Is sacrificing the phrenic nerve during thymoma resection worthwhile?†

Sarah Hamdia, Olaf Mercierab,*, Elie Fadelb, Sacha Mussotb, Dominique Fabreab, Maria Rosa Ghignac,c, Vincent de Montprevillec, Benjamin Besseb,d, Cécile Le Pechouxc, François Leroy Ladurieab, Thierry Le Chevaliereab, and Philippe Dartevellaeab,e

a Service de Chirurgie Thoracique Vasculaire et de Transplantation Cardiopulmonaire, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, France
b Institut d’Oncologie Thoracique, Le Plessis-Robinson, France
c Département de Radiothérapie, Institut Gustave Roussy, Villejuif, France
d Département d’Oncologie Thoracique, Institut Gustave Roussy, Villejuif, France
e Service d’Anatomopathologie, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, France

† Corresponding author. Centre Chirurgical Marie Lannelongue, Service de Chirurgie Thoracique, Vasculaire et de Transplantation Cardiopulmonaire, 133 Avenue de la Résistance, 92350 Le Plessis-Robinson, France. Tel: +33-1-40948695; fax: +33-1-40948562; e-mail: o.mercier@ccml.fr (O. Mercier).

Received 22 September 2013; received in revised form 4 December 2013; accepted 11 December 2013

Abstract

OBJECTIVES: Locally advanced thymoma can often involve the phrenic nerve (PN) due to its location on the mediastinal pleura. However, en bloc resection including the PN may cause severe postoperative complications, especially in myasthenia gravis patients. The aim of the study was to determine whether a PN involved could be spared during thymoma resection.

METHODS: A retrospective study was conducted on patients who underwent resection of Masaoka Stage III and IV thymomas adherent, on digital palpation, to at least one PN in our institution between 1998 and 2012. An en bloc resection of the tumour with the invaded PN was performed unless patients with no preoperative PN paralysis had: both PN involved, compromised preoperative lung function, severe myasthenia gravis, severe comorbidities or minimal PN involvement (PN adherent to the edge of the tumour). All patients received postoperative radiation therapy.

RESULTS: There were 114 patients with a mean age of 57 years (range, 28–84). PN was spared in 73 patients (64%) and removed in 41 (36%). Sixty-five patients had Masaoka Stage III (57%) and 49 had Stage IV (43%); these were similar between both groups. On permanent histology, 6 (15%) of the resected PN were not involved, whereas a permanent postoperative PN palsy was found in 4 (5.4%) patients where the PN was spared. Postoperative mortality and morbidity were 0 and 15% in the spared group and 2.4 and 9.7% in the resected group, respectively (P = 0.56). Recurrence rate was significantly higher in the spared group (39.5 vs 19.5%; P = 0.02) but the 5-year disease-free survival rates (53.6 vs 66.8%, P = 0.14) and overall 5-year survival (85 vs 88%, P = 0.6) were not significantly different between the spared- and resected-PN groups, respectively.

CONCLUSIONS: Sparing the PN during thymoma resection achieved good long-term and disease-free survivals in high-risk patients comparable with en bloc PN resection. However, it carried a higher risk of recurrence despite adjuvant radiation therapy.

