Primary chest wall chondrosarcomas: results of surgical resection and analysis of prognostic factors†

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Abstract

OBJECTIVES: Wide surgical excision with tumour-free margins is the mainstay of therapy for primary chest wall chondrosarcoma (PCWC). Few studies on treatment outcome and prognostic factors of PCWC requiring chest wall resection are available. We analysed our experience on surgical treatment of PCWC with emphasis on survival and recurrence prognostic factors.

METHODS: From 1986 to 2012, 89 patients (65.2% males, median age 55 years) with PCWC were operated on. The median tumour maximum diameter was 7 cm (range 2–30 cm).

RESULTS: We performed 23 sternectomies and 66 lateral chest wall resections (median ribs resected: 2; range 1–7). Resections were extended to lung (n = 19), diaphragm (n = 13), vertebral body (n = 6) or clavicle (n = 1). Negative margins were obtained in 85.4% of cases. Chest wall reconstruction was obtained mainly by prosthetic non-rigid or rigid materials and muscle flap coverage. In the last years, 3 patients received a sternal replacement with cadaveric allograft, and 2 had a chest wall reconstruction with titanium bars and 17 with a rib-like prosthesis. Perioperative mortality and morbidity rates were 0 and 12.4%, and 5- and 10-year overall and disease-free (on R0 resec-

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INTRODUCTION

Chondrosarcoma, although rare (annual incidence of about 2–3 cases per million in the adult population), is the most common bone sarcoma in adults with a predilection for central (pelvis) and axial (femur) parts of the skeleton [1]. Fifteen percent of chondrosarcomas are located in the thoracic cage, making it to be the most frequent primary malignant chest wall tumour [2]. The treatment for this tumour has not improved or changed over time: chondrosarcoma is relatively radio-insensitive and most of chemotherapeutic regimens are ineffective. Therefore, the radical surgical resection with wide margins represents the cornerstone and the only curative option in the treatment of this chest wall tumour [2, 3]. The requirement of broad tumour-free margins often leads to the necessity of complex chest wall resection and reconstruction techniques, particularly when the tumour is of large diameter or is located posteriorly next to the vertebral or involves the sternum. For these reasons, an early diagnosis when the tumour is small increases the possibility of a curative treatment, minimizing the need for extended resections. In addition, the recent advances in prosthetic and biological materials, and the evolution of surgical techniques have increased the options for reconstruction, improving the chance of radical resection, allowing a better maintenance of chest stability with the reduction of respiratory dysfunction and reducing the risk of infection [4–6]. Due to its rarity, very few institutional reports with few cases [2, 3, 7–9] and only a population-based national study [10] with about 100 cases have been reported on primary chest wall chondrosarcoma (PCWC), making it difficult to analyse the outcome, the prognostic factors and the evolution of
treatment. The aim of our study was to review the experience on surgical treatment of PCWC, evaluating the surgical and clinical short- and long-term results and trying to identify prognostic and clinical risk factors for local recurrence and metastases.

