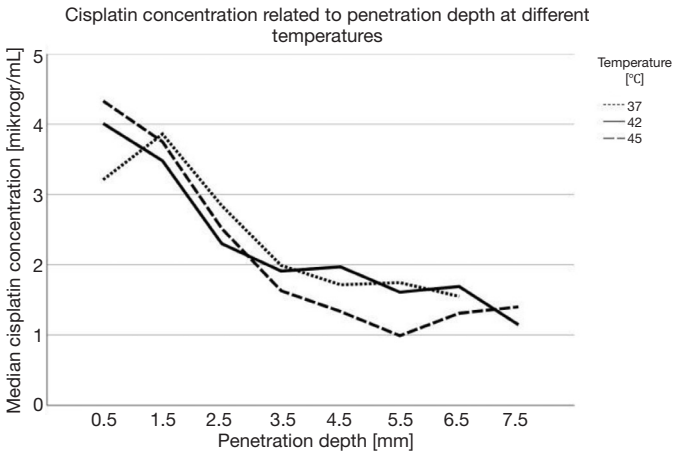

Figure 1 In decorticated tissue the median concentration of cisplatin decreased with increasing depth of penetration without significant difference at various temperatures.

the different platinum concentrations per tissue depth multiplied by the dilution factor. In addition, the current data were compared with previous data of our group (42 ℃, without decortication). Due to the principle of graphite furnace AAS, we detected platinum instead of cisplatin itself. Thus, for better comparability with the common literature, the measured platinum concentrations were converted into cisplatin concentrations by using the following equation: $n_{platinum} = n_{cisplatin}$; $m_{cisplatin} = (M_{cisplatin} / M_{platinum}) \times m_{platinum}$, whereby n is the concentration of the respective species in µg/mL and M is the mole mass of the respective species. Provided that platinum is not or only in negligible quantity in the human body, we assume the measured platinum dose is equal or at least near to the exposed cisplatin dose.

Statistical analysis

Data collection and statistical analysis was performed by using IBM SPSS Statistics 25. The samples were characterized per lab parameters [absolute frequency (n), median (med), quartile (Q1/Q3), range].

Differences in functional maximum penetration depth (defined as a depth with a cisplatin concentration higher than 1 µg/mL) between temperatures (37, 42 and 45 ℃) were assessed by Kruskal-Wallis-H-test and between decorticated versus non-decorticated tissue by Mann-Whitney-U-test. Due to the small sample size, non-parametric methods were used.

Based on repeated measures, mixed linear models (MLM) were used to assess the correlation of cisplatin concentration and penetration depth as well as the differences of cisplatin concentration in decorticated tissue between different temperatures (37, 42, 45 ℃) and between decorticated and non-decorticated tissue at 42 ℃. Parameter estimation of MLMs was based on maximum likelihood method and autoregressive repeated covariance type was used as the correlation of cisplatin concentration between the measurements (penetration depth) gets less as penetration depth gets further apart. Estimates and 95% confidence interval (CI) were reported.

The two-sided level of significance was set at $P \leq 0.05$. The analysis was only explorative and thus no adjustment for multiple testing was conducted.

Results

The tissue samples (n=46) included seven decorticated samples at 37 ℃, 13 decorticated samples at 42 ℃, 14 non-decorticated samples at 42 ℃ and 12 decorticated samples at 45 ℃. General trends of cisplatin concentration are shown in *Figures 1* and *2*. Further information about penetration depth and concentration of cisplatin are presented in *Table 1*.

The overall maximum penetration depth of cisplatin was 7.5 mm (limited by our method), with a median of 4.5 mm (n=46, Q1/Q3 =3.5/5.8; range, 2.5–7.5). The functional maximum penetration depth (defined as a depth with a cisplatin concentration higher than 1 µg/mL) did not significantly differ in decorticated tissue between various temperatures (P=0.243; *Figure 3*) but between decorticated and non-decorticated tissue at 42 ℃ (P<0.001; *Figure 4*).

