

**Combination of regional and systemic chemotherapy:
An effective induction therapy for advanced and inoperable
non-small cell lung cancer**

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Abstract

Background: The objective was to establish the feasibility and toxicity of regional chemotherapy using an isolated thoracic perfusion (ITP) technique as induction chemotherapy followed by surgery in advanced non-small cell lung cancer (NSCLC).

Patients and Methods: 22 chemotherapy-naive patients with NSCLC (median age of 57 years, stage III – IV disease with metastases only in the thoracic region, Karnofsky index > 60), received two cycles of regional plus systemic chemotherapy with a treatment-free interval of 4 weeks. The cytostatic regimen consisted of 10 mg/m² mitomycin, 25 mg/m² navelbine and 30 mg/m² cisplatin during ITP followed by low-dose systemic chemotherapy with 250 mg/m² 5-fluoruracil and 20 mg/m² cisplatin given as a continuous infusion on day 1– 4. 4 weeks after the second treatment. The patients were re-evaluated for response and surgery was carried out if possible.

Results: All 22 patients could be assessed for toxicity, response and survival. There were 19 / 22 remissions (CR 1; PR 12; MR 6) corresponding to a regression rate of 86.4 %. 16 / 22 patients could be resected. This corresponded to a resectability rate of 72.7 % (13 complete resections R0, 1 R1, 2 R2). Side effects were transient and acceptable with no treatment- or surgery-related deaths. Median survival has not been reached after an observation time of 15 months. The estimated 1-year survival rate was 67.3 %.

Conclusions: Regional chemotherapy using an ITP application form is highly effective in advanced NSCLC stage III - IV leading to a high rate of resectability with an encouraging survival outcome.

Key words

Non-Small Cell Lung Cancer (NSCLC); Thoracic perfusion; Regional chemotherapy; Systemic chemotherapy; Induction chemotherapy; Mitomycin; Navelbine; Continuous cisplatin

Introduction

Non-small cell lung carcinoma (NSCLC) remains the leading cause of cancer deaths in both men and women. In 1999, it was predicted that approximately 171,600 people would be diagnosed with lung carcinoma, and 158,900 deaths would occur. (14) NSCLC accounts for approximately 75% of all lung carcinomas and 35% of patients with NSCLC will present with stage IIIA or IIIB disease (12). The majority of these patients with mediastinal involvement are not amenable to surgical resection, and primary radiation therapy alone results in 5-year survival rates of only 3-7% and median survival times of 6-11 months (9).

Since the majority of these patients ultimately die of distant metastases, recent efforts to improve their intermediate and long-term survival have focused on neoadjuvant chemotherapy (with or without radiotherapy) as an induction regimen followed by surgical resection. The ideal trial would address the effect of chemotherapy (with or without radiotherapy) on the survival of patients with clinically visible and mediastinoscopically proven N2 disease.

The theoretical advantages of the neoadjuvant approach include systemic as well as local effects such as:

- early control of distant micrometastatic disease
- prevention of visible tumor seeding at surgery
- an increase in resectability of neoplastic lesions that are technically unresectable at diagnosis
- a reduction of tumor mass before definitive radiotherapy

- decreased incidence of positive margins at surgery
- feasibility of less radical surgery with organ preservation
- in-vivo assessment of the effects of chemotherapy and / or radiotherapy

Moreover, early chemotherapy has been associated with greater efficacy and improved drug delivery to tumor cells via an intact vasculature. Disadvantages of the neoadjuvant approach include morbidity and mortality related to the side effects of induction chemotherapy and an increase in surgical morbidity and mortality as well as a delay in prior definitive surgery.

The poor outcome of patients with unresectable stage IIIA/B NSCLC who are treated with thoracic radiation therapy (TRT) alone is poor. Chemotherapy in combination with TRT has therefore been evaluated. The introduction of combined modality treatment has improved the median and long-term survival rates for these patients (5,11,15,26,27).

