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Phase II Trial of Trimodality Therapy for Malignant Pleural Mesothelioma (EORTC 08031).

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ABSTRACT

Purpose

EORTC 08031 phase II trial investigated the feasibility of trimodality therapy consisting of induction chemotherapy followed by extrapleural pneumonectomy and postoperative radiotherapy in patients with cT3N1M0 or less malignant pleural mesothelioma.

Patients and methods

Induction chemotherapy consisted of 3 courses of cisplatin 75mg/m^2 and pemetrexed 500mg/m^2. Non-progressing patients underwent extrapleural pneumonectomy followed by postoperative radiotherapy (54Gy, 30 fractions). Primary endpoint was "success of treatment" and secondary endpoints toxicity, overall and progression-free survival.

Results

Fifty-nine patients were registered, 1 was ineligible. Median age was 57 years, cT1/T2/T3: 36/16/6, cN0/N1: 57/1. Fifty-five patients received 3 cycles of chemotherapy with only mild toxicity. Forty-six patients (79%) were operated and 42 (74%) had extrapleural pneumonectomy with a 90-day mortality of 6.5%. Postoperative radiotherapy was completed in 37 patients (65%). Grade 3/4 toxicity persisted after 90 days in 3 patients (5.3%). Median overall survival time was 18.4 months (95% CI 15.6-32.9) and median progression-free survival was 13.9 months (95% CI 10.9-17.2). Only 24 patients (42%) met the definition of success (one-sided 90% CI 0.36-1.00).

Conclusion

Although feasible, trimodality therapy in patients with mesothelioma was not completed within the strictly defined timelines of this protocol and adjustments are necessary.

KEYWORDS

Malignant mesothelioma, chemotherapy, thoracic surgery, radiotherapy, prognosis, staging, phase II trial

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm arising from the surface serosal cells of the pleural cavity. It is a highly lethal disease with a grim prognosis. The incidence of MPM will be increasing rapidly in certain countries until approximately 2020 [1].

Different staging systems for MPM exist [2]. Although mainly related to surgical data, the TNM-based classification proposed by the International Mesothelioma Interest Group (IMIG) is most often used [3]. Precise determination of disease extent is difficult and response evaluation is even more complicated as the classical criteria are not reliable. The use of perpendicular diameters as proposed by Byrne and Nowak in the modified Response Evaluation Criteria in Solid Tumors (RECIST) seems to be more accurate [4].

MPM has long been surrounded by therapeutic nihilism as neither chemotherapy, radiotherapy nor surgery have been proven to be effective as a single treatment modality [1]. Moreover, quality of published evidence is poor and no definite guidelines have been established, even for early stage disease [5]. The role of surgery in providing maximal debulking is controversial and has not been determined yet [6,7]. A major breakthrough was obtained with two randomized trials showing significant activity of the combination of cisplatin and the folate antagonists, pemetrexed or raltitrexed, with a significantly improved median survival time (MST) in patients with MPM [8-10].Similar to locally advanced lung cancer, induction chemotherapy has been proposed to increase the complete resection rate of MPM. In a Swiss multicenter trial cisplatin and gemcitabine were given as induction therapy followed by extrapleural pneumonectomy (EPP) and postoperative radiotherapy to incompletely resected areas [11]. For patients undergoing EPP an encouraging MST

of 23 months was obtained. The European Organisation for Research and Treatment of Cancer (EORTC) initiated a phase II trial to evaluate the feasibility of trimodality therapy in a multicenter international setting (EORTC 08031).

PATIENTS AND METHODS

General Objective and Outline

The objective of EORTC 08031 trial (EudraCT-2004-004273-28; NCT00227630) was to explore the feasibility of induction chemotherapy followed by EPP and high-dose postoperative radiotherapy in patients with limited malignant pleural mesothelioma. A general outline and CONSORT diagram are provided in fig. 1. The protocol was approved by the Ethical Committees of each participating institution (see acknowledgement) and written informed consent was obtained from every patient.

Endpoints

Primary endpoint was “success of treatment” which is defined as a patient who received the full protocol treatment within the defined timeframes, who was still alive 90 days after the end of protocol treatment without progression and without evidence of grade 3-4 toxicity at 90 days after the end of protocol treatment. Secondary endpoints included the toxicity of the trimodality treatment, overall survival and progression-free survival.

