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Induction chemotherapy, concurrent chemoradiation, and surgery for Pancoast tumor. Mature results of a feasibility trial

Short title: **Multimodality treatment of Pancoast tumor**

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ABSTRACT [200 *words*]

Traditional treatment of Pancoast tumor with local approaches – surgery, radiotherapy, or a combination of both, - leads to poor outcome because of high rate of uncomplete resection and lack of systemic control. Aim of the present prospective feasibility study was to determine whereas a trimodality approach improves local control and survival.

Patients with stage IIB to IIIB Pancoast tumor received induction chemotherapy (three courses of split-dose cisplatin and etoposide or paclitaxel) followed by concurrent chemoradiotherapy (a course of cisplatin/etoposide combined with 45 Gy hyperfractionated accelerated radiotherapy). After restaging, eligible patients underwent surgery 4 to 6 weeks postradiation.

Thirty-one consecutive patients with T3- (81%) or T4- (19%) Pancoast tumor were enrolled in the study. Induction chemo-radiotherapy was completed in all patients without treatment-related deaths. Grade 3 to 4 toxicity was observed in 32% of cases. Twenty-nine (94%) patients were eligible for surgery. Complete resection was achieved in 94% of patients. Postoperative mortality rate was 6.4%, and major complications arose in 20.6% of patients. Median survival was 54 months with 2- and 5-year survival rates of 74% and 46%, respectively.

This intensive multimodality treatment of Pancoast tumor is feasible and improves local resectability rate and long-term survival as compared with historical series.

KEYWORDS

Chemotherapy – lung cancer – neoadjuvant therapy – radiotherapy – surgery

INTRODUCTION

Until the early 90's, standard therapy of Pancoast tumor (superior sulcus tumor, SST) was based on local treatment modalities – surgery, radiotherapy, or a combination of both, – under the assumption that SST is a locally invasive disease, and that the prognosis could be improved mainly by achieving an effective local control.[1-5] Thereafter, Pancoast tumor with ipsi- or contralateral mediastinal lymph node metastases has been, and continues to be, considered as a prognostically inoperable disease.

Nevertheless, long-term results of the local therapy alone, even with complete resection and without detectable nodal or distant metastases at the time of treatment, are not satisfying, particularly when compared with them of lung cancer infiltrating the chest wall in other locations.

The role of induction chemotherapy for NSCLC has been extensively investigated in the past decade. Many trials have demonstrated survival advantages for patients with stage IIIA/B NSCLC treated by induction chemotherapy or chemo-radiotherapy and surgery versus standard protocols including surgery, radiotherapy, or both.[6-8]

The promising results of an intensive multimodality approach – a combination of chemotherapy, hyperfractionated accelerated chemoradiotherapy, and surgery – our group administrated in stage IIIA/B NSCLC, have been the conceptual background to test it in patients with Pancoast tumor.[8,9]

This was also supported by the findings of recent studies showing induction chemo-radiotherapy and surgery to afford high local resectability rates and long-term disease control for patients with SST.[10-12]

MATERIAL AND METHODS

Patient Selection

Patients with a histologically or cytologically confirmed diagnosis of NSCLC of the superior sulcus, with or without Pancoast syndrome, were eligible for this prospective feasibility study.

After complete staging, including obligatory mediastinoscopy, only patients without evidence of distant metastases – i.e. with stage IIB to IIIB disease using the criteria reported by Mountain[13] – were accepted onto this trial. Further eligibility criteria included a World Health Organization (WHO) performance status of 0 to 2, age 18 to 75 years, no prior treatment for lung cancer (surgery, chemotherapy, or radiotherapy), and no other concurrent or previous malignancy. Tumor staging was performed by chest radiograph, computed tomographic (CT) scans of the chest, upper abdomen, and brain, abdominal ultrasound, radionuclide bone scan, bronchoscopy, including multiple biopsies of prospective bronchial resection margins, and, routinely, cervical mediastinoscopy. In case of suspected subclavian artery invasion, an angiographic CT scan or a magnetic resonance imaging (MRI) of the thorax was performed. A comprehensive, interdisciplinary risk analysis was performed before starting treatment and preoperatively after restaging procedures and included cardiopulmonary function tests such as lung function testing, ventilation-perfusion nuclide scintigraphy to assess prospectively postoperative residual lung function, ECG and stress ECG, echocardiography, and duplex ultrasound examination of peripheral arteries if clinically indicated. Characteristics that rendered patients ineligible/functionally inoperable were a prognosticated postoperative FEV_1 of less than 1.0 L, a cardiac infarction or unstable angina pectoris in the 6 months before study entry and cardiac disability of class III or greater (New York Heart association criteria). All patients were required to have a normal WBC count (>4,000/μL) and platelet count (>150,000/μL), renal function (serum creatinine level <1.2 mg/dL), and hepatic function (serum bilirubin level <1.5 mg/dL). All patients were fully informed about the nature and purpose of this study by a pulmonologist/thoracic surgeon and a medical oncologist and gave written informed consent before the start of treatment.

Study Design

Eligible patients were planned for three courses of chemotherapy with cisplatin 60 mg/m^2 intravenously (IV) on days 1 and 7 (or 8) and etoposide 150 mg/m^2 IV on days 3, 4, and 5. Since 1999, etoposide was replaced by paclitaxel 175 mg/m^2 IV on day 1. We decided to move from etoposide to

paclitaxel in order to reduce the rate of haematologic toxicity; in fact, most grade 3-4 leukopenia and thrombocytopenia occurred in the first study period (33% vs. 18%, *P*=.360). The cycles were repeated every 22 days. Administration of the following chemotherapy course on day 22 was postponed if patients had a WBC count less than 2,500/μL or platelet count less than 100,000/μL until these values were reached. Dose reductions were performed for grade 4 leukopenia or grade 3 leukopenia associated with infection (70% of etoposide dose) or grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding (50 mg/m^2 of cisplatin). In case of reversible creatinine elevations with values between 1.5 and 2.0 mg/dL during the interval, the cisplatin dose was reduced to 50% in the next course. Rarely, if creatinine values rose above that value or seemed to persist, cisplatin was replaced by 150 mg/m^2 carboplatin and treatment was carried on.

Normally, during the tenth week of treatment, the concurrent chemoradiotherapy was started combining twice-daily hyperfractionated accelerated radiotherapy (1.5 Gy per fraction >6 hours apart, 5 days a week, to a total dose of 45 Gy over a period of 3 weeks) with one course of chemotherapy that consisted of cisplatin 50 mg/m^2 IV on days 2 and 9 (after the start of radiotherapy) and etoposide 100 mg/m^2 on days 4, 5 and 6. The planning target volume contained the primary tumor with a margin of 1.5 cm enclosing the ipsilateral supraclavicular region, the ipsilateral hilum, the ipsilateral mediastinal, and the subcarinal lymph nodes up to 4.5 cm below the carina with a margin of 0.5 to 1.0 cm. For N2 disease, the contralateral upper and lower paratracheal nodes were included with a margin of 0.5 cm, but not the contralateral hilum. Paraesophageal nodes below the plane of the heart valves were only treated if significantly enlarged on CT scans.