Several groups have shown that this approach is feasible in patients with stage III disease, who usually have better response rates than patients with stage IV disease. (4,16) Moreover, three small randomized trials comparing surgery alone with a combined program of induction therapy followed by surgery have shown prolonged survival in the combined modality arms. (23,24,25)

Since local control remains a substantial problem in patients with unresectable stage III NSCLC, strategies designed to enhance local control stand to make further improvements in the long-term outcome of patients with this disease. This pilot study was designed to incorporate the isolated thoracic perfusion treatment (ITP) planning into a strategy of induction therapy followed by surgery in the treatment of patients with primarily unresectable stage IIIA/B

NSCLC (1,8,17). In order to improve the effectiveness of chemotherapy in advanced and inoperable NSCLC, we aimed to increase the regional cytostatic drug concentration in the thoracic region by means of a regional administration form – isolated thoracic perfusion (ITP). Thoracic perfusion means the limitation of the greater circulation to the thoracic region by placing two balloon catheters in the aorta and vena cava as well as two Esmarch bandages around the base of both arms. Pharmacokinetic studies on this administration form using different cytostatic drug such as doxorubicin, melphalan, FUDR, cisplatin or mitomycin have shown a 6- to 10-fold increase in loco-regional drug concentrations as compared to systemic administration (10,18,19,22)

The aim of this study was to evaluate the toxicity profile and efficacy of a combined cytostatic regimen comprising regional and systemic chemotherapy in unresectable stage III NSCLC patients. This regimen consisted of a combination of regional chemotherapy (mitomycin, navelbine and cisplatin) using an isolated thoracic perfusion technique (ITP) as application form and systemic chemotherapy with 5-fluorouracil and cisplatin given continuously at a low dosage over 4 days (2,11). This report is the first to incorporate ITP into an inductive treatment strategy for NSCLC and describes the Phase I results of the trial.

Patients and Methods

Patient selection

Eligibility criteria for study entry included the following patients with histologically or cytologically confirmed unresectable or metastatic NSCLC

stage III A (bulky mediastinal involvement), stage III B or stage IV with metastases defined only to the thoracic region and an acceptable performance status with a Karnofsky index of 60 and more. Patients with severe arteriosclerosis, concurrent severe cardiac, metabolic or infectious disease were excluded from the trial. An adequate baseline organ function was defined as a WBC count of at least 3,000/NT., liver and renal function within normal limits, and acceptable spirometric values allowing general anesthesia. Patients who had a previous history of chemotherapy, radiotherapy or presence of active infection were excluded from this study. All patients gave written informed consent.

Patient evaluation

A complete history, physical examination, complete blood cell count with differential serum biochemistry, urinalysis, spirometry, bronchoscopy, computer tomography (CT) scan of the chest and upper abdomen, and ECG were obtained at baseline. Patients were monitored throughout treatment by recording history, toxic events, and complete blood cell counts. Serum clinical tests were repeated just before the start of each chemotherapy cycle. Tumor response was evaluated by CT scan after two cycles of treatment. Repeated mediastinoscopy was not included in the post chemotherapy evaluation.

Response definition

Definitions of response (i.e. partial or complete response), stable disease and progressive disease were based on the standardized response criteria established by the World Health Organization (WHO). Responses were

assessed after a second therapy cycle with CT scan and determination of tumor marker levels if positive. Survival and response were both determined in all enrolled patients and calculated starting from the beginning of ITP treatment.

Treatment plan

The treatment plan consisted of a combination of regional plus continuous systemic chemotherapy. For regional chemotherapy, the following cytostatics were administered during ITP via central venous line on day 1: 10 mg/m² mitomycin, 25 mg/m² navelbine and 30 mg/m² cisplatin. To prevent severe bone marrow dysfunction and to activate immune function 300 µg GM-CSF was administered during ITP. As systemic chemotherapy, 250 mg/m² 5-fluoruracil and 20 mg/m² cisplatin were administered as a continuous infusion over 4 days via central venous line starting after the end of ITP. The treatment-free interval was 4 weeks. In leucocytopenia or thrombocytopenia, WHO grade 3 or 4, the next therapy cycle was postponed until the white blood cell count was > 3000 /dl and platelet count > 100,000 /dl. Granulocyte-stimulating factors (G-CSF) were given if required. Antiemetic therapy was started preoperatively using 8 mg dexamethasone and 3 mg Granisetron was administered intravenously. Treatment was discontinued if the disease progressed, or major toxicity was manifested or on the decision of the patient and / or physician.

Surgical technique

Under general anesthesia, both femoral vessels were exposed via an inguinal approach. After systemic heparinization with 150 I.U. heparin / kg, both vessels were cross-clamped and two three-lumen 12-French balloon catheters (PfM, Cologne, Germany) were inserted (Fig. 1). Under x-ray control, both

balloons were insufflated in the aorta just above the celiac axis and in the inferior caval vein below the right atrium. In order to reduce the perfusion volume, Esmarch bandages were insufflated around the base of both arms (occlusion pressure: 250 mmHg). Cytostatics were given via central venous line in the first two minutes after starting perfusion; perfusion time was 20 minutes.