Patient Selection Criteria

General selection criteria are provided in table 1.

Therapeutic Regimens

Chemotherapy

Induction chemotherapy consisted of 3 cycles of pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1 every 3 weeks. Folic acid (350-600 µg PO daily) and vitamin B12 (1000 µg IM) supplementation was started 7 to 14 days before the first dose of chemotherapy. Dexamethasone (4 mg PO, twice daily) was given on the day before, the day of, and the day after each dose of chemotherapy. Folic acid was continued until 21 days after the last dose of chemotherapy and vitamin B12 injection was repeated on day 64.

Response assessment

Response was evaluated by repeat chest computed tomography according to the modified RECIST criteria [4]. Patients with a clinical response or stable disease underwent surgical resection.

Surgery

Surgery was performed at least 3 weeks after the last dose of chemotherapy with a maximum interval of 8 weeks. An EPP was performed in order to achieve a complete resection of all gross residual tumor. This included removal of the entire ipsilateral lung, parietal pleura, and also diaphragm and pericardium which were both reconstructed with a soft tissue patch. Resectability was determined during thoracotomy.

Radiotherapy

Radiotherapy was initiated at least 30 days after surgery but within 84 days after surgery in patients who recovered from surgery, with a performance status WHO 0-2

and without disease progression on clinical examination and/or planning CT-scan. Using 3 D-conformal radiotherapy, a dose of 54 Gy was delivered to the entire hemithorax, thoracotomy incision and sites of chest drains in once-daily fractions of 1.8 Gy. A joined review of the contoured clinical target volume (CTV) with the thoracic surgeon was strongly recommended. The CTV included the entire ipsilateral thoracic cavity from lung apex to insertion of the diaphragm, ipsilateral mediastinal pleura, ipsilateral pericardial surface, and full thickness of the thorax at the sites of thoracotomy and chest tube incisions. The mediastinum was not routinely incorporated in the CTV, except at sites of proven disease. A boost-CTV was given to sites of gross or microscopic residual disease. The V20 which is the volume of healthy lung tissue receiving a total dose of ≥ 20 Gy, could not exceed 15 %. Overall radiotherapy treatment time could not exceed 45 days.

Toxicity

Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [12].

Follow-up

The follow-up visits were scheduled at 42 and 90 days after the administration of the last protocol treatment. Physical examination, evaluation of clinical symptoms and disease extent by chest X-ray and CT-scan were performed. Further follow-up was performed at 3-months interval during the first year and every 6 months thereafter.

Statistics

To determine the “success of treatment” a one step Fleming testing procedure was used with α set at 0.10 and ß at 0.05. P_0 was set at 40 % and defined as the largest success rate which if true implied that this trimodality treatment did not warrant further investigation. P_1 was set at 60 % and defined as the lowest success rate which if true implied that the trimodality treatment did warrant further investigation. Under these hypothesis the total sample size was calculated to be 52 eligible patients. When a success rate of 60 % would be obtained in the studied population, the combined trimodality treatment should be further investigated.

RESULTS

The study was activated in July 2005 and closed in August 2007. Accrual proceeded as planned. CONSORT diagram is depicted in fig. 1. In total 59 patients were registered from 11 centres. One patient was ineligible because chemotherapy was started before registration. There were 46 male and 12 female patients with a median age of 57 years (range 26-67). All patients had pathologically proven MPM and underwent cervical mediastinoscopy. Performance status was 0 in 22 patients (37.9 %) and 1 in 36 (62.1 %). Known asbestos exposure was present in 44 patients (75.9 %). Clinical T stage at baseline was T1 in 36 patients (62.1 %), T2 in 16 (27.6 %) and T3 in 6 (10.3 %). Clinical N stage was N0 in 57 patients (98.3 %) and N1 in 1 (1.7 %). Associated chronic disease was present in 18 patients (31.0 %), mainly hypertension and diabetes. One registered patient refused any treatment after obtaining a second opinion.