**MATERIALS AND METHODS**

We reviewed the data of 89 patients (58 males and 31 females, median age 55 years, range 15–82 years) affected by PCWC and operated on during a period between 1986 and 2012 in four Italian Thoracic Surgery Units (Istituto Nazionale Tumori in Milan, University Hospital in Padua, Azienda Ospedaliera San Camillo Forlanini in Rome and University Hospital in Siena). The following data were registered: gender, age, localization, tumour size, histological grade, type of resection and reconstruction, surgical margin, induction and adjuvant treatments, recurrence and survival. Tumour size was designated by the greatest dimension as measured from the surgical specimens. Diagnostic work-up included a standard chest X-ray and a total body computed tomography (CT) scan in all cases, to delineate the extent of the bone, soft tissue, pleural and mediastinal involvement and to exclude a disseminated disease. When appropriate, magnetic resonance was used (suspicion of spinal cord, mediastinal or thoracic outlet involvement). Since 2000 a positron emission tomography-CT scan was added to the work-up. All patients were treated surgically and the histological diagnosis was made by a preoperative or intraoperative biopsy. The sites of the tumour were: the ribs in 60 (67.5%) cases with a median of two ribs involved (range 1–7), the sternum in 19 (21.3%) cases, the ribs and spine in 6 (6.7%) cases, and the ribs and sternum in 4 (4.5%) cases. The surgical policy in treating PCWC was, in general, as follows: skin incision including the site of the previous biopsy, the invaded skin or previously irradiated tissues; in case of lateral chest wall localization a wide resection including the affected ribs with at least 3-cm free margin proximally and distally to the tumour was performed. In the event of a sternal involvement, the type of resection depended on the dimension and the location of the tumour and, in all cases, resection included the adjacent sternocostal cartilages on each side. Partial sternectomy was defined as the resection of <90% of longitudinal diameter; subtotal sternectomy was defined as the resection of the majority of the sternum sparing a small part of the manubrium with sternoclavicular joints; and complete sternectomy was considered the entire sternal resection comprising the sternoclavicular joints and the medial part of clavicles. When the tumour invaded the posterior area involving the vertebral or the adjacent intrathoracic structures, an attempt of resection extended to any other structure invaded was tried. The resection was considered complete or radical if surgical margins were macroscopically and microscopically free from tumour and incomplete if margins were macroscopically intraluminal or microscopically positive. Owing to the retrospective fashion of the study we were unable to define radical resection as wide (>2 cm margin free from tumour) or marginal (<2 cm margin free from tumour) as suggested by Enneking et al. [11] and reported in other studies [10]. Resection and reconstruction were performed as a one-stage procedure in all cases; the type of reconstruction and the materials used varied on the basis of extension and location of the surgical resection and over time with the introduction in clinical practice of new materials. Non-rigid prostheses included: 2-mm expanded polytetrafluoroethylene (ePTFE) patch (Gore Dualmesh Plus, W.L. Gore & Associates, Flagstaff, AZ, USA), polypropylene (Marlex) mesh (Bard, Inc., Murray Hill, NJ, USA or Chevron Phillips Chemical Co, The Woodlands, TX, USA) or Prolene mesh (Ethicon, Inc, Sommerville, NJ, USA) (Fig. 1A and B). As rigid prosthetic materials we used mostly Marlex mesh–methylmethacrylate sandwich. Other materials were: titanium bars and screws (SynthesTM, Solothurn, Switzerland) associated with a non-rigid mesh [5] (Fig. 1C and D) and recently, at the University of Padova, the cryopreserved allograft of cadaveric sternum with attached costal cartilages [6]. The bone graft was harvested from a suitable donor under a complete aseptic technique and treated with antibiotic solution for 72 h at +4°C and then submitted to cryopreservation at ~80°C. These processes guarantee the sterility of the graft and the absence of immunogenic capacity. On ordering, the graft was thawed and transferred inside double sterile bags in an ice container (with this protocol the graft can be stored in the refrigerator at +4°C for a maximum of 1 week). At the time of use, the graft was taken out of sterile bags and washed with saline solution. The graft was tailored to perfectly fit the defect and fixed with titanium plates and screws above at the level of manubrium in case of a subtotal sternectomy or clavicles in case of a total sternectomy, and to the ribs bilaterally (Fig. 2A and B). Since 2004, the ‘rib-like’ technique has been used by the Istituto Nazionale Tumori in Milan [4]. This technique is based on three principles: (i) to reconstruct the entire sternochondral plate or lateral chest wall, reproducing sternocostal joints or ribs, (ii) to maintain permeable intercostal spaces and (iii) to reproduce the tridimensional shape of the resected specimen. To achieve these goals, a mid-size chest aluminium cast was obtained from a plaster mould reproducing, in negative, costal arches and the sternum, and all prostheses were modelled using this cast. The sternal or costal prosthesis is obtained with a three-step process lasting ~20 min. First, a polyester multifilament knitted mesh (Surgimesh Pet, Aspide Medical, La Talauderie, France) is stretched over the cast; once fixed, the prosthesis shape is designed over the mesh. Then, a radiopaque acrylic resin (Menec Cranio, Tecres Medical, Verona, Italy) is modelled over the mesh, filling the sternocostal tracks of the cast. Finally, the prosthesis is further reinforced by dripping and modelling methyl methacrylate resin (CranioPlastic Type 1 Slow set, DePuy International Ltd, Blackpool, UK) in the tracks. Once the exothermic reaction is completed, redundant mesh is cut away and the prosthesis is washed and fixed to the costal and, eventually, clavicular stumps (Fig. 2C and D). When required, a myo- or myocutaneous flap was used to cover the prosthesis, employing the latissimus dorsi, the pectoralis major and the serratus anterior muscle as the most frequent choice.

Overall survival was calculated from the date of operation to death or date of the last follow-up (June 2013) for those patients who survived; disease-free survival was calculated for those patients who received a radical resection from the date of operation to the date of the first evidence of recurrence.

Statistical analysis was performed with SPSS Statistics 22.0; data were expressed as absolute numbers, percentage, mean or median values. Survival curves were calculated with the Kaplan–Meier method; the log-rank test was applied for univariate analysis of factors predicting survival and the Cox proportional hazard test was used for multivariate analysis of survival and recurrence prognostic factors.

