Institutional report - Thoracic oncologic

Induction chemotherapy, cytoreductive surgery and intraoperative hyperthermic pleural irrigation in patients with stage IVA thymoma


Abstract

The optimal treatment for Masaoka stage IVA thymoma remains controversial. Whilst extrapleural pneumonectomy (EPP) has been proposed, we sought to examine the results of our institutional preference for induction chemotherapy, cytoreductive surgery and intraoperative hyperthermic pleural irrigation. We undertook a retrospective study of patients undergoing surgery for Masaoka stage IVA thymoma following induction chemotherapy over a three-year period at our institution. Between February 2007 and February 2010, 42 patients underwent surgery for thymoma. Six patients underwent surgery with intent to perform cytoreductive surgery and intraoperative hyperthermic pleural irrigation. Complete cytoreductive surgery was not feasible in one patient and thymectomy only was performed. One patient had re-operation for recurrent disease 24 months after the first operation and there were therefore seven procedures undertaken in six patients during the study period. There were no in-hospital deaths. Median follow-up was 18.8 months (range 1.5–31.9 months). One patient died 14 months postoperatively from an acute cardiovascular event. The four remaining patients are alive and well with no evidence of disease recurrence. Multimodality therapy consisting of induction chemotherapy and cytoreductive surgery is a safe, feasible treatment for stage IVA thymoma. Our experience suggest that full pleurectomy is an alternative to EPP.

1. Introduction

The treatment of stage IVA thymoma is controversial. Although surgery has an established role as part of multimodality treatment, the exact choice of surgical procedure is debated. Whilst some propose a radical approach with extrapleural pneumonectomy (EPP) [1, 2], proponents of lung conserving techniques argue that with good long-term survival of patients with stage IVA thymoma, in excess of 45% at 10 years [3], EPP is not warranted given its attendant risks. Moreover, whilst the mortality of EPP is <7% in specialized centres, completion of multimodality treatment is reduced to <50% in most series [4, 5].

An alternative approach of cytoreductive surgery and hyperthermic intrathoracic perfusion chemotherapy (HITOC) with chemotherapeutic agents has been utilised in the treatment of stage IVA thymoma with 0% mortality in a small series [6]. However, the technique is cumbersome and may be associated with significant morbidity [6]. Povidone-iodine is a widely used antiseptic agent principally used for skin preparation prior to surgery, however its use has also been advocated for prevention of tumour seeding at the time of abdominal surgery [7] and its antitumour properties on mesothelioma cells have been demonstrated in vitro [8].

We favour cytoreductive surgery and hyperthermic pleural lavage with povidone iodide for stage IVA thymoma. Our objectives were to conduct an observation study to examine the results of our institutional preference for induction chemotherapy, cytoreductive surgery and intraoperative hyperthermic pleural irrigation over a three-year period.

2. Methods

We undertook a retrospective review of consecutive patients referred to a single surgeon (L.L.L.) who underwent surgery for stage IVA thymoma following induction chemotherapy over a three-year period. The data represents a consecutive series of patients undergoing resection of stage IVA thymoma with curative intent at the Guy’s Hospital, London, UK during the period February 2007–February 2010. Operations were carried out by a single surgeon (L.L.L.) at the institute.

Patients diagnosed with stage IVA thymoma received induction chemotherapy. All patients underwent chest computer tomography (CT)-scan prior to and following completion of induction chemotherapy. Thoracotomy was the preferred approach. Full pleurectomy was undertaken from apex to diaphragm and from anterior to posterior hilar
mediastinal pleural reflections. Where necessary, extended resection was undertaken of pericardium, parenchyma and diaphragm. In the case of diaphragmatic resection reconstruction was performed utilising a polytetrafluoroethylene (PTFE) mesh (2 mm Dual Mesh, GORETEX, WL Gore and Associated, Flagstaff, USA). Following completion of resec-
tion, hyperthermic pleural lavage using a total of 5–6 l sterile water and povidone-iodine (dilution 1 in 10) at 40–
41 °C was undertaken such that contact time was > 15 min.