Statistical analysis

Overall and progression-free survival curves were generated using the Kaplan – Meier method starting from the date of diagnosis. Both disease progression and death were regarded as endpoints for progression-free survival.

Results

Patient characteristics

Between March 1998 and October 2000, 22 concurrent patients could be accrued in this study. Characteristics of the 22 eligible patients (listed in Table I) included a median age of 57 years (range, 43 to 74 years), Karnofsky index status of 80 and less in 59 % of the patients and adenocarcinoma as the predominant histological subtype (45 %). There were 10 patients in bulky stage III A and another 11 in stage III B with 6 / 11 with T4 tumors. One patient was in stage IV because of contralateral pulmonary metastases. In one patient, a third cycle of ITP and systemic chemotherapy was added in order to attain further shrinkage of a centrally located T4 tumor. In another patient with stage III B disease due to supraclavicular lymph node involvement, the strategy was switched to local radiotherapy and ITP using paclitaxel and gemcitabine alone.

Toxicity

During 45 cycles of regional and low-dose continuous systemic chemotherapy, grade 3 leucocytopenia was observed in only 3 cases (6.7 %) (Table 2). There was no episode of febrile neutropenia. Grade 3/4 anemia and thrombocytopenia was not observed and there were no bleeding episodes. Febrile reactions were frequent owing to administration of single dose of GM-CSF during ITP, but did not exceed grade 1 / 2. Despite the use of cisplatin in this regimen, vomiting was not severe and manageable. Alopecia was manifested in only one case. The surgical procedure of ITP did not have to be terminated prematurely due to disturbance in blood pressure parameters in any patient. Signs of pneumonitis or pulmonary fibrosis were not observed in any of these cases. Grade 2 esophagitis occurred only in the patient who received

radiotherapy plus second line chemotherapy. There were no signs of esophagitis in any other cases.

Surgical procedures

A resection of primary tumor and mediastinal lymph node metastases was possible in 16 out of 22 cases after improvement in the general condition as well as lung function parameters in response to therapy. Complete pneumonectomy was carried out in 7 cases, whereas a lobectomy or bilobectomy was necessary to resect visible tumor in the remaining 9 cases. Histological evaluation revealed a complete resection (R0) in 13 cases, whereas resection was incomplete in three cases (R1 1/16, R2 2/16).

Complications

After 45 ITP procedures, a superficial wound infection occurred that did not prolong the stay in hospital in one case. No wound infection and only one postoperative pneumonia was observed. One early bronchial stump insufficiency occurred after dextrolateral pneumonectomy. In the same case, a toxic lung edema requiring prolonged mechanical ventilation had to be treated. In another case, a late bronchopleural fistulation after left-sided upper lobectomy was observed.

Response

The overall response rate of the 22 patients who could be evaluated for response was 59 % (4.5 % CR and 54.5 % PR), but 6 other patients attained a minor response leading to a regression rate of 86.3 %. In this special situation,

we have to bear in mind that resectability will be not defined by shrinkage of 50 % or more as defined in WHO criteria.

Looking at changes in lung function, the most interesting parameter – one-second Forced Expiratory Volume FEV₁ – changed dramatically after the first ITP procedure as sign of response. Nearly all patients responding to this treatment had an increase in or stabilization of FEV₁. This improvement in lung function opens the way for operation and resection in this group of patients (Fig. 2, 3). For the entire group, the mean FEV 1 before chemotherapy was 69.23 % and after treatment 74.78 %. Mean increase in FEV 1 for responding patients after the first ITP was 8.37 % (range 0 – 56 %) whereas the three patients not responding to therapy showed a fall in lung function parameters.

Histology

Resected tumour tissue was cut in 10 different pieces and each piece was investigated for visible tumor regression using a semiquantitative technique. Under fortyfold magnification, 10 fields of vision were examined for the percentage of regressive tumor cells using the following histologic signs of tumor regression :

- Nucleus edema
- Karyorhexis
- Loss of mitosis
- Cytoplasma edema
- Sporadic tumor cell necrosis
- Cell dissociation

The relation of damaged tumor tissue to tumor cells unaffected by therapy was determined by percentage . The results of this evaluation are shown in Table 3. Interestingly in all resected specimen desmoplastic changes could be documented especially in mediastinal lymphnodes.