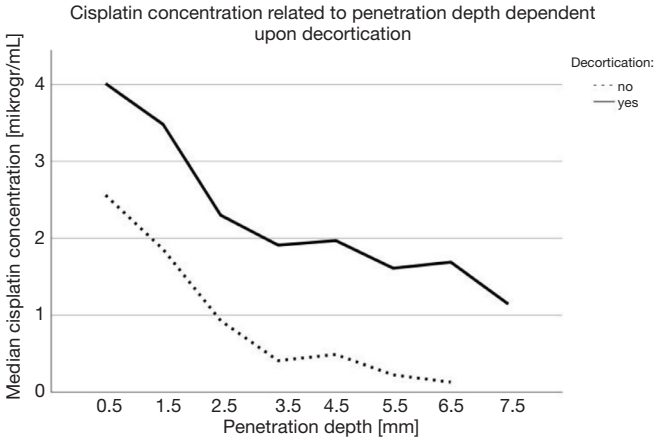

Figure 2 The median concentration of cisplatin (µg/mL) decreased with increasing depth of penetration at 42 °C with a significant difference upon the tissue was decorticated or not.

Table 1 Descriptive statistics: penetration depth and cisplatin concentration related to temperature and decortication

	37 °C decorticated				42 °C not decorticated				42 °C decorticated				45 °C decorticated			
	n	Median	Q1	Q3	n	Median	Q1	Q3	n	Median	Q1	Q3	n	Median	Q1	Q3
MPD	7	5.50	3.50	6.50	14	4.50	3.50	4.50	13	4.50	4.50	5.50	12	6.00	4.50	7.25
functional MPD	7	3.50	2.50	5.50	14	1.50	1.25	2.50	13	4.50	3.50	5.50	12	6.00	3.75	6.50
CC at 0.5 mm	6	3.21	1.81	4.68	12	2.56	1.65	3.17	13	4.01	2.75	5.68	12	4.33	2.62	5.71
CC at 1.5 mm	7	3.86	2.18	4.77	14	1.86	1.14	2.98	13	3.48	2.38	5.11	12	3.75	3.02	5.06
CC at 2.5 mm	7	2.84	2.15	3.52	13	0.93	0.44	1.07	12	2.30	1.43	3.30	12	2.52	1.84	3.98
CC at 3.5 mm	6	1.99	1.41	2.79	13	0.41	0.13	0.72	13	1.91	1.03	2.64	12	1.63	1.30	2.56
CC at 4.5 mm	4	1.71	0.78	2.20	9	0.49	0.16	0.77	11	1.97	.99	2.58	10	1.34	0.91	1.94
CC at 5.5 mm	4	1.75	1.61	2.37	2	0.23	0.19		5	1.61	1.20	2.36	8	0.99	0.69	1.16
CC at 6.5 mm	2	1.55	0.81		1	0.13	0.13	0.13	2	1.69	1.54		6	1.31	1.22	1.63
CC at 7.5 mm	0				0		.		2	1.15	0.88		3	1.40	0.91	

CC, concentration of cisplatin [µg/mL]; MPD, median maximum penetration depth [mm]; functional MPD, median maximum penetration depth [mm] with a cisplatin concentration higher than 1 µg/mL; Q1/Q3: first/third quartile.

Two MLMs were computed: MLM 1 for decorticated tissue to compare cisplatin concentration between temperatures and MLM 2 to compare cisplatin concentration between decorticated and non-decorticated tissue at 42 °C. Results are presented in *Table 2*. In both cases, the cisplatin concentration decreased significantly with increasing penetration depth (P<0.001). The cisplatin concentration decreased approximately 0.5 µg/mL per 1 mm of penetration depth. The mean cisplatin concentration did not differ between various temperatures in decorticated tissue (P=0.985). However, the mean cisplatin concentration was significantly higher in decorticated compared to not decorticated tissue at 42 °C (mean difference =1.34 µg/mL; 95% CI: –2.25, –0.44; P=0.005).