Patients with locally advanced (stage IIIB) SST were routinely offered elective cranial irradiation, because of a significant risk of CNS relapse.[14] Prophylactic cranial irradiation (PCI) was started after the end of the fourth chemotherapy cycle at day 9 of thoracic irradiation. A total dose of 30 Gy in 3 weeks was given with a daily fraction of 2 Gy to the brain and the meninges above the foramen magnum.

Two weeks after the completion of radiotherapy, complete restaging except of mediastinoscopy was performed and was followed by definitive surgery, if suitable, 4 to 6 weeks after the end of radiation.

The standard surgical technique to access the upper thoracic inlet was first a limited anterior thoracotomy in the second intercostal space in order to expose and to cut the anterior end of the first one to three ribs and to evaluate the ventral boundaries of tumor growth, as well as to exclude an invasion of the subclavian vessels. In case of vascular involvement, the incision could be extended to

a transmanubrial approach, as described by Grunenwald.[15] After wound closure, the patient was re-placed for a standard posterolateral thoracotomy. Through the posterior access the pleural cavity was routinely opened in the 5th intercostal space and the extent of resection accurately defined. In patients with macroscopic vertebral infiltration, an operative multidisciplinary team with orthopaedic surgeons performed an *en bloc* vertebral resection. Depending on the dimensions of the primary tumor, a variable amount of lung tissue was removed *en-bloc*; the operative procedures included wedge resections, segmentectomies, lobectomies, or pneumonectomies as indicated. In all cases a systematic lymphadenectomy of the interlobar, hilar, and ipsilateral mediastinal lymph node stations was performed (for right-sided thoracotomies: stations Nr. 2, 4, 7, 8, 9, 10, and 11; for left-sided thoracotomies: stations Nr. 4, 5, 6, 7, 8, 9, 10, and 11, according to the *new Regional Lymph Node Classification for Lung Cancer Staging*).[16]

Response and Toxicity Evaluation

Before and after treatment, patients were staged using International Union Against Cancer (UICC) criteria.[13] Toxicities were assessed using the Common Toxicity Criteria (CTC, version 2.0), Radiation Therapy Oncology Group (RTOG) acute radiation toxicity criteria, and RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation toxicity criteria. Surgical resection was defined as complete if following criteria were satisfied: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumor; and the highest mediastinal node removed to be negative. Whenever there was involvement of resection margins, extracapsular nodal extension, unremoved positive lymph nodes, the resection had to be defined as incomplete. Responses to treatment were assessed using standard World Health Organization (WHO) criteria.[17]

Survival Analysis

All patients were monitored every 3 months for the first 2 years from the end of treatment and from then on every 6 months. Survival was measured from the first day of chemotherapy until death, loss to follow-up, or the time of evaluation for this report. Event-free survival was calculated from the first day of chemotherapy until any event occurred, such as tumor progression, incidence of a second cancer, death due to toxicity or secondary conditions, or death due to second malignancy.[18] Survival curves were estimated by the method of Kaplan and Meier.[19] Differences in the curves between groups of

patients were evaluated using a log-rank test.[20] Differences between categorical and continuous variables were comparatively analyzed using Pearson's χ^2-test and Student's *t*-test, respectively. All given *P* values are two-tailed.

Primary end points of the study were overall survival and disease-free survival. Secondary end points were treament-related morbidity and mortality as well as the rate of local relapse as a marker for symptom (pain) palliation.

RESULTS

Eligible population

Between 1993 and 2001, thirty-one consecutive patients with untreated, non-metastatic NSCLC of the sulcus superior were observed at the Ruhrlandklinik, Essen and the West German Cancer Center, University of Essen, Germany. Age ranged from 31 to 75 years (median: 55 years). There were 27 males and 4 females, with a median WHO-performance status score of 1. Almost all patients referred to physician because of pain on the shoulder area or the arm; the median delay between onset of symptoms and diagnosis of a Pancoast tumor was 3 months (range 1-12 months). In most patients lung function tests showed no significant impairment. During the same time interval we excluded another 9 patients from trial: five had been previously treated by radiotherapy alone, and 4 had proved distant metastases at the time of diagnosis.

Twenty two (71%) of the enrolled SST were right-sided and 9 (29%) left-sided. At the presentation, 25 tumors (81%) infiltrated only the bony and soft tissue structures of the upper thoracic inlet, and were thus classified as cT3; in the remaining 6 cases (19%) an involvement of the subclavian vessels, vertebral bodies, or both (cT4), was also detected. After completion of staging, including cervical mediastinoscopy, one (3.2%) patient revealed to have lymph node metastases in the hilar station (cN1), 8 (25.9%) patients in the ipsilateral mediastinum ($cN2_{mediast}$), and one (3.2%) patient in the contralateral mediastinum ($cN3_{mediast}$); 21 (67.7%) patients had no evidence of nodal spreading (cN0). The clinical characteristics are summarized on table 1.

Induction therapy

All eligible patients underwent the planned induction therapy without treament-related deaths. The first 22 (71%) consecutive patients received cisplatin/etoposide, the remaining 9 (29%) cisplatin/paclitaxel. Treatment compliance was high: twenty-seven (87.1%) patients completed the chemo-radiation protocol. Two (6.5%) patients received two of the three scheduled cisplatin/etoposide cycles because of toxicity. In another 2 cases induction chemotherapy with cisplatin/paclitaxel had to be stopped after the first cycle. Preoperative chemo-radiation was delivered at the median dosis of 45.0 Gy (95% CI: 44.5-45.8 Gy); all patients received the concurrent cycle of chemotherapy.

The incidence of severe treatment-related complications due to toxicity is presented on table 2.

Surgical treatment

Out of the 31 patients initially eligible for the multimodality treatment, two (6.5%) patients were not suitable for surgery: one was medically inoperable due to impaired cardiac and pulmonary function at the ultimate risk assessment, and the second one refused operation. At restaging before surgery no complete remission could be detected. Post-treatment CT scan of the chest showed a partial response in about one half (48.3%) of the patients, and no significant change in tumor volume in the remaining 51.7%. In the patient with cN3-disease repeat-mediastinoscopy was attempted, but should have be stopped because of technical difficulties due to scarred mediastinum.