Keywords: Mediastinal tumour • Thymoma • Phrenic nerve • Surgery

INTRODUCTION

Surgical resection has been advocated as the most effective treatment of thymomas, provided that a complete resection is performed. Indeed, completeness of resection has been demonstrated to be the most important determinant of postoperative survival [1–3]. Due to its anatomical course along the mediastinal pleura adjacent to the thymus at the level of the upper mediastinum, the phrenic nerve (PN) has been shown to be involved in up to 33% of patients with advanced stage thymomas (Masaoka Stage III and IV [1, 4]) [5, 6]. When the involvement is unilateral, PN resection is possible and leads to the loss of one-third of vital capacity [7]. However, though there are situations where PN resection could be well tolerated, there are some concerns about its sacrifice in patients with bilateral PN involvement, minimal PN involvement, compromised preoperative lung function and associated myasthenia gravis, and in young patients at risk of requiring repeat thoracic surgery. As thymomas are slow-growing radiosensitive tumours, the role of PN-sparing surgery combined with postoperative radiation therapy has been investigated for a long time. Indeed, good long-term results have been reported after R1 thymoma resection followed by postoperative radiation therapy [8]. Yano et al. [7] reported in a small series that sparing the PN could achieve similar long-term survival when compared with PN resection, and maintain similar postoperative pulmonary function tests. However, the higher risk of local recurrence remains a concern. Whether PN-sparing surgery combined with adjuvant radiotherapy is a reasonable option in...
high-risk patients or in patients with a minimally involved but non-paralysed PN remains unknown. The objective of this study was to compare the postoperative course and long-term results of patients who had advanced stage thymomas invading the PN where the PN was spared or sacrificed due to clinical indications.

METHODS

A retrospective study was conducted on patients who underwent resection of Masaoka Stage III and IV thymomas invading at least one PN in our institution between January 1998 and December 2012. The study was approved by the Institutional Review Board of Marie Lannelongue Hospital. An en bloc resection of the tumour and the invaded PN was performed unless in patients without preoperative PN paralysis (elevation of the diaphragmatic dome on plain chest X-ray): both PN involved, compromised pre-operative lung function, severe myasthenia gravis, comorbidities or minimal PN involvement (PN adherent to the edge of the tumour) were found. Massive and extensive PN involvement was a contraindication to preservation. The final decision of PN sparing was made by the staff surgeon at the time of the surgery. Two groups of patients were studied and compared with each other: the resected-PN group (R0 resection) and the spared-PN group (R1 resection). When specimens were available, pathology was reviewed by the study pathologists who verified the diagnosis and the histological classification according to World Health Organization (WHO) 2004 classification. The need for neoadjuvant chemotherapy or adjuvant radiation therapy was decided based upon a multidisciplinary tumour board discussion. Briefly, neoadjuvant chemotherapy was offered to patients initially deemed unresectable. Radiation therapy with a boost targeting R1 resected areas was offered to patients after resection. Most of the patients received 50 Gy of adjuvant radiation therapy with an additional 4 Gy boost at the level of the PN, if spared. Our chemotherapy protocol included a platinum salt. Postoperative follow-up consisted of a postoperative chest X-ray at 1 month followed by a chest computed tomography at least once a year or sooner if patients complained of symptoms.

Recurrence was defined as the appearance of new disease on follow-up radiographic imaging after a complete or incomplete (nerve-sparing) resection. Time to recurrence was defined as the date of initial resection to the date of recurrence diagnosis. Overall survival was calculated from the date of thymoma resection to the date of death or the date of last follow-up. Disease-free survival was defined as the time interval from the date of thymoma resection to the date of last follow-up or the date of disease recurrence or progression.

Statistical analysis

All results were expressed as means ± standard deviation and analysed by the non-paired t-test using Fisher’s exact method. Categorical variables were expressed as percentages and distribution was assessed with the χ² test. Survival rates were calculated by life-table analysis. Kaplan–Meier curves were plotted and compared using the log-rank test for univariate analysis. Statistical analyses were performed using Statview V (Abacus Concept, Berkeley, CA, USA). Statistical significance was defined as P < 0.05.

RESULTS

Population of the study

Among the 290 patients operated on for thymoma during the study time period, 114 (39%) patients had a Masaoka Stage III or IV meeting the criteria of the study. There were 65 males and 49 females with a mean age of 57 years (range, 28–84). We had complete follow-up for the entire cohort. Mean follow-up was 56 months (range, 1–210) from the date of surgery to death or last follow-up. All clinical, surgical and pathological characteristics are shown in Tables 1 and 2. Forty-two (37%) patients had myasthenia gravis and thymoma was diagnosed by routine chest computed tomography. Forty-three (38%) patients had other symptoms such as dysphagia, chest pain, fatigue or superior vena cava syndrome. Finally, 29 (25%) patients were asymptomatic.