Chemotherapy

In 55 patients (94.8 %) 3 cycles of chemotherapy were administered and in 3 patients (5.2 %) 2 cycles. Three patients received carboplatin instead of cisplatin. Median relative dose intensity of cisplatin was 98.9 % (range, 75.1-106.8), and of pemetrexed 99.5 % (range 75.4-104.2). Dose reductions of cisplatin were necessary in 4 patients (6.9 %) due to fatigue, neuropathy, nausea, combined hearing loss and increased creatinine levels, and of pemetrexed in one patient only (1.7 %) due to fatigue. Grade 3-4 toxicity is listed in table 2. In eligible patients who started treatment (57 patients) radiological response after chemotherapy was complete response in 14 patients (24.6%), partial response in 11 patients (19.3%), stable disease in 24 patients (42.1%), progressive disease in 5 patients (8.8%) and not assessable in 3 patients (5.3%).

Surgery

Considering the 58 eligible patients, surgical treatment was administered in 46 (79.3 %). Twelve patients (20.7 %) had no surgery because of progressive disease (8.6%), poor physical condition (1.7%), toxicity (1.7%), pulmonary emboli (1.7%) and no initiation of therapy after a second opinion (6.9%).

Preoperative lung function showed a median forced expiratory volume in one second of 76.0 % (range, 50.0-115.0), a median forced vital capacity of 80.0 % (range, 43.0-116.0), and median diffusion capacity for CO of 71.0 % (range, 35.0-112.0). In 33 operated patients the tumor was on the right side (71.7 %) and in 13 patients (28.3 %) on the left side. EPP was performed in 42 patients (91.3 % of operated patients and 73.7 % of eligible patients who started treatment). The other patients had partial pleurectomy or exploration only due to unresectable disease.

R0 resection was obtained in 30 patients (52.6 % of eligible patients who started treatment), R1 in 10 (17.5 %), R2 in 3 (5.3 %) and unknown in 1 (1.8 %). Reoperation was necessary in 6 patients because of bronchopleural fistula in 2, postoperative hemorrhage in 2, infection at the thoracotomy incision in 1, and diaphragmatic eventration in 1 patient. Mortality at 30 and 90 days was 6.5 % due to pulmonary embolism, combined lung edema and pneumonia, and progressive disease. Postoperative complications were observed in 38 patients (82.6 %) mostly supraventricular arrhythmias. Grade 3-4 complications are listed in table 2. Pathological T0 was observed in 2 patients, T1 in 5, T2 in 19, T3 in 15, and T4 in 4. Pathological N0 was present in 35 patients, N1 in 2, N2 in 6 and Nx in 2. After central pathological review 31 patients (53.4 %) had epithelial cell type, 18 (31.0 %) mixed histology, 2 (3.4 %) unknown and 7 (12.1 %) are missing. Complete agreement with local pathologist was present in 38 (65.5 %) cases, minor disagreement in 10 (17.2 %) and full disagreement in 3 (5.2 %)

Radiotherapy

Postoperative radiotherapy was initiated in 38 patients and completed in 37 (63.8 % of all eligible patients) . In 11 patients administration of radiotherapy was temporarily interrupted. Intensity modulated radiotherapy was given in 14 and 3 D-conformal radiotherapy in 24 patients. Median radiotherapy dose was 54.0 Gy (range, 43.2 - 54.0). In 18 patients a chest wall bolus was given. Median V20 to the contralateral lung was 2.0 % (range, 0.0 - 30.4). Median maximum dose to spinal cord was 43.3 Gy (range, 9.5 - 52.5). Two patients died after radiotherapy due to pneumonia, one having Aspergillus infection. Grade 3 - 4 toxicity of radiotherapy is listed in table 2.

Follow-up

Trimodality treatment was completed in 37 patients (64.9 %) and median treatment duration was 184.0 days. Median follow-up time was 19.3 months (95% confidence interval (CI), 17.4 - 25.0). Grade 3 - 4 toxicity 90 days after end of protocol treatment persisted in 3 patients (5.7 %) due to bronchopleural fistula in 2 patients and grade 3 radiation pneumonitis in 1 patient. Recurrences detected during follow-up were locoregional in 6 patients (16.2%) and distant metastases in 10 patients (27%) Regarding the primary endpoint only 24 patients (42.1 %) met the definition of success (one-sided 90 % CI for proportion of success 0.36 - 1.00). Reasons for failure are listed in table 3. If some flexibility is allowed by relaxing the treatment timelines only, there are 4 additional patients who can be considered a success. Performing a supplementary sensitivity analysis in all 57 patients who were eligible and started treatment, the total number of successes becomes 28 if these 4 patients are added. The corresponding 90 % one-sided CI is 0.399 - 1.00. This is in the borderline of declaring the study a success.