Twenty-nine patients were operated on with the technique described above 4-6 weeks after completion of radiotherapy. Most patients (22 of 29; 76.0%) underwent standard lobectomy with systematic nodal dissection. The only one left-sided pneumonectomy was indicated by central tumor growth into the fissure. Segmentectomy or wedge resection were performed in the remaining 6 (20.6%) patients, in whom intraoperatively only a small apical tumor mass was assessed. Reconstruction of the bony plane of the chest wall was necessary in 15 (51.7%) patients; in the remaining 14 patients scapula and shoulder girdle were able to afford enough stability to the rib cage. No paradox has been observed postoperatively.

Thirty-day mortality rate was 6.9%: one patient died of bacterial pneumonia and ARDS, and a second one of myocardial infarction and pneumonia. Major complications arose in 3 (10.3%) patients. Two patients suffered a pleural empyema with bronchial fistula, and another patient underwent re-thoracotomy due to postoperative bleeding.

Treatment results at pathologic examination

Regarding to the histologic type, there were 11 (37.9%) squamous cell carcinomas, 10 (34.5%) adenocarcinomas, 4 (13.8%) large cell carcinomas, 2 (6.9%) adenosquamous carcinomas, and 2 (6.9%) poorly differentiated non-small cell carcinomas, not otherwise specified.

The microscopic examination revealed the completness of resection (R0) in 29 (100%) en-bloc specimens. In 13 (44.9%) cases no viable tumor could be found; in another 7 (24.1%) small islands of tumor cells had survived embedded in diffuse scarring tissue. Thus, a complete or “near complete” response to induction treatment was observed in 20 (69.0%) patients. In another 4 (13.8%) cases a clearly detectable tumor regression led to downstaging of disease. Non-responders were 5 (17.2%)

patients; one of them was detected to have an unsuspected lymph node metastasis in the supraclavicular fat tissue, that was en-bloc resected, and was therefore classified as having N3-disease. Table 3 shows the surgical-pathological characteristics of the series.

Survival analysis

With date of point on March 15, 2004, ~~Mean~~ median follow-up time for the entire group was 40 months (95%CI: 35-74 months; range: 24-134 months). No patient was lost to follow-up.

The actuarial overall survival at 2 and 5 years for the entire population was 74~~.2~~% and 46~~.0~~%, respectively, with a median survival time of 54 months. Regarding the disease-free survival, 2- and 5-year rates were 67% and 52%, respectively.

A major role in determining the prognosis was played by the clinical stage: 55% of the patients with stage IIB SST were alive at 5 years, while none of the 7 patients with stage IIIA reached this limit. Interestingly, patients with stage IIIB SST had a better outcome as compared with them with stage IIIA (figure 1). Positive mediastinoscopy findings led to poorer prognosis, as shown in figure 2: 5-year survival rates were 21% for cN2-3 $_{\text{mediast}}$ cases vs. 54% for cN0-1 cases (P = .02). Nevertheless, we observed long-term survivors also in the group with mediastinal lymph node metastases, with a median survival time of 28 months. The presence of viable tumor cells in the resected specimen worsened the prognosis, as shown in figure 3: 5-year survival rates were 63% for the complete responders versus 35% for the partial responders (P = .10). The extent of lung resection did not influence the long-term outcome. Interestingly, patients undergoing paclitaxel-based induction therapy had a higher 5-year survival rate as compared with patients treated with etoposide (76% vs. 31%; P=.16).

Pattern of tumor relapse

There were 11 events in 9 (29%) patients: one (3.2%) patient suffered a local recurrence, 7 (22.6%) patients distant metastases, and one (3.2%) patient both at the same time. One patient developed a metachronous second primary cancer in the contralateral lung 39 months after treatment of his Pancoast tumor, was radically operated on, and died of distant metastases (brain) 13 months later. Local recurrence arose in the ipsilateral lung in a case, and in the chest wall in the second one.

The most common site of distant relapse was the brain, which was affected in 4 (12.9%) patients. One of these patients had been treated with prophylactic cranial irradiation (PCI). PCI seems to afford a fair

margin of protection: out of 13 treated patients (high-risk group), only one (7%) developed brain metastases, while among 14 untreated patient (low-risk group), 3 (21%) had cerebral recurrence (*P=ns*).

In our analysis, none of the investigated factors was able to predict the onset of cancer relapse: neither clinical stage, nor T- or N-classification, nor response after induction therapy. Although SST recurred with higher frequency in stage III patients as compared with stage II patients (50% vs. 29%), in case of T4-tumor as compared with T3-tumor (50% vs. 36%), in patients with cN2-3$_{mediast}$ as compared with cN0-1 disease (44% vs. 36%), and after partial response as compared with complete or “near complete” response to induction therapy (40% vs. 33%), none of these differences was statistically significant.

DISCUSSION

Offering patients with Pancoast tumor an appropriate treament with definitive relief of symptoms and reliable chance of cure has been a major challenge for thoracic surgeons, radiation and medical oncologists in the past decades. In 1956, Chardack and MacCallum reported the first long-term survivor after en bloc surgical resection and adjuvant radiotherapy with 65 Gy.[1] In the 1960's the combination of radiotherapy and surgery became the standard of care for Pancoast tumor.[2] The basic assumption was that SST represents a particular form of bronchogenic carcinoma which tends to grow locally, infiltrating the surrounding structures of the upper thoracic inlet with lesser propensity to spread to distant sites. Therefore, main goal of the treatment was to achieve a stable local control of disease, premise for relapse-free as well as symptom-free outcome. Whereas surgery was almost always part of treatment in patients with local, potentially resectable disease, radiotherapy alone was offered patients with medically inoperable or metastatic disease. Over 40 years, a large number of series with variable treatment modalities has been published (table 4). In most patients a satisfying, durable control of shoulder/arm pain could be achieved; nevertheless, complete resection of the tumor despite of "radical" irradiation and extended surgery was possible in only two thirds of cases, and median survival did not reach 18 months in the majority of reports.

Recent strategies to improve the treatment outcome have included intensification of radiation therapy (dose per time unit; hyperfractionated accelerated radiation), and concurrent application of chemotherapy together with radiation (concurrent chemoradiation) to achieve additive antitumor effects.[56] In our previous study ~~protocol~~ on stage IIIA/B NSCLC, the rationale for choosing accelerated hyperfractionated radiotherapy at the dose of 45 Gy in combination to concurrent chemotherapy ~~was chosen~~ in contrast to the conventional fractionation has been extensively explained.[8] This treament modality was expected to improve locoregional control and also to shorten the time until definitive surgery, thereby minimalizing risks due to fibrotic reactions in the tumor bed and mediastinum.

