Predictors of long-term survival following radical surgery for malignant pleural mesothelioma

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Abstract

OBJECTIVES: The aim of radical surgery for malignant pleural mesothelioma (MPM) is to achieve greater survival than from chemotherapy alone. Although adverse overall prognostic factors have already been determined, our aim was to identify the most important factors affecting long-term survival arbitrarily defined as >24 months.

METHODS: We retrospectively reviewed the records of 252 patients (35 females; 193 epithelioid and 59 biphasic; 112 extrapleural pneumonectomy (EPP); 140 extended pleurectomy decortication (EPD)) who survived for at least 90 postoperative days. We tested for factors affecting overall cancer-related mortality and specific clinical factors predicting the 24-month survival.

RESULTS: The overall median survival was 18.2 (SE 1.3, 95% CI 15.8–20.7 months). There was no difference in survival between EPP and EPD (P = 0.92). One hundred and twenty-eight patients received induction, adjuvant or palliative chemotherapy. Seventy-seven (30.6%) patients survived for >24 months. On univariate analysis, age at operation over 60 years (P = 0.044), pT4 stage (P = 0.041), any lymph node metastases (P = 0.002), biphasic cell type (P = 0.00) and no administration of chemotherapy (P = 0.00) were associated with decreased survival. On multivariate analysis, age <60 (P = 0.018, OR = 0.7), epithelioid disease (P = 0.001, OR = 0.56) and negative nodes (P = 0.009, OR = 0.67) were associated with increased survival and no administration of chemotherapy (P = 0.00, OR = 1.9) with decreased survival. Factors predicting survival over 24 months included: age at operation under 60 (P = 0.014), epithelioid histology (P ≤ 0.00), negative nodes (P = 0.002) and chemotherapy (P = 0.022).

CONCLUSIONS: These results support a policy of accurate preoperative tissue diagnosis, nodal staging and induction chemotherapy prior to radical surgery for MPM, which can result in long-term survival. Trials investigating the role of surgery should be focused on confirming and refining these selection criteria.

Keywords: Malignant pleural mesothelioma • Surgery • Pleurectomy decortication • Extrapleural pneumonectomy • Predictors of survival

INTRODUCTION

Many consider malignant pleural mesothelioma (MPM) to be invariably fatal and therefore do not consider radical surgery to be justified. However, there are many reports of long-term postoperative survival in selected subgroups of patients. One of the main goals of research for MPM is to identify predictors of long-term survival that could be employed in patient selection before treatment. Experts worldwide consider the treatment paradigm to be removal of all macroscopic disease with surgical resection and then treat residual microscopic disease with additional local and systemic treatment [1]. The aim of our study was to determine whether we could retrospectively determine predictors of long-term survival in our cohort of patients who had radical surgery for malignant pleural mesothelioma (MPM).

METHODS

From the prospective departmental mesothelioma database, we identified 252 consecutive patients who underwent radical surgery over a period of 12 years (2000–12) for epithelioid or biphasic cell type and survived longer than 90 days after surgery. We excluded patients who died within 90 days: we assume these deaths were not related to the disease process itself but to associated comorbidity.

We intentionally excluded sarcomatoid cell type as this type of disease is to our experience associated with poor outcome, and we have stopped offering radical surgery to sarcomatoid disease patients for the last few years [2].

Operations were performed in a standard fashion removing all macroscopic disease, including pericardium and diaphragm. Pericardium was reconstructed using synthetic polypropylene or polyglactin mesh and diaphragm was reconstructed using Gore Dualmesh, W.L. Gore & Associates, Newark, DE, USA.
The endpoint was the survival from the diagnosis of the disease, and we tested whether the following factors had any impact on long-term survival: age, gender, cell type, operation, pT stage, pN stage and chemotherapy.

Age: Mean and median age were 59 years; therefore, we divided the sample into two groups, younger and older than 60.

pT Stage: We arbitrarily created two groups with early (pT1–2) and advanced (pT3–4) disease.

pN stage: We arbitrarily created two groups, node-negative (pN0) and node-positive (pN1–2) patients.

Chemotherapy: We merged all three chronological categories of chemotherapy (preoperative/induction/neoadjuvant, early postoperative/adjuvant and late/palliative) in one group and tested it against the group that did not receive chemotherapy.

Data were obtained from patients’ records, electronic patients’ information systems, and correspondence and telephone communication with the patients’ General Practitioners where necessary. Categorical data tests were performed using Fisher’s exact test. Univariate survival analysis was performed using the Kaplan-Meier method with the log-rank test. Multivariate survival analysis was performed using a forward stepwise Cox regression model. P-values of <0.05 were considered statistically significant. All statistical analysis was performed using the IBM SPSS Statistics Version 20 software, IBM Corporation.