The surgical approach was a median sternotomy. An anterior thoracotomy was added in 5 patients to allow full exposure of the tumour. All patients underwent extended thymectomy and resection of adjacent organs including the lung (n = 41), the pericardium (n = 39), superior vena cava or left brachiocephalic vein (n = 12) and the pleura (n = 70). The PN was resected in 41 (35.9%) patients (R0 resection) and spared in 73 (64.1%) patients (R1 resection). The spared-PN group included 2 patients (1.9%) with bilateral PN invasion requiring one-sided PN resection and contralateral PN sparing resulting finally in R1 resection. The resected-PN group had significantly more asymptomatic patients than the spared-PN group (36 vs 19%, P = 0.043) (Table 1). Apart from management of the PN, the surgical procedure was similar in both groups (Table 2). There were no differences between groups regarding the Masaoka stage or the WHO pathology classification. Most of the cases were B2–B3 thymomas. Interestingly, six resected PN did not show any sign of involvement on final pathology. Postoperative radiation therapy was performed in 80 patients (70%). Twenty patients did not receive postoperative radiation therapy due to a complicated postoperative course, personal choice or for unknown reasons. However, the same percentage of patients received radiation in both groups (75% vs 79%, P = 0.2).

<table>
<thead>
<tr>
<th>Table 1: Clinical features of spared- and resected-PN groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Preop FEV-1</td>
</tr>
<tr>
<td>Coronary disease (other)</td>
</tr>
<tr>
<td>Cancer history</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

PN: phrenic nerve.
Neoadjuvant therapy was given more frequently to the spared-PN group than to the resected-PN group (33 vs 13%, \( P = 0.015 \)).

Postoperative course: 30-day mortality and morbidity

The morbidity rate was not different between the spared-PN and the resected-PN groups (14 vs 9.7%, \( P = 0.56 \)). The complications were acute respiratory distress syndrome (ARDS) (n = 3), myasthenia crisis (n = 4), bleeding (n = 4), myocardial infarction (n = 1), acute pulmonary embolism (n = 1), septic shock (n = 1) and tamponade (n = 1). Resection of the PN resulted in clinical PN paralysis in all 41 patients of the PN resection group. After PN-sparing surgery, 4 (5.4%) patients developed postoperative PN paralysis as diagnosed by diaphragmatic dome elevation on routine follow-up chest X-ray at 1 month. One patient of the resected-PN group died from infected ARDS. The 30-day mortality was 0% for the spared-PN group and 2.4% for the resected-PN group.

Recurrences and disease-free survival

Recurrence of thymoma was diagnosed in 38 patients, 30 (39.5%) from spared-PN surgery and 8 (19.5%) from sacri
cified-PN surgery. Recurrence rate was significantly higher in the spared-PN group (39.5 vs 19.5%, \( P = 0.03 \)). The pattern of recurrence included pleural implants (n = 21), lung recurrences (n = 23), venous recur-
rences (n = 3) or systemic metastases (n = 3). Recurrences in the spared-PN group occurred signi
cificantly more frequently within the pleura (23 vs, 7.3%, \( P = 0.02 \)). Mean time to relapse was 22 months in the spared-PN group and 32 months in the resected-PN group \( (P = 0.47) \). The 5- and 10-year disease-free sur-
vival rates of the resected-PN group were higher than those of the spared-PN group (53.6 and 40.8% vs 66.8. and 66.8%, respectively, \( P = 0.14 \)). Most of the recurrences were reoperated on and the de-
cision for additional radiation or chemotherapy was made on a case-by-case basis depending on the tumour board consensus (Table 3, Fig. 1).