**RESULTS**

We performed 23 (25.8%) sternectomies: a partial or subtotal sternectomy was carried out in 18 cases; in 4 it involved the upper
part of the sternum with resection of the manubrium and the medial part of clavicles, in 14 it comprised the middle or lower body of the sternum and was extended to the ribs in 4 cases. A total sternectomy was required in 5 cases. Sixty-six (74.2%) patients underwent chest wall resections without sternal involvement: the median number of resected ribs was 2 with a range from 1 to 7. Resections were extended to the lung in 19 (21.3%), to the diaphragm in 13 (14.6%), to the vertebral body in 6 (6.7%), to the pericardium in 5 (5.6%), to the liver in 1 (1.1%) and to the clavicle in 1 (1.1%). Reconstruction of the anterior defect after sternectomy was obtained with rigid prosthetic materials in 15 cases (‘rib-like’ technique in 7 patients, Marlex mesh–methylmethacrylate sandwich in 4 patients, allograft of cadaveric sternum in 3 patients, and titanium bars and Marlex mesh in one case). Non-rigid prostheses were employed in 8 cases (4 ePTFE Dualmesh, 2 Marlex mesh and 2 Prolene mesh). Lateral chest wall reconstruction was not required in 22 (33.3%) out of 66 patients with small or posterior defects. The reconstruction was carried out with prosthetic materials in 44 (66.7%) patients: non-rigid \( n = 28 \) (63.6%) and rigid \( n = 16 \) (36.4%). As non-rigid prostheses we used a Prolene mesh in 11 cases, a Marlex mesh in 10 cases and an ePTFE patch in 10 cases. Rigid reconstruction was carried out in 10 cases with the ‘rib-like’ technique, in 2 cases with Marlex mesh–methylmethacrylate sandwich, in 2 cases with titanium bars and ePTFE Dualmesh, and in 2 cases with a vertebral body rigid stabilization with bars and screws. A myo- or myocutaneous flap was used in 37 (41.6%) patients to cover the prosthesis, employing most frequently the latissimus dorsi (46%), followed by the pectoralis major (37.8%), the rectus abdominis (8.1%) and the serratus anterior (2.7%) muscles. Surgery was performed after induction chemotherapy in 4 (4.5%) patients and chemo-radiotherapy in 1 (1.1%) patient; indications for induction therapy were: the presence of pulmonary metastases at diagnosis \( n = 2 \) or high-grade tumours with invasion of surrounding structures and doubtful resectability \( n = 2 \). The median dimension of the tumour was 7 cm (range 2–30 cm) and tumour-free margins were obtained in 76 (85.4%) patients. Histological examination showed a G1 tumour in 30 (33.7%) cases, G2 in 38 (42.7%) and G3 in 21 (23.6%) cases. There was no perioperative mortality. Complications were seen in 11 (12.4%) patients: 2 infections of the prosthesis that required a reintervention for removal, 2 prolonged cases of fever solved with antibiotics, 1 skin incision dehiscence, 1 pneumoencephalus, 1 pneumonia, 1 respiratory insufficiency requiring temporary tracheostomy, 1 atrial fibrillation, 1 seroma and 1 rupture of a titanium bar that was removed. Twenty-four (26.9%) patients received adjuvant treatment after surgery: 11 (12.4%) radiotherapy, 9 (10.1%) radio-chemotherapy.
and 4 (4.5%) chemotherapy; indication for adjuvant therapy were: incomplete resection, metastatic disease at presentation or dedifferentiated tumours. After a median follow-up of 74 months (range 4–323 months), 55 (61.8%) patients were alive (46 with no evidence of disease, 8 with local recurrence operated and 1 with metastatic disease to the lung operated) and 34 (38.2%) were dead (30 for disease recurrence and 4 for unrelated causes). Five- and 10-year overall survival rates were 67.1 and 57.8%, respectively; 5- and 10-year disease-free survival rates (calculated on 76 patients who received a radical resection) were 70. and 52%, respectively (Fig. 3). Favourable outcome (univariate analysis) was seen for G1 tumours ($P < 0.0001$), negative surgical margins ($P = 0.005$), no adjuvant treatment ($P < 0.001$) and diameter ≤6 cm ($P = 0.005$) (Figs 4 and 5). Independent predictors of better survival (multivariate analysis) were negative surgical margins ($P = 0.0001$), G1 tumours ($P = 0.02$), age ≤55 years ($P = 0.006$) and dimension ≤6 cm ($P = 0.006$) (Table 1). Thirty-nine (43.8%) of the 89 treated patients had local recurrence ($n = 15$), distant metastases ($n = 20$) or both ($n = 4$) of the chondrosarcoma. Hence, the local control rate for the thoracic wall was 78.7%. The median time to recurrence was 20 months (range 2–109 months), with distant metastases appearing earlier than local recurrence (median 17 vs 23 months). Twenty

![Figure 2](https://example.com/fig2.png)  
**Figure 2:** (A) Reconstruction of the chest wall after sternectomy by using a cryopreserved cadaveric sternum, (B) fixed with titanium bars and screws. (C) Reconstruction of the sternum and (D) the anterolateral chest wall by the 'rib-like' technique.