RESULTS

There were 217 male (86%) and 35 (14%) female patients with a mean age of 59 (14–78) years. One hundred and ninety-three (77%) of the patients had epithelioid pathology and the remaining 59 biphasic. One hundred and twelve (44%) of the patients underwent extrapleural pneumonectomy (EPP) and 140 (56%) extended pleurectomy decortication (EPD).

Pathological staging is detailed in Table 1. We were aware that the procedure performed could be a confounding factor [3–5]; therefore, we tested for differences in the characteristics between these two groups: EPP vs EPD.

Gender distribution was similar (95/17 male/female for EPP and 122/18 male/female for EPD); P = 0.7.

Patients that had EPP (n = 112) were significantly younger (74 of 112, 66% of EPPs were younger than 60) than EPD patients (52 of 140, 37%); P = 0.000. Cell-type distribution was similar: EPP, 86 (77%) epithelioid and 26 (23%) biphasic; EPD, 107 (76%) epithelioid and 33 (24%) biphasic; P = 1.

pT-stage distribution was similar: EPP, pT1–2 31 (28%) and pT3–4 81 (72%); EPD, pT1–2 46 (33%) and pT3–4 94 (67%); P = 0.41. Accurate pN staging was available for 237 patients (15 were staged as pNx, as there were no lymph nodes described in the histopathology report).

pN-stage distribution was slightly different with a larger proportion of EPP patients being node negative: EPP, pN0 55 (49%) and pN1–2 57 (51%) and EPD, pN0 45 (36%), pN1–2 80 (64%); P = 0.048. Information as to whether the patients received chemotherapy was available for 230 patients. One hundred and twenty-eight (56%) patients received induction, adjuvant or palliative chemotherapy. Of 109, 62 (57%) of EPP patients received chemotherapy compared with 66 of 121 (55%) EPD patients; P = 0.79.

We therefore concluded that the two groups defined by the type of operation were broadly similar in characteristics with the only significant differences being age (younger patients in the EPP group) and borderline nodal involvement difference (slightly higher node-positive proportion in EPD), both of which could potentially favour better survival in the EPP group.

The median follow-up was 70 (3–120) months. Results of univariate survival analysis are presented in Table 2. The overall median survival was 18.2 (SE 1.3, 95% CI 15.8–20.7) months. There was no difference in survival between males and females (P = 0.59) or EPP and EPD (P = 0.92).

On univariate analysis, age <60 years (P = 0.044; Fig. 1), epithelioid histology (P = 0.00, Fig. 2), negative lymph nodes (P = 0.002; Fig. 4) and chemotherapy (P = 0.00; Fig. 5) were all associated with increased survival. Advanced pT stage when grouped as pT1–2 and pT3–4 failed to demonstrate any difference in survival; we, therefore, tested for two new groups, pT1, pT2 and pT3 grouped together vs pT4: this showed decreased survival in the pT4 group (P = 0.041; Fig. 3).

On multivariate analysis (Cox regression forward stepwise method) age <60 years (P = 0.018, OR 0.7, 95% CI 0.51–0.94), epithelioid histology (P = 0.001, OR 0.56, 95% CI 0.39–0.79) and negative lymph nodes (P = 0.009, OR 0.67, 95% CI 0.49–0.9) were all associated with increased survival, while the absence of chemotherapy (P = 0.00, OR 1.9, 95% CI 1.39–2.54) was a negative predictor of survival.

Seventy-seven (30%) patients survived more than 2 years. Using Fisher’s exact test, we compared the proportions of the patients with the identified factors affecting survival between this group and the group that survived <2 years (n = 175, 70%); age <60 (P = 0.014), epithelioid cell type (P = 0.001), negative nodes (P = 0.002) and patients that received chemotherapy (P = 0.022) were all factors with increased incidence in the longer surviving group and therefore associated with increased survival.

DISCUSSION

Identifying prognostic factors in patients with MPM is one of the main areas of research in the attempt to find the appropriate modalities of treatment for this incurable disease. In the late 1990s,
European [6] and North American [7] research groups analysed large cohorts of patients enrolled in clinical trials trying to identify the patients who were more likely to benefit from chemotherapy. The EORTC study [6] identified poor performance status (PS), high white blood count (WBC), a probable/possible diagnosis of mesothelioma, male gender and sarcomatoid disease as adverse prognostic factors, while the CALGB study [7] concurred that PS and WBC are adverse prognostic factors and added as favourable factors age <49 years and haemoglobin >14.6 g/dl. These findings were validated by other researchers [8] but these cohorts of patients did not include patients who had radical surgery aimed at removing all macroscopic disease.