Induction chemoradiotherapy for SST

Despite aggressive local therapy modalities for SST, the most common site of first relapse in the reported series was local, occurring in 40% of patients.[57] The need of more effective measures for local control of SST, and the promising results of an intensive multimodality approach – a combination of chemotherapy, hyperfractionated accelerated chemoradiotherapy, and surgery – our group tested in

stage IIIA/B NSCLC,[8,9] have been the conceptual background to design a prospective feasibility trial for patients with Pancoast tumor. This was also supported by the findings of recent studies showing induction chemo-radiotherapy and surgery to afford high local resectability rates and long-term disease control for patients with SST. Martínez-Monge and coworkers[10] reported the results of the first phase II trial with a multidisciplinary approach, which included 1-3 cycles of neoadjuvant chemotherapy (MVP or MCP regimen) followed by simultaneous preoperative chemotherapy and external beam irradiation (46-50 Gy); treatment-related mortality was high (3/18 patients, 16.6%). Surgery with intraoperative radiotherapy (IORT) boost was performed in 15 patients, with a 76.4% resectability rate. Pathologic complete response was recorded in 70.5% of patients, and 4-year survival rates for the entire population and the ypT0-subgroup were 56.2% and 87.5%, respectively. Attar and associates[23] in 1998 reported on 11 patients without nodal involvement treated with a course of induction carboplatin and paclitaxel concurrently with radiation therapy at the dose of 60 Gy. Complete resection rate was not stated, but the 5-year survival rate was 72%. A large prospective multiinstitutional trial (Intergroup 0160)[11] of the Southwest Oncology Group enrolled 111 eligible patients with SST, and 102 had the planned induction treament including 2 cycles of cisplatin and etoposide chemotherapy concurrent with radiation at the dose of 45 Gy. There were 3 treatment-related deaths (2.7%), with CTC 3-4 grade toxicity in over 40% of patients. Eighty-three (75%) patients underwent thoracotomy, and 75 (90.4%) had a complete resection. Fifty-four (65%) specimens showed either a pathologic complete response or minimal microscopic disease. The planned additional boost chemotherapy could be administered to 47 (42%) patients. The 2- and 5-year survival rates were 55% and 41% for all eligible patients, and 70% and 53% for the complete resection subgroup, respectively. In comparison to the Intergroup 0160-trial, we registered in our study no induction treatment-related mortality, and a slightly lower toxicity (32% vs. 40%). We recorded a comparable pathologic major response rate after induction therapy (69% vs. 65%), as well as similar 5-year survival rates. Wright and coll.[12] in a retrospective study compared preoperative radiotherapy (40 Gy) and surgery with induction chemo-radiotherapy (50 Gy with concurrent cisplatin-based chemotherapy) and surgery in node-negative SST. In the former group of patients complete resection could be accomplished in 80% of patients, while in the latter group in 93% (P = .15). The pathologic response from the induction treatment was complete or near complete in 35% of RT patients and in 87% of the CT/RT patients (P = .001). Two-year and 4-year survival rates were 49% and 49% in the RT group, and 93% and 84% in the CT/RT group (P = .001). Of interest, the incidence of local

recurrence was 30% in the RT patients and 0% in the CT/RT patients (*P* = .02). In a recent report of the JCOG Lung Cancer Surgical Study Group from Japan,[55] 62 patients without mediastinal lymph node involvement underwent a trimodality approach with two cycles of MVP chemotherapy and concurrent radiotherapy at the total dose of 45 Gy. Forty-nine (79%) of them received surgical therapy, and 43 (88% of operated patients) had pathologic complete resection. Microscopic complete response was observed in 9 (18%) of cases. Treatment related mortality was 4% and one-year survival rate 76%.

In comparison to the above mentioned studies, our induction treatment protocol was well tolerated, without treatment-related deaths and with an acceptable incidence of major grade toxicity. There was a high compliance rate (87%) to the scheduled chemotherapy and concurrent chemoradiation. All eligible patients underwent surgery within the optimal time window after completion of radiotherapy, and postoperative mortality and morbility did not differ significantly from the published series of neoadjuvant treated, locally advanced NSCLC.

Major challenge of surgical treatment for SST was to achieve a complete resection despite of technical difficulties offered by the anatomy of the upper thoracic inlet. For this purpose, several surgical approaches have been proposed.[2,15,41] As previously described, our surgical access of choice for Pancoast tumor was a combined approach including a limited anterior thoracotomy through the second intercostal space and a classical posterolateral thoracotomy, which allows an anatomical resection of the lung as well as an accurate mediastinal lymph node staging in all cases. A widening of the anterior access was not necessary in our series, because an infiltration of the subclavian vessels has been always excluded.

We have to critically discuss our finding of 100% of microscopically free resection margins. In fact, in the two patients who suffered a local recurrence we can reasonably consider the R0-status as a false negative: in the first one lung cancer relapsed in the residual lobe after segmentectomy, and in the second one in the ipsilateral chest wall close to the prosthetic implant. As a result, we achieved a “true” complete resection in 27 out of 29 patients (93.5%).

We observed a high rate of pathologic complete response: this is a consistent finding throughout all the studies for SST treated by induction chemo-radiotherapy, but should be emphasized, when considering that in other stages IIIA/IIIB disease the pathologic complete response rate after multimodality treatment is around 10%. The particular anatomy of the region to be irradiated, the

introduction of chemotherapy as radiation sensitizer, and the advances of radiation techniques may have played a crucial role in improving local response to therapy.

In contrast to all cited studies, our eligibility criteria included also positive mediastinoscopy, in the conviction that an aggressive multimodality therapy may afford a chance of cure even in such a unfavourable group of patients. In fact, median survival of cN2-3 $_{mediast}$ patients was 28 months, with a 5-year survival rate of 21%, whereas in historical series no long-term survivors have been reported after palliative radiotherapy for Pancoast tumor with mediastinal lymph node involvement. The rationale for an aggressive treatment protocol including surgery of N2-Pancoast tumor was also based on the expected good palliation of pain. Pancoast tumor treated by radiotherapy alone recurs locally – with related symptoms – in as high as 60% of patients.[30,32] In our series only 2 patients suffered a local recurrence; thus, a durable local control was achieved in 94% of cases.

In patients with locally advanced NSCLC who undergo induction treatment followed by surgery, the pattern of failure shifts towards distant failure, notably the brain (15% to 30% incidence as the first site of relapse). Particularly, the expected incidence of brain metastasis as a first site of recurrence in Pancoast tumor is 24%.[28] Brain metastases cause considerable morbidity and disability, thus the prevention or delay of brain relapse may improve the quality of the patient's remaining life, even if the survival is not affected. The late toxicity of PCI is not well characterized, but many studies found no major impairment in neurocognitive functioning attributable to PCI in patients who received moderate total radiation doses and doses per fraction.[58] We observed brain relapse in 13% of patients: 7% in patients treated with PCI (high-risk group), and 21% in untreated patients (low-risk group). Although this difference is not significant, PCI seems to offer a protection angainst brain metastases, particularly in patients with more advanced disease. Nevetheless, an accurate staging including MRI of the brain before starting treatment is mandatory to avoid the Will Rogers-phenomenon as well to exclude patients with an unfavourable prognosis from such a complex multimodality approach.