Discussion

A big challenge in the surgical therapy of MPM are the residual tumor cells on the lung surface even after complete decortication. The objective of the additional HITOC after surgical cytoreduction with macroscopic complete tumor resection is the eradication of those remaining tumor cells

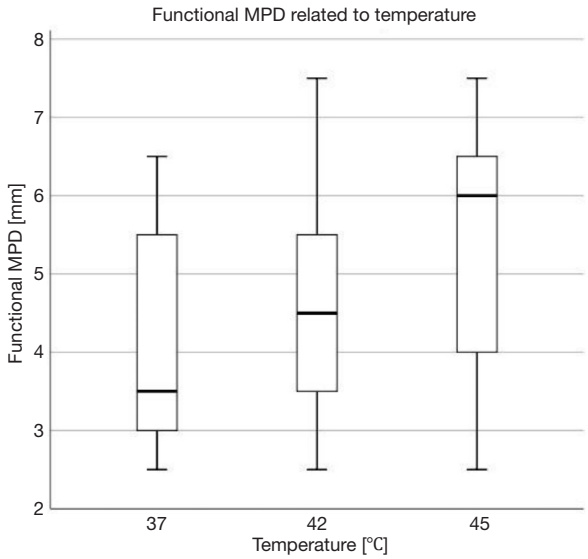

Figure 3 Temperature (℃) does not significantly vary functional maximum penetration depth [mm] in decorticated tissue; functional MPD: functional maximum penetration depth.

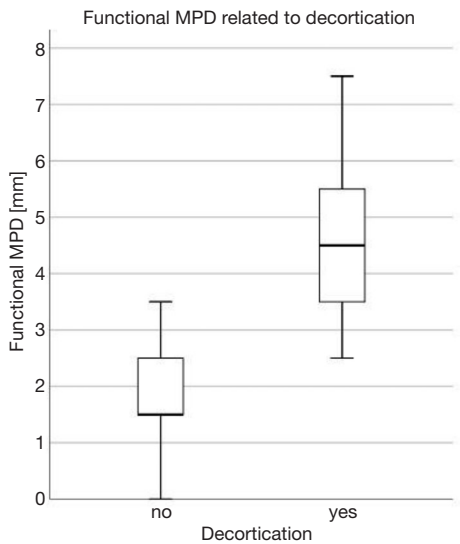

Figure 4 Decortication does significantly vary functional maximum penetration depth [mm] at 42 ℃, functional MPD, functional maximum penetration depth.

in order to improve local tumor control and by that the patients´ survival. However, the local effects of the HITOC including chemotherapeutic agents (e.g., cisplatin) on the lung tissue remain unclear. A previous ex-vivo-study of our group estimated the penetration depth of cisplatin in not decorticated lung tissue to be 3–4 mm at 42 ℃ (15).

Table 2 MLM of cisplatin concentration related to temperature and decortication

	n	Estimate‡	95% CI		P
MLM 1					
Penetration depth	182	−0.46	−0.57	−0.35	<0.001
Temperature (℃)					
37	36	2.62	1.96	3.29	0.985
42	71	2.70	2.22	3.17	
45	75	2.68	2.20	3.16	
MLM 2					
Penetration depth	135	−0.54	−0.69	−0.40	<0.001
Decortication					
No	64	1.54	0.91	2.18	0.005
Yes	71	2.89	2.25	3.53	

MLM 1: The mean cisplatin concentration in decorticated tissue decreased with increasing penetration depth (on average 0.46 µg/mL per 1 mm; P<0.001) but did not differ between temperatures (P=0.985). MLM 2: The mean cisplatin concentration decreased with increasing penetration depth at 42 ℃ (on average 0.54 µg/mL per 1 mm; P<0.001) and was higher in decorticated tissue than in not decorticated tissue (P=0.005). MLM, mixed linear model. ‡, estimate of cisplatin concentration.