Overall survival

The overall survival of the 114 patients was 85.8% at 5 years and 79.1% at 10 years. There was no difference in overall survival between the spared-PN and sacrificed-PN groups (85 and 74.8% vs 88 and 88%, respectively, \( P = 0.6 \)) (Table 3, Fig. 2).
non-myasthenia patient within the resected-PN group secondary to a super-infected ARDS.

The decision to keep the PN was made by the staff surgeon at the time of the surgery. When entirely surrounded by the tumour, the PN was not preserved. Indeed, extensive dissection of the PN could induce permanent paralysis. While all postoperative PN paralysis resolved in the previous report by Yano et al. [7], we report 4 cases of permanent PN paralysis based on chest X-ray 1 month after surgery. These PN would have been damaged during the blunt dissection. Given the uneventful postoperative course of these 4 patients, these PN should certainly have been resected. Surgeons may sometimes have overestimated the postoperative risk. Operative strategy was based on the balance between the functional risk of PN paralysis and the oncological risk of R1 resection. Conversely, 6 patients had PN resection with no signs of invasion on final pathology. This decision was likely made due to peritumoural inflammation mimicking PN tumoural invasion. The decision of sparing or resecting the PN remains challenging and predictive factors of phrenic invasion other than paralysis are yet unknown.

Almost all series describing the surgical management of thymomas indicate that initial Masaoka stage, completeness of the resection and WHO classification are strong independent predictors of recurrence [10–14]. Our series of thymomas invading the PN seem to have a higher risk of recurrence since they were Masaoka Stage III or IV, mainly B2–B3 WHO classification thymomas. Moreover, by sparing the PN, the resection was incomplete, and thus, it is not surprising that the spared-PN group had a higher rate of disease recurrence. Most of the recurrences in the spared-PN group were found at the level of the pleura despite postoperative radiation therapy. It has to be emphasized that despite the decision of treating all patients with adjuvant radiation therapy, only 78% of them received the treatment. Thus, even though adding radiation therapy after complete resection is still debated, there is no doubt that radiation therapy is useful after incomplete resection. Radiation therapy was well tolerated and we did not find any post-radiation paralysis. Our recurrence rates, though higher in the spared group, are consistent with previously reported post-surgical recurrence rates [2, 12–14] ranging from 10 to 43% depending on Masaoka stage and on type of resection (complete/incomplete). However, our time to recurrence appears to be shorter, given that all reported median progression-free intervals are approximately 50 months [14]. Despite the higher rate of recurrence, overall survival did not differ between patients with or without PN-sparing surgery. Patients have had good long-term survival despite local recurrences since thymomas are slow-growing tumours and all recurrences were promptly diagnosed and treated during follow-up. In our series, there were 15 long-term survivors (>120 months) in the spared-PN group and 3 in the resected-PN group. There is no consensus on thymoma recurrence management but several reports have highlighted good long-term results of surgical resection in association with chemo or radiation therapy [10, 14]. In our series, all patients diagnosed with thymoma recurrence underwent surgical resection followed or preceded by chemo and/or radiation therapy.

Taken together, these results suggest that sparing the PN during thymoma resection may be a good decision, provided (i) PN dissection does not damage the nerve and as little as possible residual tumour tissue is left surrounding it, (ii) adjuvant radiation therapy is provided and (iii) a close follow-up is performed to diagnose and treat any recurrence. Although our series is the largest one focused on PN preservation, it remains a retrospective study over a 20-year