Data was collated from patient’s medical records and follow-up by clinical review and was the UK NHS tracer service.

3. Results

Forty-two patients underwent resection of thymoma between February 2007 and February 2010. During this three-year period six patients with stage IVA thymoma underwent seven procedures with intent to perform cyto-
reductive surgery and intraoperative hyperthermic pleural irrigation. Four patients (67%) were female. The age range
was between 47 and 59 years with a mean age of 56 years. Half of the patients (3) presented with or were known to have myasthenia gravis, whilst the remainder did not. World Health Organisation (WHO) staging was B1 in one patient, B2 in two patients and B3 in the remaining three patients. Three patients had previously undergone surgery to resect thymoma. Two of these three patients had pre-
viously undergone resection of stage I thymoma 10 and 20 years previously, respectively. One other patient under-
went re-thoracotomy and resection of pleural metastases 24 months following thoracotomy, thymectomy and resec-
tion of pleural metastases for stage IVA thymoma. During the study period, all patients underwent induction chemo-
therapy. Five patients received between three and six cycles of platin-based therapy together with etoposide; one patient received cyclophosphamide, adriamycin and cispla-
tin. Radiological assessment post-chemotherapy showed that four patients had stable disease and two patients had a good response.

Three patients underwent thymectomy, pleurectomy and extended resection. One patient underwent diaphragmatic
resection, in another both diaphragm and pericardium were resected and in one other rib resection was undertaken. In one patient, complete cytoexcit ductive surgery was not fea-
sible at operation and thymectomy/debulking only was performed. Of the seven procedures performed on six patients, four were undertaken via anterior or posterior lateral thoracotomy, one via median sternotomy and one via both thoracotomy and median sternotomy.

There were no in-hospital deaths. Complications occurred in two patients. One patient developed methicillin-resistant Staphylococcus aureus (MRSA) pneumonia requiring intu-
bation and ventilation. One other patient developed post-

thoracotomy pain syndrome. Median length of stay for the seven procedures was eight days (range 5–17 days). Median follow-up was 18.8 months (range 1.5–31.9 months). One patient died 14 months postoperatively from an acute cardiovascular event. One patient underwent re-operation for recurrent disease 24 months after the first operation. The four remaining patients who underwent surgery with curative intent remaining are alive and well with no evi-
dence of disease recurrence.

4. Discussion

The treatment of stage IVA thymoma is controversial. Immunotherapy, systemic chemotherapy, radiotherapy and surgery have all been utilised as part of multimodality therapy [9]. Indeed even in patients with locally advanced and initially unresectable thymoma, induction chemother-

apy followed by resection, a radiation and consolidation chemotherapy lead to good overall survival rates (95% at five years, 79% at seven years) [10]. Median survival rate
of 91%, 78% and 65% at three, five and 10 years with no operative mortality have been achieved in a group of 18 patients undergoing surgery as part of multimodality therapy [1]. Therefore, although surgery has an established role as part of multimodality treatment even in advanced stages of thymoma, the exact choice of surgical procedure is the subject of debate.

Whilst some propose a radical approach with EPP [1,2], proponents of lung conserving techniques argue that with good long-term survival of patients with stage IVA thymoma in excess of 45% at 10 years [3], EPP is not warranted given its attendant risks. Moreover, whilst the mortality of EPP is < 7% in specialized centres, completion of multimodality treatment is reduced to < 50% in most series [5]. In a highly selected group of five patients undergoing EPP for stage IVA thymoma, there was no in-hospital mortality and one patient (20%) developed major complications [2]. In a small series of patients undergoing EPP as part of multimodality treatment for stage IVA thymoma, complications occurred in two of three patients undergoing four such procedures. One patient developed nephrotoxicity, whilst another developed wound dehiscence requiring re-operation. One further patient underwent staged bilateral procedures without adverse effect [6]. Despite the excellent results of these small series of highly selected patients, there is no doubt that EPP is a maximally invasive procedure that is associated with significant morbidity and mortality even in experienced centres.