Median overall survival time for all 57 patients who were eligible and started treatment was 18.4 months (95 % CI 15.6 - 32.9) and 1-year survival rate 70.2 % (95 % CI 56.5 - 80.3) (fig. 2). Median progression - free survival for all 57 patients who were eligible and started treatment was 13.9 months (95 % CI 10.9 - 17.2) and 1-year survival rate 54.4 % (95 % CI 40.7 - 66.2) (fig. 3). Median overall survival time for the 37 patients who completed trimodality treatment was 33 months. The median was hardly reached and longer follow-up is needed in these patients to obtain a more precise figure.

DISCUSSION

The role of surgical treatment in patients with MPM remains controversial. This relates to the indications and extent of surgical resection [5,6]. In selected patients EPP provides maximal tumor clearance with an acceptable mortality and morbidity in specialized centers [13,14]. In a compiled series from 3 large institutions 663 patients undergoing EPP or pleurectomy/decortication between 1990 and 2006 were analyzed [15]. Operative mortality was 7 % for EPP and 4 % for pleurectomy/decortication. Significant factors related to survival were stage, epithelial cell type, type of resection, multimodality therapy and gender. Although less radical, pleurectomy/decortication has emerged as a potential debulking procedure, not only providing better palliation but also improved local control and possibly even survival [16,17].

Due to the ineffectiveness of single modality therapy in patients with MPM, trimodality therapy has recently emerged as a new treatment strategy to improve prognosis [18]. To improve resectability rate and local control, induction chemotherapy is combined with aggressive surgery and postoperative radiotherapy. Pemetrexed has been shown to be among the most active agents and is currently used in induction trials [9]. In a retrospective study of 60 patients, 4 regimens of induction chemotherapy were used [19]. EPP was performed in 54 patients (75 %) followed by hemithoracic radiotherapy in 30 patients (50 %). The best survival was noted in those patients without mediastinal nodal involvement who completed the trimodality therapy. For patients with N0 disease, 5-year survival rate was 53 %.

Although the introduction of pemetrexed was a major step forward in the palliative treatment of mesothelioma patients, current results are unlikely to improve further without the addition of targeted or biological agents interacting more specifically with

causal pathways in the cellular behavior of mesothelioma. No such agent is currently available for association with induction chemotherapy.

In contrast to other tumor types and non-small cell lung cancer, the current induction chemotherapy regimens induce little necrosis and pathological complete responses, questioning their presumed role in facilitating resection and reducing their efficacy of clearing micrometastatic disease. As such, their adjuvant administration might merit further attention in radically resected patients having completed postoperative radiotherapy.

The primary endpoint was not reached in our study as only 24 patients (42.1 %) were a success according to the predefined criteria. Post-hoc these criteria might be considered unrealistic, but they were predefined arbitrarily in 2003 by an expert multidisciplinary committee within EORTC-Lung Cancer Group and considered a minimum in order to proceed further with trimodality treatment in this disease.

Nevertheless, the results of EORTC 08031 merit further consideration for a number of reasons. Its overall results confirm the outcome of 2 comparable multicenter phase II trials with multimodality treatment [11,20].Their endpoints as survival, mortality, response rate and compliance to induction chemotherapy are comparable to the ones observed in EORTC 08031, suggesting that their success of treatment as defined in EORTC 08031 will be likely equivalent (table 4).

Secondly, in a subsequent sensitivity analysis, relaxing somewhat the strict timeline criteria, a number of additional patients met all other criteria and can be considered “successes”, increasing the likelihood of the study meeting its endpoint.