The introduction of combined chemo-radiotherapy as induction therapy has significantly modified the expected outcome of treatment of Pancoast tumor. The improvement of surgical complete resection rates and long-term survival after trimodality approach as opposed to local therapy modalities, alone or in combination, is well displayed in figure 4 and 5, respectively.

The results of this feasibility trial suggest that an intensive multimodality approach based on combination chemotherapy, hyperfractionated accelerated chemoradiotherapy, and definitive surgery is well tolerated. It affords a high local resectability rate, a high rate of complete or near complete

tumor response, an acceptable incidence of treatment-related mortality and morbility, and a stable control of disease, both at local and distant site.

Future trials should investigate the role of new combinations of chemotherapeutic agents both as treatment for occult metastases and as radiation sensitizers to improve local control of disease, now that a baseline pathologic response rate has been estabilished for the standard regimen with cisplatin and etoposide.

The optimal surgical approach includes a combined access with an anterior (cervico-)thoracotomy to define the ventral boundaries of tumor infiltration and eventually resect the involved subclavian vessels, as well as with a posterolateral thoracotomy to perform a radical lung resection and a complete hilar and mediastinal lymphadenectomy.

Prophylactic cranial irradiation seems to offer an adequate protection angainst brain metastases, particularly in high-risk patients with locoregionally advanced disease, and should be added in treatment protocols of further studies.

When considering that a large randomized trial with patients with SST will be probably not performed because of the relative rarity of the disease, the present clinical evidence from several phase II studies, including ours, suggests induction chemoradiotherapy and surgery to be recommended as modern standard of care for Pancoast tumor.

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TABLES

Table 1. Clinical characteristics of eligible patients (*N = 31*)

Clinical features		No. of patients	Percent of all patients
Gender			
Male		27	87
Female		4	13
WHO performance status			
0		1	3
1		30	97
Lung function: FEV_1			
≥2.0 L		27	87
<2.0 L		4	13
Leading symptom			
Pain (shoulder, plexus)		26	84
Horner syndrome		1	3
Pancoast syndrome		2	7
Haemoptysis		1	3
Cough		1	3
Duration of symptoms			
<3 months		18	58
3-6 months		5	16
>6 months		8	26
Clinical stage			
IIB	cT3N0M0	17	55
IIIA	cT3N1M0	1	3
IIIA	cT3N2M0	6	19
IIIB	cT3N3M0	1	3
IIIB	cT4N0M0	4	13
IIIB	cT4N2M0	2	7

Table 2. Grade 3-4 toxicity of induction chemo-radiotherapy in eligible patients (*N = 31*)

Toxicity type	No. of patients	Percent of all patients
Esophagitis	5	16
Leukopenia	4	13
Anemia	4	13
Thrombocytopenia	4	13
Nausea	2	7
Vomiting	2	7
Thromboembolism	2	7
Stomatitis	1	3

Table 3. Surgical treatment of eligible patients (*N* = *29*)

Surgical data		No. of patients	Percent of all patients
Response evaluation before surgery			
Complete response		0	—
Partial response		14	48
Stable disease		15	52
Lung resection			
Wedge resection		3	10
Segmentectomy		3	10
Lobectomy		22	77
Pneumonectomy		1	3
Chest wall resection			
1 rib		1	3
2 ribs		4	14
3 ribs		13	45
4+ ribs		11	38
Vertebral body resection			
1 hemivertebrectomy		1	3
3 hemivertebrectomies		1	3
Plexus resection			
T1 root		25	86
C8-T1 roots		4	14
Chest wall reconstruction			
None		14	48
Polyglactic acid-Mesh		12	42
Polypropylene/polyethylene-Mesh		2	7
Other prosthetic replacement		1	3
Completeness of resection			
R0		29	100*
R1		0	—
R2		0	—
Histology			
Squamous cell carcinoma		11	38
Adenocarcinoma		10	35
Large cell carcinoma		4	13
Adenosquamous carcinoma		2	7
Carcinoma, not otherwise specified		2	7
Pathologic stage			
0	ypT0N0M0	13	45
IA	ypT1N0M0	5	17
IB	ypT2N0M0	2	7
IIB	ypT3N0M0	7	25
IIIA	ypT3N2M0	1	3
IIIB	ypT3N3M0	1	3

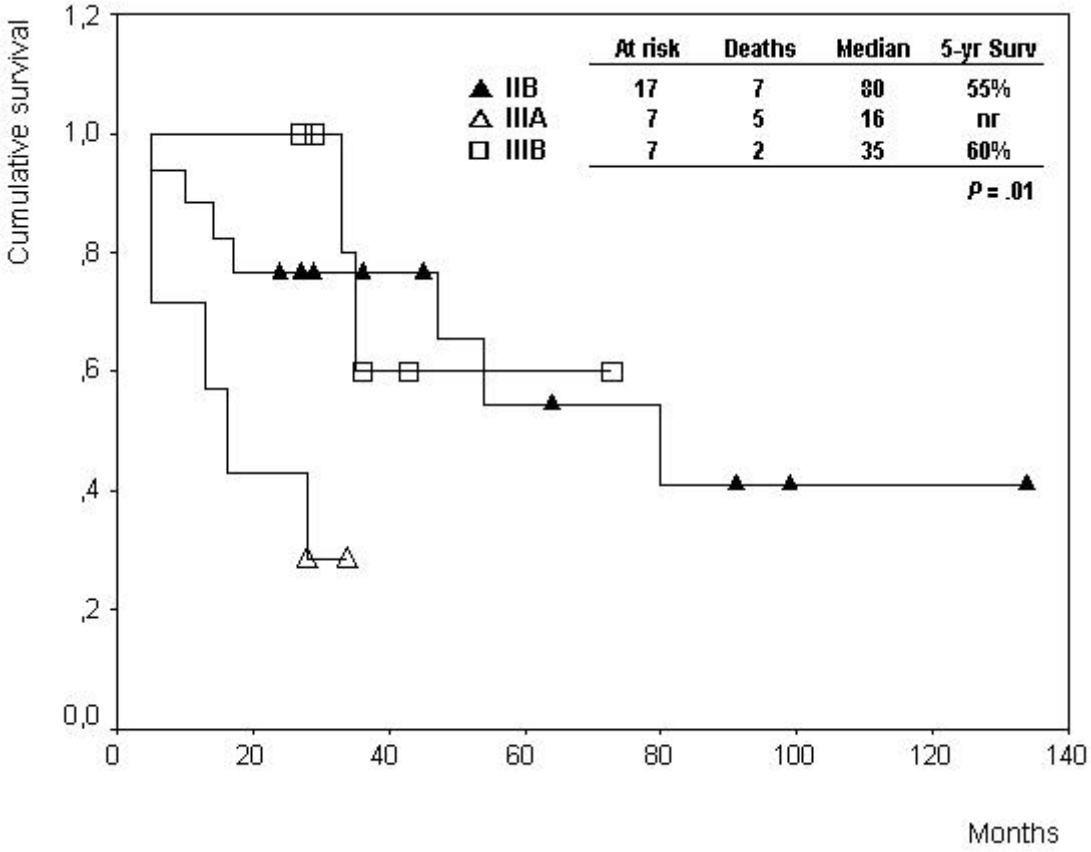
* See *Discussion* for detailed analysis.