The association between extrapleural lymph node involvement, resection margins and cell type and adverse outcome after EPP was identified in 1999 by Sugarbaker et al. [3]. Flores et al. in 2007 [6] added asbestos exposure, smoking, symptoms and laterality, while Yan et al. in 2009 [9] found that EPP, postoperative chemotherapy and radiotherapy were associated with survival. Interestingly, other researchers have found EPD to have marginally better survival than EPP [5]; this could be explained by the finding that EPD patients had earlier stage disease, something that did not occur in our experience [4]. Furthermore, other researchers have identified new adverse prognostic factors, such as tumour spread at the resected previous incision [10].

Recently, we have examined the impact of lymph node involvement in the survival of our cohort of patients that underwent radical surgery and found no difference in survival between pN1 and pN2 disease [11]. This finding was in line with the initial analysis of the IASLC database [12] and led to our decision to group pN1 and pN2 disease in one group and compare it with pN0 in the present study.

This was also one of the stimuli for the present study. We have identified in the past adverse prognostic factors in the retrospective studies we conducted but we have never looked specifically to identify whether these factors could be used to identify the patients who are likely to survive longer from the larger cohort of patients we would assess for radical surgery.

In contrast to previous studies identifying prognostic factors [1,5], gender was not associated with survival in our study; neither was the type of operation (EPP or EPD). The advantage of EPP would be that it could potentially achieve better clearance, even R0 resection. In this present study, the deaths within 90 days were not included in the analysis; therefore, the oncological outcome of EPP is not confounded by early mortality. Still, the survival is very close to that of EPD: 19.2 vs 16.2 months, P = 0.92, Table 2. The counter argument to the efficacy of EPD would be that, by definition, to achieve R1 resection with EPD, you are dealing with earlier stage disease [5]; otherwise, an EPP would be required. We have addressed this argument in 2012 [4] when we showed that, to our experience, EPD was at least as effective as EPP in oncological outcome in locally advanced (T3–T4) disease. And, in the current study, the proportion of advanced disease (pT3–pT4) is nearly identical between the two operation defined groups (Table 1).

Unsurprisingly, age (Fig. 1) is a significant factor as well as the cell type (Fig. 2).

We cannot do much about the age of our patients, as the reality is that we can expect our patients to become older as we move away from the era of the uncontrolled use of asbestos: the patients who develop mesothelioma now are more likely to be the ones with lesser exposure and, as a result, longer latency period and disease presentation later in their lifetime [13]. This is another argument in favour of EPD as the procedure of choice: older people do not tolerate extrapleural pneumonectomies very well.

In our experience [14], perioperative mortality after EPP increased exponentially in patients older than 65.

The appropriate management of biphasic disease, however, is still an area that remains obscure. We have previously argued in favour of operating in biphasic disease, in contrast to sarcomatoid [2] and, in the present study, the survival figures for biphasic disease (median of 12 months, Fig. 2, Table 2) are close to the one published in the initial analysis of the IMIG database: median of 13 months [12]. This sits halfway between the median for epithelioid (19 months) and sarcomatoid (8 months). Nearly a quarter (23%, Table 1) of our patients suffer from biphasic disease. Shall we continue to offer EPD to them, or would a simpler, palliative pleurectomy/decortication instead of a radical procedure serve them better?

As far as the local extent of disease is concerned, it appears that the tumour needs to reach the pT4 stage to affect survival (Table 2, Fig. 3). This might reflect inherent weaknesses of the current staging system which, for this exact reason, is undergoing revision [15]. Or it might be a true reflection of the extent of the disease, thus verifying the characterization of pT4 as unreatsectable disease by the IMIG group [16].

Nodal infiltration is also an adverse prognostic factor (Fig. 4, Table 2). There could be an argument for routine invasive pre-operative nodal staging [11]. The problem is that it appears that N1 is no different from N2 in prognosis [11,12] and, therefore, most invasive modalities, cervical mediastinoscopy being the gold standard, will not sample N1 nodes and will not identify the node-positive cohort. EBUS could potentially be used to sample hilar nodes but the sensitivity and negative predictive value of EBUS remain suboptimal [17].