**DISCUSSION**

Our study demonstrates that sparing the PN during thymoma resection achieves a similar long-term survival when compared with a complete resection. These results are consistent with a previous report by Yano et al. [7] showing that survival was also similar after resection or preservation of the PN, whereas patients with a spared-PN nerve showed better postoperative vital capacity and forced expiratory volume in one second (FEV-1) regardless of associated lung resection. Interestingly, we found that the postoperative complication rate, specifically, those of respiratory complications were not significantly higher in the resected PN group. However, in our study, patients with spared PN were selected by the surgeon to be at a higher postoperative risk. Hence, compared with the resected-PN group, the spared-PN group had more patients with coronary artery disease, myasthenia gravis and preoperative symptoms or larger tumours requiring neoadjuvant chemotherapy. PN-sparing surgery may have protected some patients from life-threatening complications caused by the larger surgery. Indeed, preoperative risk factors were the only different variables between the two groups of patients, which were otherwise similar in Masaoka stage, associated surgical resections or postoperative radiation therapy. In addition, myasthenia gravis is known to be a strong postoperative risk factor, leading some surgeons to avoid extended surgeries in such patients due to a high risk–benefit ratio [9]. The only postoperative death occurred in a
period. These results need to be validated by a multicentre prospective cohort study supported by national or international networks/organizations involved in thymoma treatment.

CONCLUSIONS

Sparing the PN during thymoma resection achieved good long-term and disease-free survivals in high-risk patients comparable with en bloc PN resection. However, it carried a higher risk of recurrence despite adjuvant radiation therapy. A further prospective cohort study focused on PN management during thymoma recurrence despite adjuvant radiation therapy. A further prospective study of nerve-sparing surgery for invasive thymoma in 2002, not only distinguished between unilateral and bilateral involvement because this is not clear from your paper. Secondly, wouldn't the title be better as "Is sparing the phrenic nerve during thymoma resection worthwhile?" That may be better, because en bloc resection is the standard care. So if you put in more effort, you spare the phrenic nerve on one side. It may be easier to do an en bloc resection. And then, are you really sure that the recurrence rate you had is not resulting in a higher mortality and morbidity rate in the long run? And the fourth question is: Is the short gain which you might have with sparing the phrenic nerve outweighing the long-term oncological risk of recurrence you obviously seem to have in these patients?

Dr Hamdi: During our study we have the same morbidity and mortality rates when we compare the two groups, the sparing phrenic nerve group and the resected phrenic nerve group. But we have one difference between the two groups. The postoperative radiation therapy was performed in 80 patients, and 20 patients did not receive postoperative radiation therapy due to a complicated postoperative course, a personal choice, or for unknown reasons. However, the same percentage of patients received radiation in both groups. But neoadjuvant therapy was given more frequently to the spared phrenic group than the resected group, so it’s possible to explain that we have more recurrence in one group compared with the other.

Dr E. Rendina (Rome, Italy): I agree with Professor Schmid when he says that probably the title should be changed, since the standard is sacrificing the phrenic nerve, so it’s probably better to say “Is sparing the phrenic nerve worthwhile in thymoma surgery?”

My question is the following: You are an excellent group, with huge experience in thoracic malignancies: has your policy changed now that you have done this study? Are you resecting, unilaterally of course, the phrenic nerve if spared.

Dr Hamdi: We try to do resection. I do not do the same, or do you never do this? Do you try to do a resection at once?

Dr M. Lucchi: Up around the tumour, not surrounded.

Dr Hamdi: So what are you doing now, do you resect the phrenic nerve or not?

Dr Hamdi: Now we stay with the gold standard. That is to say, when we have a large tumour, when the phrenic nerve is invaded, it’s necessary to do resection. But this study is very important because it shows that we can do surgery, we can propose surgery to patients where it was not possible before, for example, because of poor pulmonary function. So now when it’s possible to propose to the patient a complete resection where we preserve the phrenic nerve, we perform these techniques.

Dr M. Lucchi (Pisa, Italy): I would like to make a brief comment, because we also support the Marie Lannelongue Hospital policy. We started doing a prospective study of nerve-sparing surgery for invasive thymoma in 2002, not only when it’s bilateral but even when it’s just unilateral. But I think that you should give us more details about the relationship between the phrenic nerve and the tumour. When you say ‘nerve-sparing’, do you mean that the nerve is just up on the tumour or surrounded by the tumour?