Survival

After a median follow-up period of 15 months, 5 of the 22 patients had died at the time of this analysis. In 4 cases, the deaths were related to a diagnosed malignancy, whereas one died of a cardiovascular condition not related to therapy. The median duration of survival has not been reached up to now. The estimated 1-year survival rate was 67.3 %. For 10 / 22 patients in bulky stage III A, 1-year actuarial survival was 87.5 %, whereas in stage III B / IV disease (12 / 22 patients) only 58.3 % survived after one year (Fig. 4).

Comment

Combined modality therapy is now considered the standard care for patients with unresectable stage IIIA/B NSCLC and a good performance status. The trial of Dillman et al. (5) was the first major randomized trial to show that sequentially delivered chemoradiotherapy yields improved survival rates compared to radiotherapy alone. When the radiotherapy arm is compared with the combined modality arm, response rates (43 % vs. 56%, respectively; $p = 0.092$), median survival (9.6 vs. 13.7 months, respectively; $p = 0.012$), and 5-year survival rates (6 % vs. 17%, respectively) were all superior in the combined modality arm. This trial has been verified by the intergroup trial conducted by the RTOG and the ECOG. These showed similar survival advantages for the sequentially delivered combined modality arms. In addition, LeChevalier et al. (15) detected a survival advantage in a large European trial in which the combined modality arm manifested a statistically significant lowering of the rate of distant metastases compared to radiotherapy alone.

Another possible means of improving the results in NSCLC patients stage III A / B is use of inductive chemotherapy followed by surgery. Okada et al. (21) demonstrated a survival advantage for all NSCLC patients with bulky nodal involvement after induction therapy and resection in their series of 51 patients. These results could be confirmed by Stathopoulos et al. (29) in a larger trial with 359 patients, but in which the rate of resectability was very low: 6.2 %. This contrasts with the study published by De Leyn et al. (3), who attained a resectability rate of 88 % after induction chemotherapy in patients with NSCLC stage III A bulky disease.

In this study, we have tried to overcome the primary tumor cell resistance in NSCLC by means of a high local cytostatic drug concentration (8,18,19). To achieve this objective, we used a simplified technique to isolate the chest and lung (6,13). As we have shown in a previous study, ITP and low-dose continuous systemic chemotherapy is highly effective in recurrent and progressive NSCLC confined to the thoracic region (17).

The potential benefit of regional chemotherapy is to attain high local drug concentrations in the treated area by reducing systemic side effects (18).

These high cytostatic drug concentrations should lead to an increase in response rate especially in patients in whom no other negative factors such as decreased vascularity after prior radiotherapy or increased tumor cell resistance after prior chemotherapy or radiotherapy will diminish efficiency.

This pilot study has shown that thoracic perfusion (ITP) is feasible in NSCLC patients. ITP did not have to be terminated prematurely in consequence of a disturbance in blood pressure parameters in any of the cases. This is consistent with data published by Berkenstadt et al. (1) and Guadagni et al. (8), who had shown that ITP does not lead to increased cardiac stress. Our own results published earlier are consistent with these findings. Data in this study have shown an acceptable toxicity profile for these NSCLC patients who are in good to reduced general condition and performance status. There were no specific side effects associated with this particular mode of administration such as lymphatic fistulas in the groin, neurological disorders or deep-vein thromboses. This treatment with a cytostatic drug combination in the dosages and with the mode of administration mentioned above is combined with a very low rate of bone marrow depression. This raises the question as to whether an increase in dosage will lead to higher response rate.

In 1995 Johnston et al. (13) presented a special technique for isolated lung perfusion leading to an excellent separation of the lungs. The shunting rate was between 0 and 15 %, but we have to bear in mind that NSCLC is infiltrating the thoracic wall as well as the organs of the mediastinum in a high percentage of cases, so that an isolation of the lung is not necessarily appropriate to the pattern of dissemination of NSCLC.

In an animal model of bronchial adenocarcinoma, Hendriks et al. (10) demonstrated shown that an isolated lung perfusion with melphalan can prolong survival compared to no treatment or to systemic chemotherapy with the same drug and dosage. Pharmacokinetic evaluations in various mouse models have shown that using thoracic as well as lung perfusion techniques cytostatic drug concentrations of melphalan, doxorubicin, cisplatin, 5-fluorouracil and mitomycin can be attained that are 6 to 10 times higher compared to systemic administration (6,10,18,19)

In the present trial, we have chosen the cytostatics mitomycin, cisplatin and navelbine for highly concentrated regional chemotherapy (2,7). Based on good results in the inductive treatment of NSCLC reported by Jeremic et al. (11), we combined the regional administration form with a low-dose continuous systemic chemotherapy comprising cisplatin and 5-fluorouracil. The objective was to reduce the gastrointestinal side effects of cisplatin and diminish the risk of hearing loss after high cisplatin concentrations.