The difference in survival achieved with chemotherapy is probably the most striking finding of this study (Table 2, Fig. 5). Chemotherapy as an adjunct to radical surgery nearly doubles the median survival (from 12.4 to 22.1 months); the group that did not have chemotherapy has a hazard ratio of 1.9 (95% CI 1.39–2.54), nearly twice the risk. As other researchers have demonstrated in the past [9], chemotherapy as part of multimodality treatment is a significant determinant of survival. The problem in our cohort is uptake of chemotherapy: of 230 patients for whom we had valid data about chemotherapy, only 128 (56%) actually received it. If we take into consideration the fact that the early (within 90 days postoperatively) deaths are not included in this study, this is a very low percentage. This is partly due to nihilistic beliefs about the efficacy of multimodality treatment of mesothelioma and partly an error of strategy: to our knowledge, some oncologists prefer to wait for evidence of disease progression before administering postoperative chemotherapy: this might lead to patients becoming too ill because of disease progression and therefore unfit for systemic chemotherapy.

In this study, we have confirmed that long-term survival is achievable: 30% of the patients survived more than 2 years after histological diagnosis of disease and subsequent radical surgery. One might argue that this is due to the patients and the variable biological behaviour of the disease rather than surgery modifying the course of disease. We will probably never know unless we are able to conduct a randomized, controlled trial that would compare radical surgery plus or minus any other modality of treatment with no treatment at all; there would be serious ethical implications if we were to follow that road; we simply cannot deny treatment to a large number of patients that would be fit for...
Table 2: Univariate analysis survival results (median, survival in months from the diagnosis of disease)

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<th>Median survival</th>
<th>SE</th>
<th>95% CI</th>
<th>Significance, P</th>
<th>1 year (patients at risk)</th>
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<td>Male (n = 215)</td>
<td>18.2</td>
<td>1.5</td>
<td>15.4–21.1</td>
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<td>66%</td>
<td>36%</td>
<td>20%</td>
<td>13%</td>
<td>9%</td>
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<td>Female (n = 35)</td>
<td>18.5</td>
<td>2.4</td>
<td>13.7–23.3</td>
<td>0.99</td>
<td>65%</td>
<td>31%</td>
<td>25%</td>
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<td>&lt;60 years (n = 126)</td>
<td>19.1</td>
<td>1.7</td>
<td>15.8–22.4</td>
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<td>76%</td>
<td>41%</td>
<td>20%</td>
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<td>11%</td>
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<td>≥60 years (n = 126)</td>
<td>14.4</td>
<td>2.4</td>
<td>9.7–19</td>
<td>0.044</td>
<td>56%</td>
<td>30%</td>
<td>22%</td>
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<td>EPP (n = 112)</td>
<td>19.2</td>
<td>1.6</td>
<td>16.3–22.5</td>
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<td>73%</td>
<td>40%</td>
<td>20%</td>
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<td>EPD (n = 140)</td>
<td>16.2</td>
<td>1.7</td>
<td>12.8–19.5</td>
<td>0.92</td>
<td>60%</td>
<td>31%</td>
<td>21%</td>
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<td>Epithelioid (n = 193)</td>
<td>20.8</td>
<td>1.3</td>
<td>18.2–23.4</td>
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<td>72%</td>
<td>43%</td>
<td>25%</td>
<td>16%</td>
<td>9%</td>
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<td>Biphasic (n = 59)</td>
<td>12</td>
<td>0.8</td>
<td>10.4–13.4</td>
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<td>48%</td>
<td>11%</td>
<td>6%</td>
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<td><strong>pT Stage (n = 252)</strong></td>
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<td>pT1–2 (n = 77)</td>
<td>22.1</td>
<td>2.2</td>
<td>17.8–26.4</td>
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<td>72%</td>
<td>43%</td>
<td>26%</td>
<td>15%</td>
<td>10%</td>
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<td>pT3–4 (n = 175)</td>
<td>16.2</td>
<td>1.4</td>
<td>13.4–18.9</td>
<td>0.078</td>
<td>64%</td>
<td>30%</td>
<td>19%</td>
<td>12%</td>
<td>6%</td>
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<td>pT1,2,3 (n = 194)</td>
<td>19.1</td>
<td>1</td>
<td>17–21</td>
<td></td>
<td>68%</td>
<td>39%</td>
<td>22%</td>
<td>14%</td>
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<td>pT4 (n = 58)</td>
<td>14.4</td>
<td>1.7</td>
<td>11.1–17.7</td>
<td>0.041</td>
<td>60%</td>
<td>25%</td>
<td>15%</td>
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<td><strong>Overall survival for (n = 252)</strong></td>
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<td><strong>pN Stage (n = 237)</strong></td>
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<td>pN0 (n = 100)</td>
<td>22.4</td>
<td>2.5</td>
<td>17.6–27.3</td>
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<td>75%</td>
<td>45%</td>
<td>26%</td>
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<td>pN1–2 (n = 137)</td>
<td>15.4</td>
<td>1.5</td>
<td>12.4–18.4</td>
<td>0.002</td>
<td>61%</td>
<td>26%</td>
<td>14%</td>
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<td>Total (n = 237)</td>
<td>18.3</td>
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<td>15.9–20.1</td>
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<td><strong>Chemotherapy (n = 230)</strong></td>
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<td>No chemo (n = 102)</td>
<td>12.4</td>
<td>1.3</td>
<td>7.7–14.9</td>
<td></td>
<td>51%</td>
<td>26%</td>
<td>12%</td>
<td>7%</td>
<td>3%</td>
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<td>Chemo (n = 128)</td>
<td>22.1</td>
<td>1.5</td>
<td>19.1–25.1</td>
<td>0.000</td>
<td>81%</td>
<td>43%</td>
<td>28%</td>
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<td>Total</td>
<td>18.7</td>
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Therefore, the closest we will get is by comparing the combination of radical surgery and chemotherapy with chemotherapy alone.