Thirdly, although the multimodality treatment procedure seems feasible, overall treatment time is long and the median duration of psychological distress consumes much of the observed improvement of survival. Subgroup analysis of a large

Scandinavian phase II trial shows an outcome of 22 months in patients with good performance status, epithelioid subtype, stage I-II and age 70 years or less, equivalent to the survival in patients subjected to multimodality treatment [21]. This finding underscores the importance of conducting a large prospective multicenter study, in which operable patients with early stage resectable MPM are randomly assigned to a surgical and a non-surgical management [22]. The feasibility of this approach is currently being explored in the Mesothelioma and Radical Surgery (MARS) trial in the United Kingdom, in which the randomisation is between EPP followed by postoperative radiotherapy and any palliative treatment including pleurodesis, following an induction treatment with chemotherapy. A pilot trial has recently been completed and randomization between surgery and no surgery was found to be feasible [23].

The conclusion from uncontrolled series that pleurectomy/ decortication might prolong survival, suggests that EPP is perhaps not the only procedure to be considered as a surgical approach and that a less invasive procedure might be preferable in selected patients, provided it is standardised [24]. It is expected that a large European multicenter randomised trial will be conducted in the coming years, addressing the role of any tumor resection in MPM. Whether the latter will include EPP remains to be determined, as the median age at presentation increases and the dropout rate will be considerable [25].

As in non-small cell lung cancer, the role of postoperative radiotherapy in MPM is controversial and based on a single uncontrolled retrospective series [26]. This additional value of postoperative radiotherapy is being addressed in an ongoing Swiss study, in which eligible patients are randomised after EPP between observation and hemi-thoracic radiotherapy [27]. Preliminary results of intensity

modulated radiotherapy (IMRT) in the adjuvant setting after EPP seems particularly promising as good local control was obtained and organs at risk such as heart or liver, were well protected [28]. However, severe pulmonary toxicity has been reported in recent studies so that it should not be recommended outside clinical trials [29]. The role of IMRT with chemotherapy and intact lung is presently being investigated in patients with unresectable disease [30].

In conclusion, although a trimodality treatment consisting of induction chemotherapy followed by extrapleural resection and postoperative radiotherapy seems feasible in selected patients with early stage mesothelioma, the results of the present study do not warrant its use outside selected institutions with high expertise and preferably in prospective clinical trials exploring ways to improve its acceptance rate and overall success.

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TABLE 1. Patient Selection Criteria

- Age < 70 years
- WHO performance status 0-1
- Fit enough to receive chemotherapy, to undergo a pneumonectomy and receive postoperative radiotherapy. The responsible physician, surgeon and radiation therapist should judge the required fitness prior to registration, taking into account the results of all the relevant (i.e. pulmonary, cardiac) examinations. Proposed exclusion criteria were: predicted post-operative FEV1 < 40% and/or VO_{2max} < than 20 ml/min/kg, significant pulmonary hypertension, significant decrease in cardiac ejection fraction (< 40%) and myocardium at risk for ischemic injury.
- Pathologically proven malignant pleural mesothelioma (all subtypes accepted)
- cT3N1M0 or less according to UICC TNM classification[3]
- No N2 or N3 lymph nodes involvement (pathologically confirmed), cervical mediastinoscopy required
- No clinical invasion of mediastinal structures (heart, aorta, spine, esophagus, etc.)
- No widespread chest wall invasion, only focal chest wall lesions are acceptable
- No clinical or radiological evidence of “shrinking hemithorax”
- No prior chemotherapy for mesothelioma
- No prior radiotherapy of the lower neck, thorax, and upper abdomen
- No secondary primary malignancy except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or prior malignancy treated more than 5 years before without recurrence
- Adequate hematological, hepatic and renal function

- Acceptable, predicted post-radiotherapy renal function, as indicated by semiquantitative isotope renography, with a relative contribution of the contralateral kidney of at least 40 %
- No pre-existing sensory neurotoxicity > grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0[12]
- No clinically significant third-space fluid (for example pleural effusions or ascites) that cannot be managed with thoracentesis or pleurodesis (according to institutional practice)
- No uncontrolled infection
- Patients of reproductive potential must agree to use a reliable method of birth control during protocol treatment and for 3 months following the end of protocol treatment. Woman of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient registration in the trial, written informed consent must be obtained and documented according to national and local regulatory requirements and the local rules followed in the institution.