The benefit of this special therapeutic strategy is

- to attain a high rate of remissions even in advanced disease
- to attain an increase in lung function enabling curative resection
- to open the way for an effective radiotherapy after curative resection

- to reduce the perioperative risk after induction therapy by minimizing radiotherapeutic tissue damage.

Our data have shown that regional chemotherapy is highly effective as induction therapy for advanced NSCLC. The treatment modality is effective in bulky stage N2 disease as well as stage III B/ IV disease confined to the thoracic region. Especially interesting in this study is the improvement in lung function parameters soon after the first ITP which makes curative resection feasible for patients in reduced condition and provides for a new technique for diagnosing response. Since all patients responding to this treatment have had an improvement in lung function parameters, lung function tests can be employed as a tool for diagnosing early response. When there is no improvement, another cytostatic regimen is required to overcome tumor-cell resistance (20,28).

The high regression rate after ITP has led to an acceptable resectability rate also for stage III B / IV patients. The short observation time does not enable definite conclusions to be drawn regarding survival after regional induction therapy plus resection, but our preliminary data are very encouraging. This means that isolated thoracic perfusion plus low-dose systemic chemotherapy using the cytostatic regimen mentioned above is a very effective tool in advanced and unresectable NSCLC.

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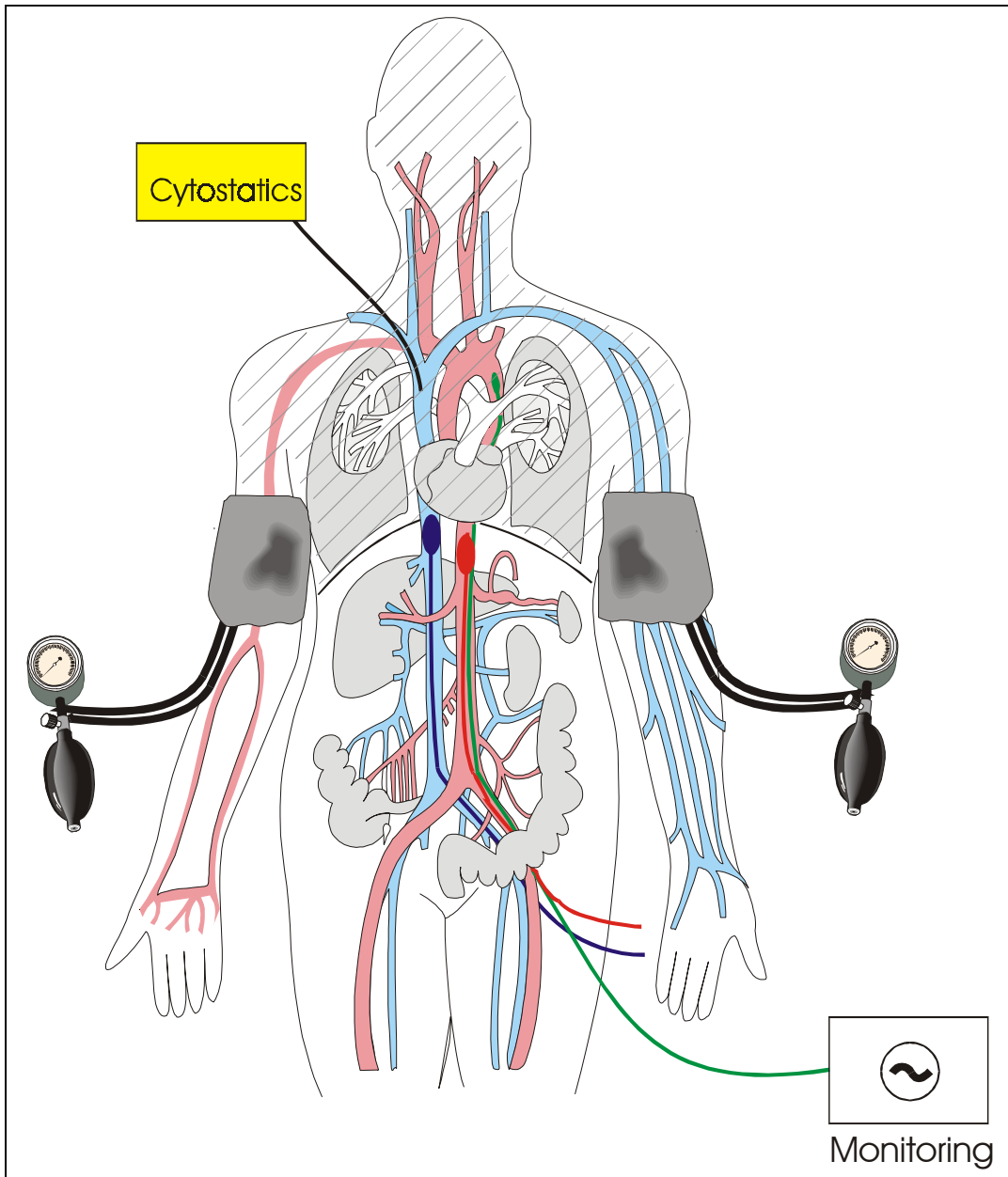
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Fig. 1 Scheme of isolated thoracic perfusion