Table 4. Treatment modalities for Pancoast tumor: Review of the literature

Author (year)	Patients (No.)	Treatment	RT dose (cGy)	Complete resection (%)	Survival		
					median (mo.)	2-yr (%)	5-yr (%)
Surgery alone							
Attar *et al.* (1979)	5	S	-	NR	36	-	-
Attar *et al.* (1998)	12	S	-	NR	36.7	-	32
Radiotherapy alone							
Bretz *et al.* (1970)]	15	RT	3,000	-	9.7	-	0
Kirsch *et al.* (1973)	23	RT	5,000	-	6.5[a] –10	-	13
Attar *et al.* (1979)	[a]29	RT	6,000	-	NR	7[c]	-
Stanford *et al.* (1980)	[a]25	RT	NR	-	NR	-	5.5[b]
Komaki *et al.* (1981)	36	RT	5,800	-	14	-	23
Van Houtte *et al.* (1984)	31	RT	5,000	-	17	-	18
Anderson *et al.* (1986)	[a]27	RT	4,800	-	7.6	-	0
Komaki *et al.* (1987)	68	RT	6,000	-	NR	38[d]	15[b,d]
Ricci *et al.* (1989)]	[a]15	RT	6,000	-	NR	6	0
Komaki *et al.* (1990)	56	RT±CT	7,000	-	NR	22	-
Terashima *et al.* (1991)	6	RT+HT	7,000	-	14	-	-
Neal *et al.* (1991)	[a]32	RT	7,000	-	NR	-	22
Taylor *et al.* (1992)	7	RT	5,400	-	14.8	-	-
Herbert *et al.* (1992)]	30	RT	6,100	-	10.3	10	0
Schraube *et al.* (1993)	[a]6	RT	5,300	-	7.6	-	0
Schraube *et al.* (1993)	22	RT	5,600	-	10.5	-	0
Fuller *et al.* (1994)	6	RT	6,000	-	6	0	0
Strojan *et al.* (1997)	22	RT	5,400	-	10	-	10[b,d]
Strojan *et al.* (1997)	[a]17	RT	3,000	-	6	-	0[b,d]
Attar *et al.* (1998)	[a]37	RT	6,000	-	6	-	0
Surgery plus radiotherapy							
Becker *et al.* (1977)	18	S+RT	NR	78	NR	-	-
Stanford *et al.* (1980)	12	S+RT	NR	50	NR	-	13.1
Hilaris *et al.* (1987)	46	S+IORT+RT	NR	63	14	-	20
Sundaresan *et al.* (1987)	9	S+IORT+RT	NR	67	24	44[c]	-
Ricci *et al.* (1989)	9	S+RT	NR	53.7	NR	-	11.1
Komaki *et al.* (1990)	24	S+RT±CT	6,000	NR	NR	52	-
Dartevelle *et al.* (1993)	29	S+RT±CT	5,600	100	21	50	31
Attar *et al.* (1998)	16	S+RT	6,000	NR	6.9	-	0
Dartevelle *et al.* (1999)	70	S+RT±CT	5,600	100	NR	-	35
Radiotherapy plus surgery							
Shaw *et al.* (1961)	18	RT+S	3,000	NR	NR	62	-
Paulson (1971)	47	RT+S	3,000	NR	NR	-	37,5
Kirsch *et al.* (1973)	12	RT+S	5,000	50	11.5	-	0
Paulson (1973)	52	RT+S	3,000	NR	NR	-	34
Paulson (1975)	61	RT+S	3,000	NR	NR	37	34
Miller *et al.* (1979)	26	RT+S	3,000	85	NR	-	32
Paulson (1979)	68	RT+S	3,000	NR	NR	-	35
Attar *et al.* (1979)	19	RT+S	NR	48	20	23[c]	-
Stanford *et al.* (1980)	16	RT+S	NR	75	NR	-	49.7
Anderson *et al.* (1986)	28	RT+S	3,000	54	24.8	-	34
Hilaris *et al.* (1987)	82	RT+S+IORT	4,000	63	23	-	29
Sundaresan *et al.* (1987)	17	RT+S+IORT	4,000	53	12	41	-
Wright *et al.* (1987)	21	RT+S	3,800	76	24	55	27
Shahian *et al.* (1987)	18	RT+S+RT	6,000	50	NR	64.2	56.1
Ricci *et al.* (1989)	28	RT+S	3,000	53.7	NR	-	34
Neal *et al.* (1991)	29	RT+S	3,000	NR	NR	-	21
Sartori *et al.* (1992)	42	RT+S	3,000	NR	14	36[c]	25
Schraube *et al.* (1993)	20	RT+S+RT	5,800	NR	12	-	18
Fuller *et al.* (1994)	13	RT+S	6,000	69	85	69	64
Maggi *et al.* (1994)	60	RT+S±RT	3,000	60	15	34[c]	17.4
Ginsberg *et al.* (1994)	124	RT+S+IORT	4,000	56	17	31[c]	26
Muscolino *et al.* (1997)	15	RT+S	4,000	NR	16.8	-	26.6
Attar *et al.* (1998)	28	RT+S	6,000	NR	21.6	-	27
Wright *et al.* (2002)	20	RT+S	3,900	80	NR	49	49[b]
Chemoradiotherapy plus surgery							
Martínez-Monge *et al.* (1994)	18	CT/RT+S+IORT	4,600	76.4	NR	56,2	56.2[b]
Attar *et al.* (1998)	11	CT/RT+S	6,000	NR	NR	-	72
Rush *et al.* (2001)	111	CT/RT+S+CT	4,500	92	NR	55	55[b]
Wright *et al.* (2002)	15	CT/RT+S	5,100	93	NR	93	84[b]
Barnes *et al.* (2002)	8	CT/RT+S	5,000	NR	NR	85.7[c]	-
Kunitoh *et al.* (2003)	62	CT/RT+S	4,500	69	NR	88	-

RT, radiotherapy; *S*, surgery; *CT*, chemotherapy; *HT*, hyperthermia; *IORT*, intraoperative (brachy)radiotherapy; *NR*, not reported.