TABLE 2. Grade 3 - 4 toxicity after chemotherapy, surgery and radiotherapy

	chemotherapy n = 57		surgery n = 46		radiotherapy n = 38	
	n	%	n	%	n	%
Hematological and biochemical						
leucopenia	1	1.8				
anemia	1	1.8	4	8.7		
neutropenie	9	15.5				
hyponatremia	3	5.2				
hyperkalemia	2	3.4				
Anorexia			1	2.2	2	5.3
Dysphagia					1	2.6
Nausea					2	5.3
Vomiting					1	2.6
Fatigue	1	1.8			2	5.3
Infection	2	3.6	1	2.2		
Pneumonia			2	4.3		
Pain	3	5.4	3	6.5	1	2.6
Dyspnea	2	3.6	5	4.7	1	2.6
Renal toxicity	1	1.8				
Septic shock	1	1.8				
Thromboembolism	2	3.6				
Atrial fibrillation	1	1.8	4	8.7		
Cardiac other			4	8.7		
Retinal detachment	1	1.8				
Empyema			1	2.2		
Hemorrhage requiring reoperation			2	4.3		
Bronchopleural fistula			2	4.3		
Post-pneumonectomy pulmonary edema			2	2.2		
Vascular (other)			1	8.7		

Other*			4*			

* other include postoperative stroke (1), obstipation (1) and hemorrhage not requiring reoperation (2)

TABLE 3. Primary endpoint - reasons for failure (number of patients)

At least 2 cycles of chemotherapy not given	1
No extrapleural pneumonectomy	15
No 54 Gy postoperative radiotherapy	21
Treatment not within time frame	27
Mortality	7
Persisting grade 3/4 toxicity	3
Progressive disease	16

Notes: data for all registered patients; some patients had multiple reasons for not reaching the primary endpoint.

TABLE 4. Prospective multicenter phase II trials of radical multimodality treatment in early stage malignant pleural mesothelioma

Variable [reference]	SAKK- trial [11]	US phase II trial [20]	EORTC 08031
N patients/n institutions	61/6	77/9	59/11
Induction regimen	Cis-gem x 3	Cis-pem x 4	Cis-pem x 3
Compliance to induction chemotherapy	95%	83%	93%
EPP	45 (*74%)*	54 (*70%)*	42 (*74%)*
Operative mortality	2.2%	7%	6.5%
pCR rate	2.2%	5%	4.8%
PORT completed	36 (*59%)*	40 (*52%)*	37 (*65%)*
Median OS [ITT] (95% CI)	19.8 m (14.6-24.5)	16.8 m (13.6-23.2)	18.4 m (15.6-32.9)
Median OS [PP] (95% CI)	23.0 m (16.6-32.9)	21.9 m (16.8-29.1)	21.5 m (17.6 - NR)
Local relapse (% PP)	NS	11 (*28%)*	6 (*16%)*
Median PFS [ITT] (95% CI)	13.5 m (10.2-18.8)	10.1 m (8.6-15.0)	13.9 m (10.9-17.2)
Median overall treatment time (range)	NS	NS	193 days (162-220)

CI: confidence interval; Cis-gem: cisplatin-gemcitabine; Cis-pem: cisplatin-pemetrexed; EPP: extrapleural pneumonectomy; ITT: intention to treat; m: months; N/n: number; NR: not reached; NS: not stated; OS: overall survival; pCR: pathologically complete response; PFS: progression- free survival; PORT: postoperative radiotherapy; PP: per protocol

FIGURE LEGENDS

Figure 1. General outline and CONSORT diagram of EORTC 08031 study.