Tables

<u>Characteristics</u>	No. of patients	%
Sex		
Male	14	64
Female	8	36
Age		
Median	57,1 years	
Range	43-74 years	
Histology		
Squamous Cell	5	23
Adenocarcinoma	10	45
Large cell	4	18
Neuroendocrine	1	5
Undifferentiated	2	9
Karnofsky index		
100	3	14
90	6	27
80	10	45
70	2	9
60	1	5

Table 1: Patient characteristics

WHO -	Grad 1	Grad 2	Grad 3	Grad 4
Leucocytopenia	8	5	3	-
Thrombocytopenia	3	2	-	-
Anemia	2	2	-	-
Vomiting	7	15	-	-
Fever	28	4	-	-
Alk. Phosphatase	2	-	-	-
Pain	3	10	-	-
GOT	1	-	-	-
Alopecia	-	1	-	-
Consciousness	1	-	-	-
Arrhythmia	3	-	-	-

Table 2: Side effects after regional plus systemic chemotherapy

Patient	T-	Regression	N-	Involved Lymphnodes (%)
t	stage	Index	stage	
1	T 3	60 %	N 1	33 %
2	T 3	60 %	N 2	Konglomerat
3	T 2	60 %	N 2	59 %
4	T 0	100 %	N 0	0 %
5	T 4	60 %	N 1	22 %
6	T 1	90 %	N 0	0 %
7	T 0	100 %	N 0	0 %
8	T 1	40 %	N 2	Konglomerat
9	T 2	30 %	N 0	0 %
10	T 1	90 %	N 0	0 %
11	T 2	30 %	N 2	30 %
12	T 3	40 %	N 1	37 %
13	T 2	30 %	N 1	50 %
14	T 3	20 %	N 1	18 %
15	T 1	30 %	N 2	Konglomerat
16	T 2	60 %	N 2	40 %