[a] Medically inoperable, metastatic disease, or both; [b] 4-year survival rate; [c] 3-year survival rate; [d] disease-free survival.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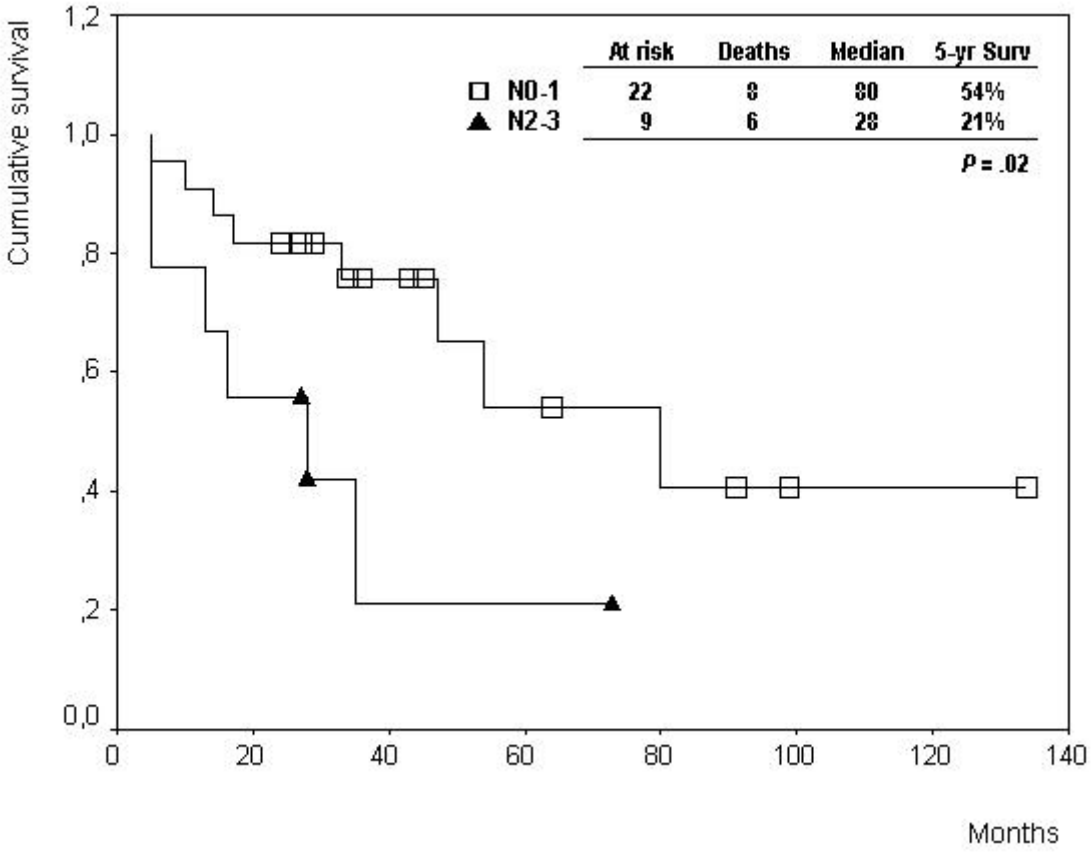
20
40
60
80
100
120
140
Months
At risk Deaths Median 5-yr Surv
IIB 17 7 80 55%
IIIA 7 5 16 nr
IIIB 7 2 35 60%
P = .01


Cumulative survival
1,2
1,0
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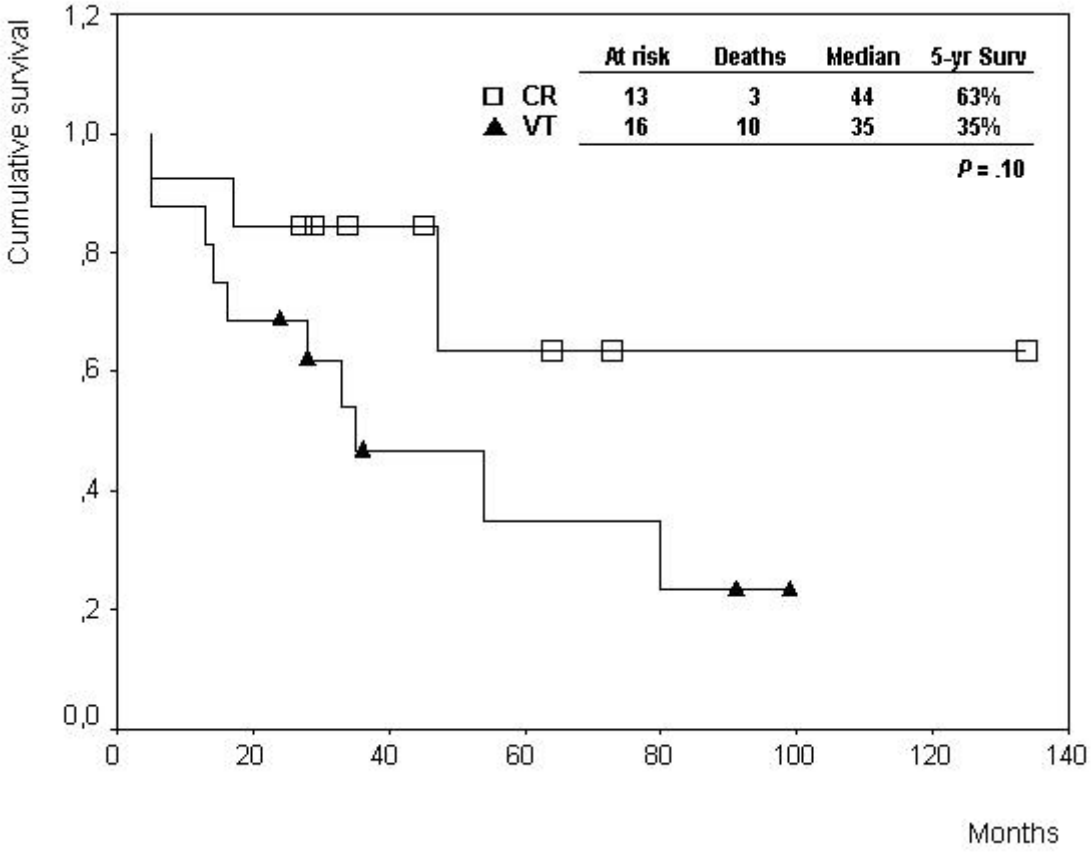
120
140
Months
At risk Deaths Median 5-yr Surv
N0-1 22 8 80 54%
N2-3 9 6 28 21%
P = .02