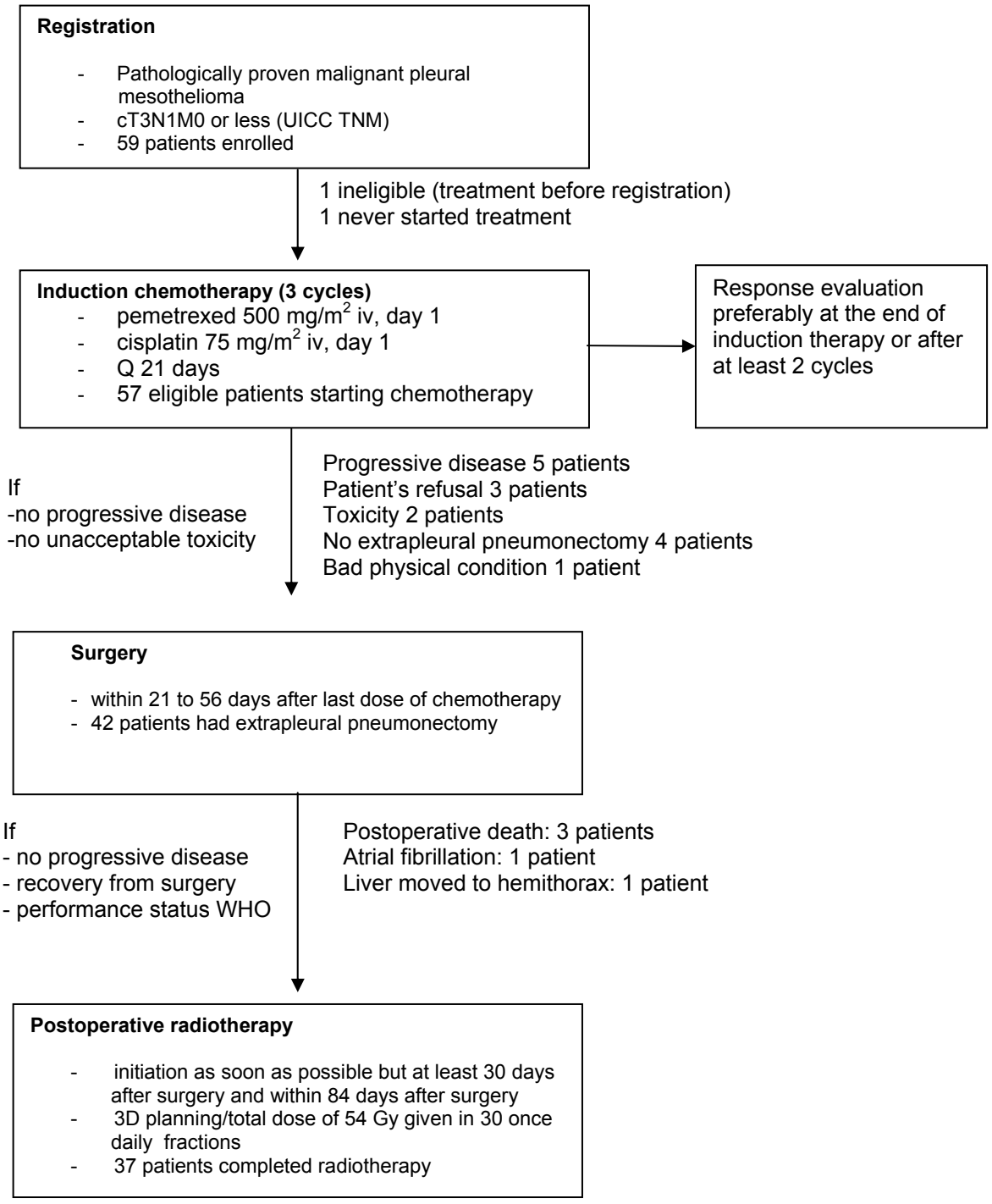


Figure 2. Overall survival for all 57 patients who were eligible and started treatment.