Dr Hamdi: Up around the tumour, not surrounded.

Dr Lucchi: We also do it when it is surrounded. If there is no preoperative diaphragmatic palsy, we try to save the phrenic nerve. And if there is R1 disease just localized along the phrenic nerve, we do radiotherapy. By means of a good cooperation with the radiotherapists, at least in our experience, the results are comparable.

Dr Hamdi: In this study, radiation therapy with a boost targeting R1 resected areas was offered to patients after resection. Most of the patients received 50 Gy adjuvant radiation therapy with an additional 4 Gy boost at the level of the phrenic nerve if spared.

Dr M. Zielinski (Zakopane, Poland): I have a question. In my institution our policy in the advanced marginal cases is, if we open the chest and see that there is an infiltration of even one nerve, sometimes we cancel the operation, we close the chest, and we send the patient for induction. Do you sometimes do the same, or do you never do this? Do you try to do a resection at once?

Dr Hamdi: We try to do resection.

ACKNOWLEDGEMENTS

We thank Jonathan Yeung for his help in writing the manuscript.

Conflict of interest: none declared.

REFERENCES


APPENDIX: CONFERENCE DISCUSSION

Dr R. Schmid (Berne, Switzerland): My first question is to ask whether you have distinguished between unilateral and bilateral involvement because this is not clear from your paper. Secondly, wouldn’t the title be better as “Is sparing the phrenic nerve during thymoma resection worthwhile?” That may be better, because en bloc resection is the standard care. So if you put in more effort, you spare the phrenic nerve on one side. It may be easier to do an en bloc resection. And then, are you really sure that the recurrence rate you had is not resulting in a higher mortality and morbidity rate in the long run? And the fourth question is: Is the short gain which you might have with sparing the phrenic nerve outweighing the long-term oncological risk of recurrence you obviously seem to have in these patients?

Dr Hamdi: During our study we have the same morbidity and mortality rates when we compare the two groups, the sparing phrenic nerve group and the resected phrenic nerve group. But we have one difference between the two groups. The postoperative radiation therapy was performed in 80 patients, and 20 patients did not receive postoperative radiation therapy due to a complicated postoperative course, a personal choice, or for unknown reasons. However, the same percentage of patients received radiation in both groups. But neoadjuvant therapy was given more frequently to the spared phrenic group than the resected group, so it’s possible to explain that we have more recurrence in one group compared with the other.

Dr E. Rendina (Rome, Italy): I agree with Professor Schmid when he says that probably the title should be changed, since the standard is sacrificing the phrenic nerve, so it’s probably better to say “Is sparing the phrenic nerve worthwhile in thymoma surgery?”

My question is the following: You are an excellent group, with huge experience in thoracic malignancies: has your policy changed now that you have done this study? Are you resecting, unilaterally of course, the phrenic nerve if spared.

Dr Hamdi: We try to do resection. I do not do the same, or do you never do this? Do you try to do a resection at once?

Dr M. Lucchi: Up around the tumour, not surrounded.

Dr Lucchi: We also do it when it is surrounded. If there is no preoperative diaphragmatic palsy, we try to save the phrenic nerve. And if there is R1 disease just localized along the phrenic nerve, we do radiotherapy. By means of a good cooperation with the radiotherapists, at least in our experience, the results are comparable.

Dr Hamdi: In this study, radiation therapy with a boost targeting R1 resected areas was offered to patients after resection. Most of the patients received 50 Gy adjuvant radiation therapy with an additional 4 Gy boost at the level of the phrenic nerve if spared.

Dr M. Zielinski (Zakopane, Poland): I have a question. In my institution our policy in the advanced marginal cases is, if we open the chest and see that there is an infiltration of even one nerve, sometimes we cancel the operation, we close the chest, and we send the patient for induction. Do you sometimes do the same, or do you never do this? Do you try to do a resection at once?

Dr Hamdi: We try to do resection.