The forthcoming Mesothelioma and Radical Surgery 2 trial which is about to open in the near future in the UK might provide the answers to a few of these questions. The trial aims to evaluate the role of EPD in the context of multimodality treatment in the management of MPM.

The trial design is such that patients will receive chemotherapy before they are randomized to either surgery or continuation of chemotherapy. This is probably the best way to increase the uptake of chemotherapy: give it preoperatively. It might also serve as a selection tool: patients who progress on chemotherapy are more likely to suffer from biologically aggressive disease and therefore less likely to benefit from local control measures, such as radical surgery.

The trial will include non-epithelioid cell types. Therefore, we will have the opportunity to define the role of surgery for biphasic as well as sarcomatoid disease. The inclusion of sarcomatoid cell type might be controversial; the reality is that we have no

Figure 1: Age-related actuarial survival.

Figure 2: Cell-type-related actuarial survival.

Figure 3: pT-stage-related actuarial survival.

Figure 4: pN-stage-related actuarial survival.

Figure 5: Chemotherapy-related actuarial survival.
randomized trial-based evidence that surgery does not modify the course of sarcomatoid disease. In our opinion, macroscopic complete resection with some form of adjuvant treatment to eliminate microscopic disease is a sound strategy for dealing with MPM. Whether this adjuvant modality is systemic chemotherapy, intracavitary chemotherapy [18], a novel treatment such as photodynamic treatment [19] or a combination of all remains to be proved. The identification of pretreatment biological predictors such as gene-ratio-based predictive test [20] or other biomarkers from tissue or blood [21] might change completely the way we manage the disease.

The limitations of our study is its retrospective nature, a certain selection bias as we selected the patients fit for radical surgery, the wide variation in provision of chemotherapy and obviously the fact that we rely on post-resectional markers (pT, pN stage) to select the patients for surgery. The reality is that we have to start from better understanding the biological behaviour of each individual patient before we select the right treatment for each individual patient. The fact that our long-term survival figures compare well with other major series [1] is especially rewarding.

Conflict of interest: none declared.

REFERENCES


APPENDIX: CONFERENCE DISCUSSION

Dr G. Friedel (Gerlingen, Germany): I think, as we heard today, the surgical treatment of mesothelioma in general is the most challenging and, in my opinion, the most disenchanting problem in thoracic cancer treatment nowadays. I personally during the last 10 years have undertaken all treatment possibilities, starting with EPP over EPD alone and with HITOC, to simple pleurectomy or talc pleurodises. The outcome was not so different. The patient with EPP died after one year and the lady with talc pleurodises was alive for 5 years and vice versa. So what are we able to do for these, as Dr Nakas stated, incurable patients, as successors of Hippocrates, not to harm any patient? The authors describe the problem correctly with good and substantial data, which are self-explanatory. There are only two problems I see. Do you have any answer as to why such a low proportion of your patients received chemotherapy?

Dr Nakas: There are a number of answers. There is a widespread nihilism from some oncologists to give chemotherapy to the patients, and even those who are willing sometimes elect to give chemotherapy only when the patient demonstrates disease progression. By that point, the patient might be PS2 or worse, so they are not fit for chemotherapy.

Dr Friedel: Is it maybe better to perform the chemotherapy in a neoadjuvant setting?

Dr Nakas: We thought about this, and actually this is the advantage of the design of the new MARS-2 trial, because the chemotherapy is going to be given up front, so at least all the patients entering the trial will have chemotherapy.

Dr Friedel: The second question is, will you still offer T4 patients EPP?

Dr Nakas: We do not offer EPP for any indication anymore.