Now, we have taken a step closer to in-vivo-conditions by both decorticating the visceral pleura and varying the temperature. Summarising, overall penetration depth was 7.5 mm due to our limited methods. The functional maximum penetration depth increased after decortication, but it does not differ at different temperatures. Second, cisplatin concentration decreased at about 0.5 µg/mL per 1 mm of penetration depth. Third, overall cisplatin concentration did not differ between various temperatures, but it was increased by decortication.

Ratto *et al.* collected lung tissue samples taken after P/D and intracavitary perfusion with cisplatin (100 mg/m^2 BSA) for 60 min and found that the cisplatin concentration is enhanced by hyperthermia (42 *vs.* 37 ℃) (19). This is contrary to our results. Cameron and Hou investigated survival rates of MPM cell lines ex-vivo that were exposed to hyperthermia of 42 ℃ and cisplatin doses of 1, 2 and 4 µg/mL (16). Combining their data with our data on decorticated tissue samples at 42 ℃, we assume survival rates of MPM cells of 15–25% at 0.5 mm and approximately 30–50% at 3.5 to 4.5 mm. In not-decorticated tissue samples at 42 ℃ the approximate survival rate would be more than

30–50% at 0.5 mm, 30–60% at 2.5 mm and even higher at a penetration depth greater than 3.5 mm. This implicates that more tumor cells are killed at a greater depth after decortication. Another study could demonstrate, that in five out of six pleural fluid samples (could be considered as a penetration depth of zero) the cytology was negative for the presence of neoplastic cells after HITOC when compared with the sample of pleural fluid taken immediately after the chest was opened (20). Opitz *et al.* even evolved another form of intracavitary chemotherapy by using the combination of fibrin glue with cisplatin being sprayed onto the resected lung surface instead of fluid agents (21). This might have an additional effect on the risk of local relapse and survival due to a longer period of exposition to the cytostatic drugs and thus higher concentrations.

The applied cisplatin dose for HITOC used to be 100–150 mg/m^2 body surface area (BSA). With increasing clinical experience and optimizing our perioperative management (7,9), we now administer a cisplatin dose of 175 mg/m^2 BSA in all our HITOC procedures and without clinically relevant renal complications due to nephroprotection (11). As described in the literature, higher cisplatin concentrations are associated with prolonged survival rates in patients with MPM (12,22). During HITOC the total amount of cisplatin of 300–350 mg/m^2 (assuming a BSA of 1.7–2.0 m^2) is diluted in approximately 4 liters of circulating volume. This corresponds to a cisplatin concentration in the perfusate of 0.075 and 0.0875 mg/mL, respectively, which is a percentage increase of 50% and 75% compared to the described concentration of 0.05 mg/mL in this study. According to the study of Cameron and Hou, a higher cisplatin concentration is associated with a higher rate of tumor apoptosis (16). Thus, experimental investigations of our group are planned with higher concentrations of cisplatin as mentioned above.

There are some limitations on our results. First, this was an in-vitro-study within a highly controlled setting. Second, the penetration depth and concentration could be different in-vivo although we sought for fast processing of the tissue sample once they were resected. Third, we measured platinum instead of cisplatin due to our method and then converted the data.

In conclusion, our study emphasises the importance of an exact and complete P/D in order to verify that the cisplatin reaches the tissue in sufficiently high dose. Therefore, it will possibly reduce the likelihood of a local relapse after a macroscopic complete tumor resection before HITOC. In the future, one of our next steps in experimental research is to steadily increase the applied cisplatin dose and to combine different cytotoxic agents in order to assess the local effects on lung tissue as well as tumor cell lines.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6307). The series "Hyperthermic Intraoperative Chemotherapy (HITHOC) in thoracic surgical oncology" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This experimental study was approved by the local Ethical Committee of the University of Regensburg (reference number: 19-1379-101). All patients signed an informed consent before participating in the study.

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