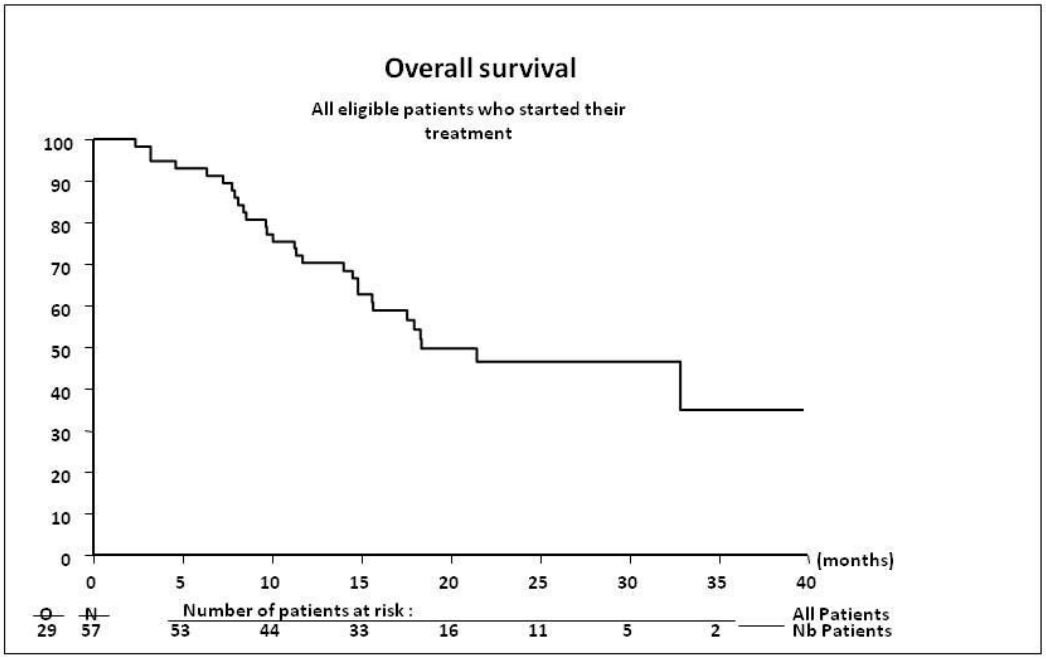
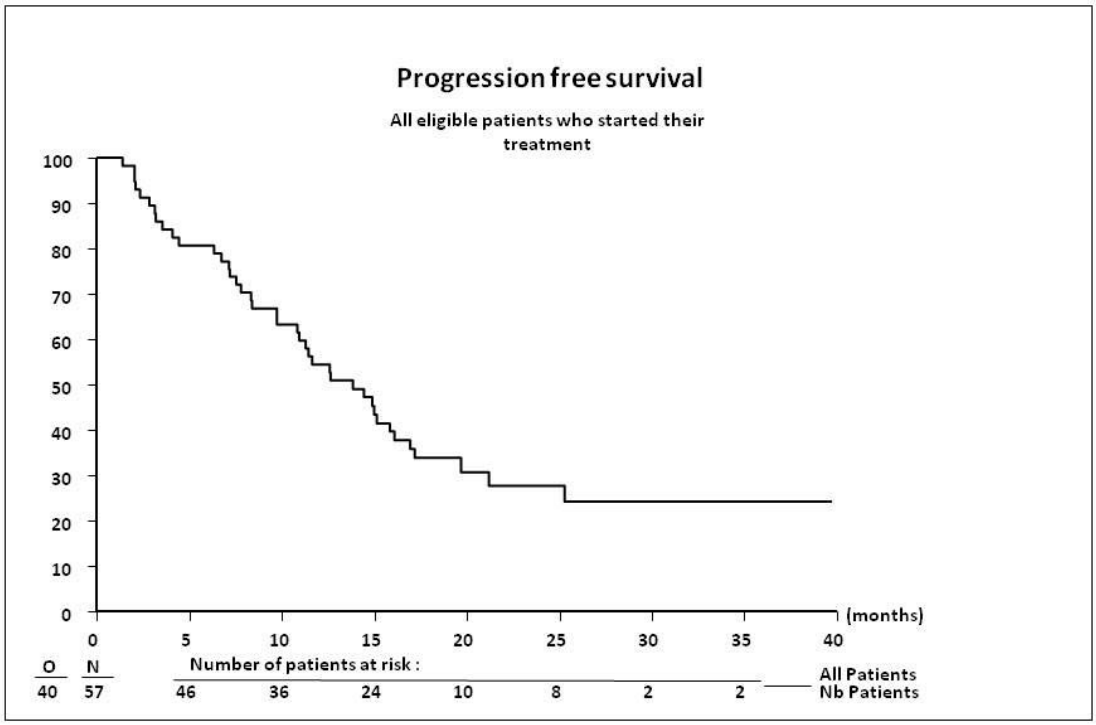


Figure 3. Progression-free survival for all 57 patients who were eligible and started treatment.


Progression free survival
All eligible patients who started their treatment
100
90
80
70
60
50
40
30
20
10
0
(months)
0
5
10
15
20
25
30
35
40
O
N
Number of patients at risk :
All Patients
Nb Patients
40
57
46
36
24
10
8
2
2