Following the success of both isolated locoregional hyperthermic chemotherapy in combination with cyto-
reductive surgery abdominal malignancy, such as peritoneal mesothelioma [11], cytoexcit ductive surgery and HITHOC have also been utilised in the treatment of pleural based malign-
ancy including mesothelioma and thymoma [12].

This alternative approach of cytoexcit ductive surgery and HITHOC with chemotherapeutic agents has been utilised in the treatment of stage IVA thymoma with 0% mortality in a small series [6]. However, the technique is cumbersome and is associated with significant morbidity [6]. Perfusion chemotherapy requires inflow and outflow catheters, a pump system, temperature sensors, heat exchanger, filters and roller pump. It adds significant time to the duration of the procedure and when performed as part of EPP mean operative time was in excess of six hours [6]. Povidone/iodine is a widely used antiseptic agent principally used for skin preparation prior to surgery; however, its use has been advocated for the prevention of tumour seeding at the time of abdominal surgery [7] in a murine model and its
antitumour properties on mesothelioma cells have been demonstrated in vitro [8].

Due to the indolent nature of thymoma together with prolonged survival even in advanced stages when considered against the morbidity and mortality of EPP, it is our institutional preference to offer cytoreductive surgery with pleural lavage as part of multimodality treatment.

In the present series, six patients underwent seven procedures with intent to perform cytoreductive surgery for stage IVA thymoma. There were no in-hospital deaths and minimal procedural morbidity. Given the undeniable morbidity and mortality associated with EPP even in large centres with considerable experience we feel that our results favour a cytoreductive approach for stage IVA thymoma. In contrast to HITHOC, which adds considerable complexity and time to the cytoreductive surgery, povidone/iodine pleural lavage is simple, cost-effective, adds little additional time to the procedure and is safe. We have more than 15 years experience of povidone/iodine pleural lavage in young patients undergoing pleural abrasion to induce pleurodesis following recurrent spontaneous pneumothorax without any adverse effects. A recent publication reported cases of permanent blindness following intrapleural administration of povidone/iodine, however, we believe this to be product related rather than the povidone/iodine itself [13].

In one patient in the present series it was not possible to achieve a complete resection due to invasion of the great vessels (superior vena cava, innominate vein and pulmonary artery) together with hundreds of pleural metastases and the patient underwent a debulking procedure. The role of debulking is controversial, partial resection may confer survival benefit over biopsy alone [14].

Pleural disease may be present at the time of first presentation or ‘drop’ metastases may occur later as disease relapse following surgical resection of an earlier stage thymoma [15]. Disease-free interval can be long and relapse may occur many years later and most surgeons recommend follow-up in excess of 20 years. We believe that performing a total pleurectomy in those patients may prevent further drop metastases by obliterating the pleural space. Relapse may be suggested by recurrence of myasthenic symptoms or on regular radiological follow-up. In the present study, five patients were stage IVA at initial presentation, whilst in one patient pleural recurrence occurred 10 years following resection of a stage I thymoma. Two of the five patients with stage IVA disease at presentation had undergone resection as part of multimodality treatment underwent reoperation for recurrent stage IVA disease 10 and 20 years later. The commonest WHO classification subtype of thymoma in the context of pleural recurrence is B3 thymoma. In the present series, B3 was the most prevalent subtype with three of six patients showing this subgrouping. Two patients we classified as B2 and one other as B1.

Whilst this series represents a non-randomized, relatively small cohort, we believe that multimodality therapy consisting of induction chemotherapy and cytoreductive surgery is a safe, feasible treatment for patients with stage IVA malignant thymoma. Although a longer follow-up is needed to assess the results of our approach, our experience suggests that full pleurectomy with extended resection where necessary is an alternative to EPP for these patients.

References


Conference discussion

Dr. F. Rea (Padua, Italy): The authors report six cases of stage IVA thymoma treated with surgery and intraoperative hyperthermic pleural irrigation with a median follow-up of <2 years. I have one comment and two questions. The comment is regarding the follow-up. In my opinion, for this kind of tumor, the follow-up is a little bit too short.
The first question is, do you have information about the entity of adhesion from this pleural irrigation in the case of reoperation? I have seen that you performed one reoperation. The second question is, if you have disease on the visceral pleura, besides the pleurectomy do you also perform decortication, and, if so, do you perform pleural irrigation?