Cumulative survival
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Months
At risk
Deaths
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5-yr Surv
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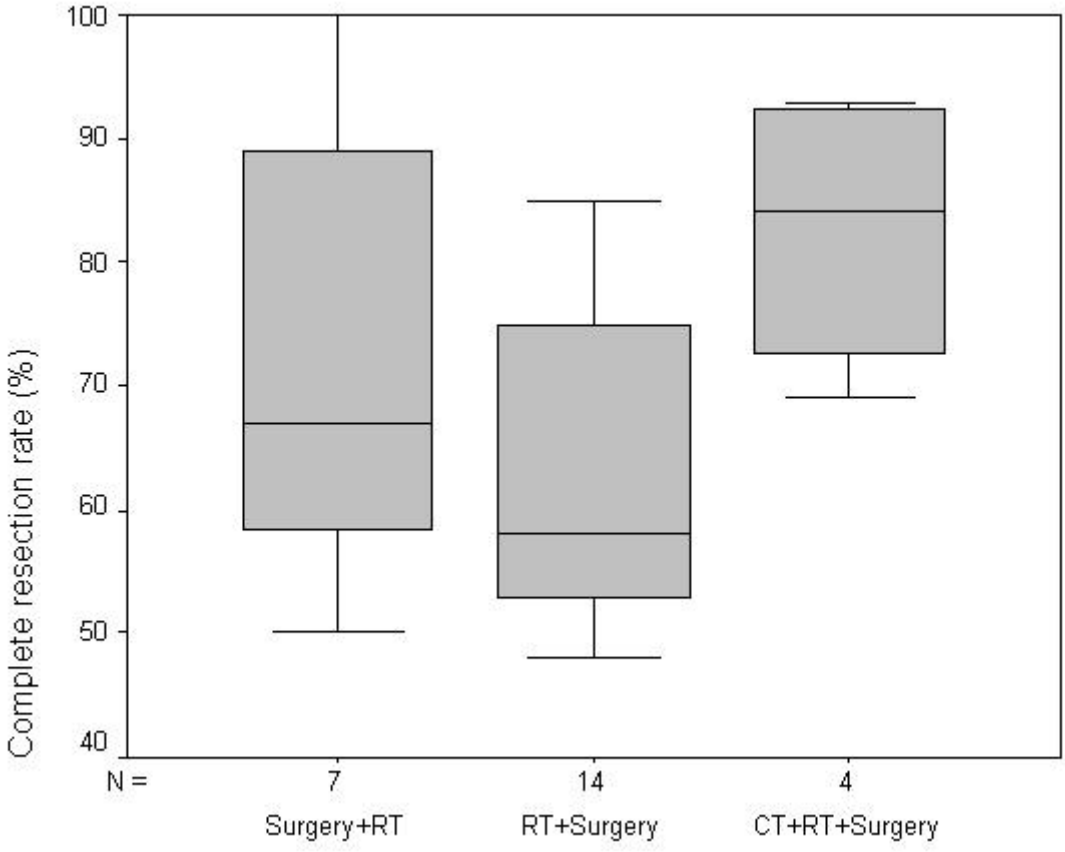
35
35%
P = .10


Complete resection rate (%)
100
90
80
70
60
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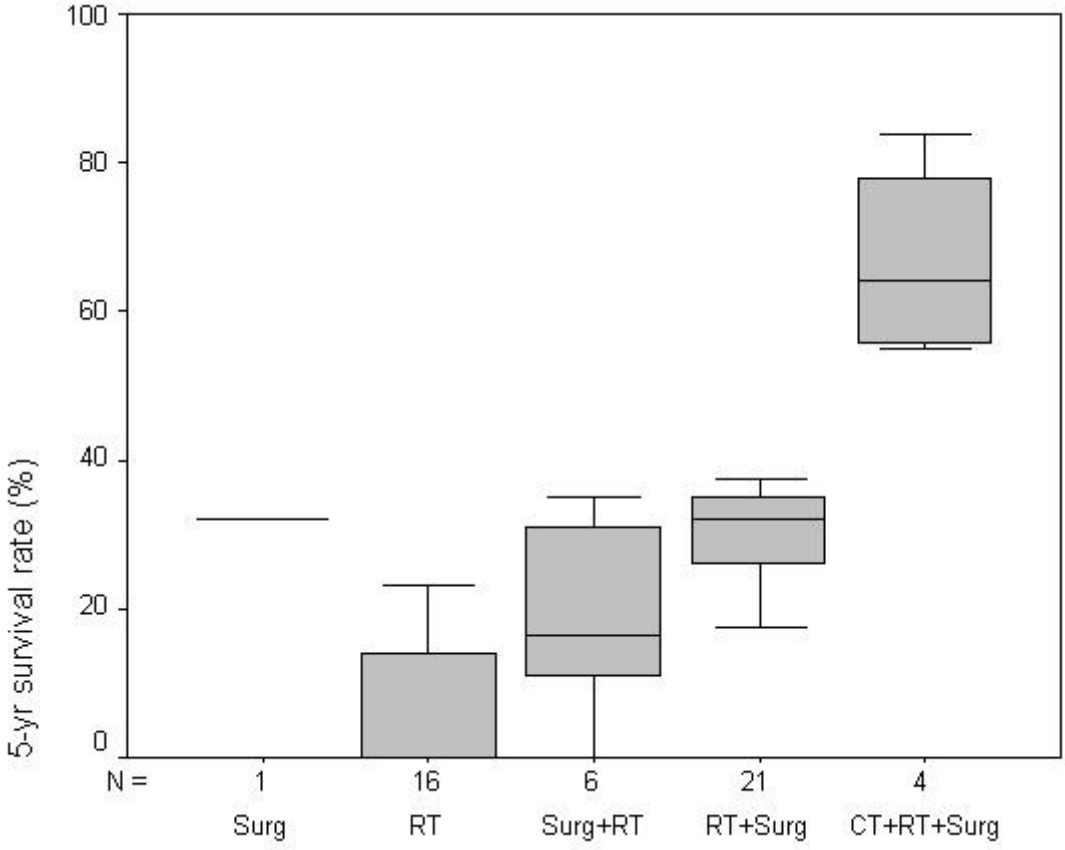
N =
7
14
4
Surgery+RT
RT+Surgery
CT+RT+Surgery


100
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5-yr survival rate (%)
N =
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16
6
21
4
Surg
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Surg+RT
RT+Surg
CT+RT+Surg