Table 3 : postoperative histologic examinations

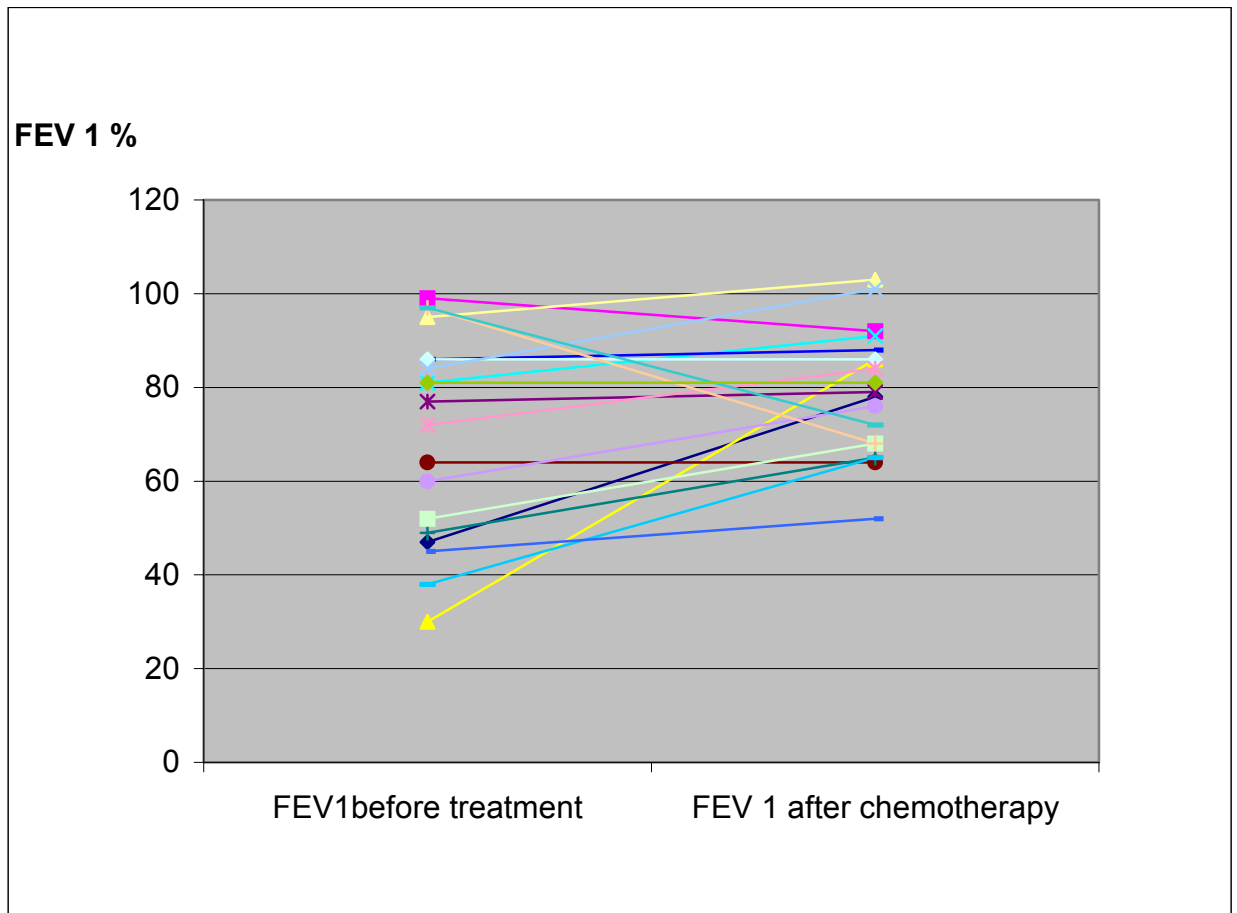


Fig. 2 Changes in lung function parameters after thoracic perfusion in the group of responding patients