**Dr. Belcher:** Taking the questions in reverse order, yes, if the visceral pleura is involved, then an attempt is made to decorticate the visceral pleura, or, if suitable, a stapled wedge resection of that area.

**Dr. Rea:** And you also do pleural irrigation?

**Dr. Belcher:** With the pleural irrigation again, yes, at a second stage, that’s right.

Regarding reoperation, I think reoperation after pleurectomy is difficult, it always is, but I don’t think that the iodine makes it any more difficult than it is already.

**Dr. R. Cerfolio** (Birmingham, Alabama, USA): The irrigation is very interesting, so I want to revisit that question. We’re now doing some thymoma work robotically (the ones that you can tell you can resect) to decrease the morbidity, and although the robotic operation is spectacular, I still worry about spreading tumor cells, just like I worry when I do them open, and so we irrigate with water. Now, I’m not talking about your stage IVs, and I know you don’t have evidence-based medicine and data to answer this, so I’m really interested in your opinion. I’m giving you your chance here to give us your opinion. Would you recommend this type of irrigation for a thymoma that you have resected to help prevent drop metastases, and, if so, what about the reoperation and the adhesions from the Betadine?

**Dr. Belcher:** You mean to irrigate centrally in the mediastinum?

**Dr. Cerfolio:** At the end of the procedure, I have resected a 3 cm thyma and I want to irrigate the chest. Now, instead of just irrigating with warm water, as I have been, should we irrigate with warm water and Betadine, and, if so, what are the advantages and disadvantages? Just your opinion.

**Dr. Belcher:** I’m not sure of the advantages, whether that will work. I don’t know. Obviously sometimes the stage IV thymoma isn’t actually in the pleural space, and if we’re only in the mediastinum, we haven’t opened the pleural space, then maybe it would prevent.

**Dr. Cerfolio:** Well, if you are doing it robotically, you’re in one pleural space or the other, so you’re working in a pleural space.

**Dr. Belcher:** Yes, and I suppose that’s the most likely perhaps, then, to seed, yes. I would say that I don’t see any disadvantage to doing that. As I say, we use this routinely in all of our young pneumothorax patients. It adds very little time to the procedure. I think that there is one adverse incident reported in the literature. I think that there would be no disadvantage in doing it.

**Dr. Cerfolio:** What about the adhesions? What about the pleural symphysis that you would see from irrigating with Betadine? Don’t people use that as a sclerotherapy?

**Dr. Belcher:** They do. At Guy’s we undertake a lot of mesothelioma work. All of those patients have had talc pleurodesis. It’s a difficult operation, but I think it’s not impossible. If it stops some patients coming to the operation, then it would probably be worth persevering a bit longer in those patients.

**Dr. Van Schil:** Dr. Lang-Lazdunski, I think you want to make a comment on the use of this therapy as adjuvant therapy.

**Dr. L. Lang-Lazdunski** (London, UK): Just a comment, yes. You do sometimes see these thymoma patients who have had a biopsy done thoracoscopically and they come back with a pleural implant. So there is a real potential for the tumor to spread when you do a thoracoscopic biopsy, and in this instance I would strongly recommend the irrigation and the Betadine. I think abdominal surgeons have accumulated a good experience with peritoneal lavage and, considering that amount of evidence and the work of others like Walter Weder’s group in mesothelioma, with Betadine, it’s cheap, it’s easy, and honestly, I think you and he and most surgeons in this room can face the adhesions induced by Betadine if you have to reoperate. That’s never a big deal.

**Dr. Van Schil:** Would you consider the use of local chemotherapy irrigation?

**Dr. Lang-Lazdunski:** As you think chemotherapy is difficult, the setup is difficult. You can induce several complications – permanent renal failure, etc. When you put in balance Betadine and cisplatin, for me the choice is made really.