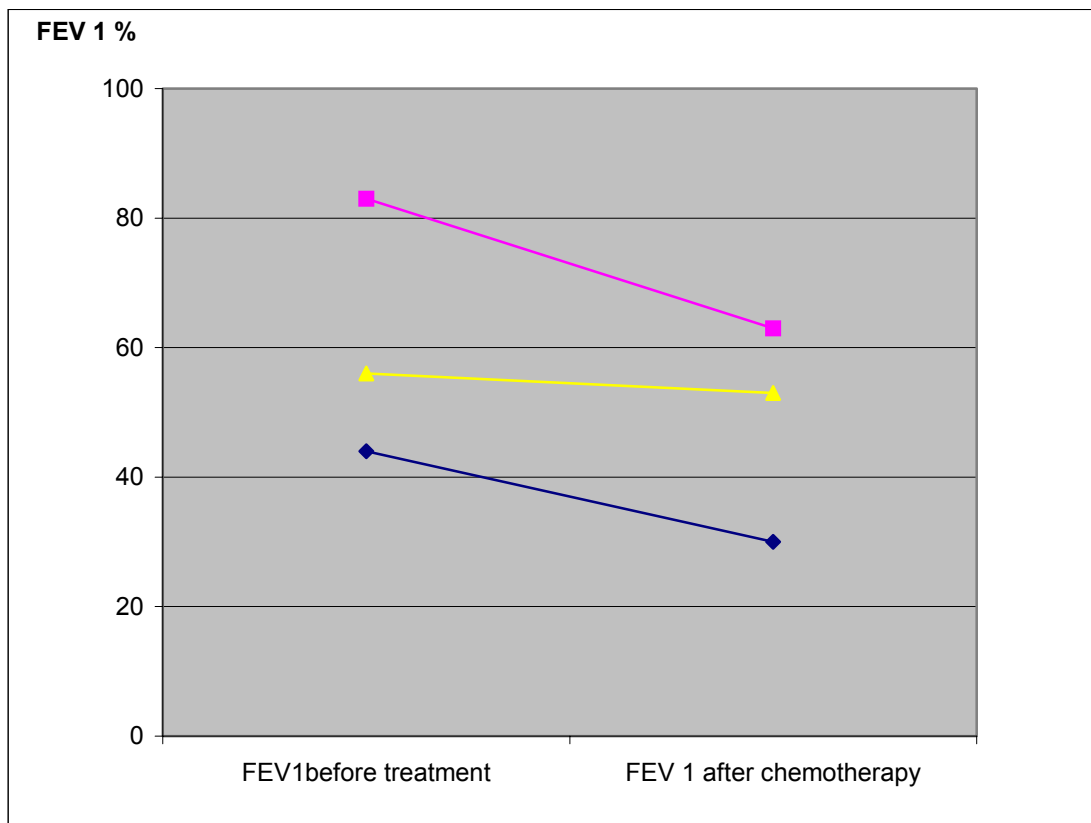


Fig. 3 Changes in lung function parameters after thoracic perfusion in the group without response

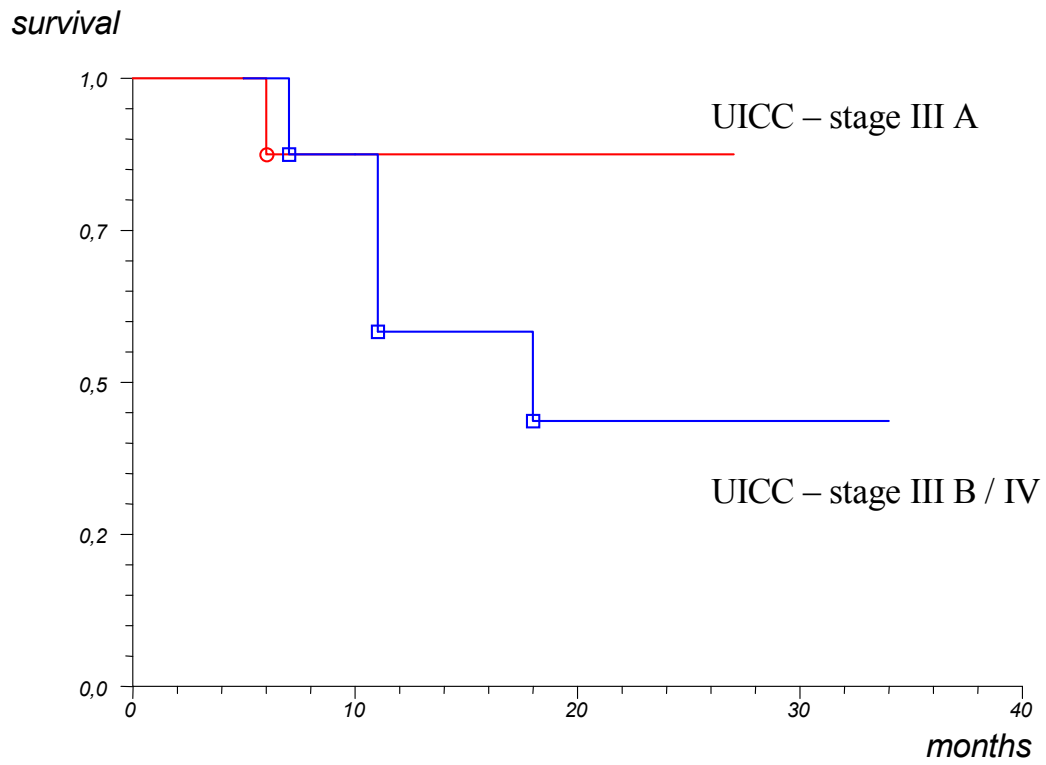


Fig. 4 Kaplan –Meier probability of survival in relation to UICC tumor stage

Legends

Table 1 Patient characteristics

Table 2 Side effects after regional plus systemic chemotherapy

Table 3 : postoperative histologic examinations

Fig. 1 Scheme of isolated thoracic perfusion

Fig. 2 Changes in lung function parameters after thoracic perfusion in the group of responding patients

Fig. 3 Changes in lung function parameters after thoracic perfusion in the group of not responding patients

Fig. 4 Kaplan–Meier probability of survival in relation to tumor stage (UICC classification)