**Dr. F. Detterbeck** (New Haven, Connecticut, USA): I used to irrigate routinely with sterile water until I read a very well-done study that demonstrated that you had to leave cells in the water for at least 15 min or else it had absolutely no effect, and I’m sure that Rob Cerfolio doesn’t have that kind of patience. I know you left it in for 15 min, but do you think that with the Betadine this is not necessary?

**Dr. Belcher:** I don’t know of any evidence of time to effect really.

**Dr. Detterbeck:** Well, it would be an easy study to do. Just get some cells and put them in a dish and see what happens in 2 min and 15 min.

**Dr. L. Lang-Lazdunski:** There were three cases of permanent blindness reported with Betadine in the New England Journal of Medicine, but honestly, I’ve been using Betadine for 20 years for irrigation of the pleural space after pleural abrasion and I’ve never seen such a complication.

**Dr. M. Lucchi** (Pisa, Italy): I have a comment about what Dr. Cerfolio said, because if he has concerns about pleural seeding from thymoma, as I also do, I think that we should discuss whether a transpleural approach to the thymoma is right or not, first of all. Second, in my centre we are also using intrapleural chemotherapy for pleural relapse from thymoma, but I have some concerns when you do an extended resection, because when you do intrapleural chemotherapy, you will do the washing and there will be some pressure, and I’m sure that some fluid goes through the diaphragm to the peritoneal cavity, and I have already seen some cases of peritoneal relapse or retroperitoneal metastasis. So I’m not sure in cases where you are doing a diaphragm resection that intrapleural Betadine irrigation is the right way. Can you comment on that?

**Dr. Belcher:** I think once you’ve decided that the diaphragm is involved arthroscopically and you’re going to communicate it to the second pleural space, and whether you seed with blood that’s spilled at the time of surgery or whether you wash with water or Betadine, I think there is always a chance that you will seed into that second space, but at least if you are washing with Betadine, hopefully you are at least necrosing some of those cells that would undoubtedly pass through that diaphragmatic space.

eComment: The crucial role of multimodality management of stage IV thymoma

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We read with great interest the article by Belcher et al. [1] describing their experience in multimodality treatment of stage IVA thymoma. This is a very controversial issue and, to date, only a few series [2–3] have investigated the role of surgery as part of multimodality treatment, the exact choice of surgical procedure being an ongoing challenging subject of debate. The authors reported very interesting results of this experimental multimodality protocol, especially in terms of morbidity and survival. Nevertheless the selection criteria of the population (six patients) seem to be not completely adequate. Indeed, as reported by the Authors, ‘three patients had previously undergone surgery to resect thymoma...’ and, therefore, they were affected by a recurrent thymoma and reassigned as Masaoka stage IV for pleural dissemination. This confounding information could heavily influence data analysis (clinical selection bias), the survival outcomes of the recurrent thymomas being substantially different from the initial stage IVA. On the other hand, the good results in these three cases of recurrent thymoma seem to suggest, as previously reported [4], the feasibility and effectiveness of the iterative surgery in the management of thymoma recurrence. Apart from this selection bias, the article offers the reader valuable information about stage IVA thymoma treatment. When surgery aimed at total removal is performed for stage IVA thymoma, a ‘complete resection’ (defined as macroscopically complete resection of pleural dissemination) is very rarely achieved and even after ‘complete resection’, the recurrence rate is very high, ranging from 33% to 80% [5]. Inspired by this topic, we have reviewed our long-term database of surgically treated thymoma, finding a 71.4% recurrence rate (10 of 14 cases) in IVA thymoma patients with a particular recurrence pattern (80% pleural recurrences). These data clearly suggest that surgical ‘complete resection’ for pleural dissemination is a considerably uncertain procedure. In this setting, all the complementary therapies, such as intraoperative hyperthermic pleural irrigation, take on a particular relevance in order to achieve better local control. For this reason, and based upon the data we have reported, we promote further investigations and warmly advocate the validation of multimodality treatment in stage IVA thymoma.

**References**