![Figure 3](https://example.com/fig3.png)  
**Figure 3:** (A) Overall and (B) disease-free survival curves.
patients were operated for local (13) or distant (n = 7) recurrence, 7 received chemo-radiotherapy, 11 were treated only with chemotherapy and 1 patient refused any treatment. The predictive factor of recurrence was histological grading (Table 2). No predictive clinical factors were found for local recurrence, while histological grade was found to be a predictive factor.
for distant metastases (odd ratio [95% confidence interval (CI)]: 0.04 [0.01–0.39]; P = 0.005).

**DISCUSSION**

Chondrosarcoma is the most frequent primary malignant tumour of the thoracic cage representing 40% of all chest wall tumours [1, 2]; despite that, it remains a rare neoplasm with an incidence of <0.5 cases per million persons per year. Differently from most other cancer forms, the results of treatment for PCWC have not changed or improved over time. There is still no effective induction or adjuvant therapy for chondrosarcoma as it is relatively radio- and chemoresistant. Studies on the mechanisms underlying this resistance are sparse. Expression of the multidrug-resistance-1 gene, P-glycoprotein, has been reported in most chondrosarcoma specimens patients had more than one extended resection.

Another hypothesis could be the large amount of extracellular matrix in this tumour, acting as an obstacle to the access of anticancer agents. Moreover, chondrosarcoma grows quite slowly, and most conventional chemotherapeutic agents work at actively dividing cells. In this context, surgery is so far the only effective form of treatment for PCWC, regardless of the size or histological grade of the tumour, as long as it is resectable [2, 3, 10]. Few studies are available on PCWC, most of them accounting for a few cases and being mono-institutional. There is a general agreement that the long-term results are relatively favourable with a reported 5-year survival rate ranging between 64 and 80% [2, 8, 10, 15]. Our results are in line with a 5-year overall survival rate of 67.1% and a complete resection disease-free survival rate of 70%. The best results are obtained when the resection is radical and includes wide (at least 3 cm) tumour-free margins [2, 3], as also reported by the recent series of the Scandinavian Sarcoma Group, with a 10-year survival of 92% in patients operated with wide margins compared with 47% for those with intralesional resections [10]. In our series, a radical resection was obtained in 85.4% of cases and the type of resection was the strongest independent predictor of survival (5-year survival rate of 78% for radical resection versus 15% for incomplete resection). A surgical resection with wide tumour-free margins is not always fulfilled, and accounts for the high incidence of postoperative local recurrences (28% of 84 cases treated at the Sloan-Kettering Cancer Center, 34% of 97 cases in the Scandinavian Sarcoma Group study, 26.7% of 15 cases treated at Rizzoli Institute, 21.3% of 89 cases in our series) [2, 3, 10]. The possibility of obtaining a radical resection depends on several factors: the localization of the tumour (difficult in the paravertebral area), the involvement of mediastinum, lung or vertebrae and the dimension. In our study the median tumour diameter was 7 cm, comparable with 8 cm reported by Widhe et al. [10]. The relative large median diameter of the tumour requires more complex and extended resections not always feasible in safety; this could explain the statistical significance of the wide diameter of the tumour (in our case >6 cm) in predicting survival. These findings underline the importance of an early diagnosis in order to allow radical resection and reduce the risk of recurrence. The results depend also on the histological grading that reflects the biological aggressiveness of the disease. According to cell differentiation, Campanacci et al. [16] grouped malignant progression into three grades: Grade 1, consisting of well-differentiated cartilaginous cells with rare and doubtful aspects of atypia; Grade 2, presenting with some atypical cells; and

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<th>Table 2: Prognostic factors for recurrence (on R0 patients): Cox analysis</th>
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<td><strong>Recurrence/number of patients</strong></td>
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<td>Extended*</td>
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<td><strong>Histological grade</strong></td>
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OR: odd ratio; CI: confidence interval.
*Some patients had more than one extended resection.
**P-values obtained by applying the Cox simple regression model.
**P-values obtained by applying the Cox multiple regression model.
Grade 3, comprising scarce cartilaginous cells in a context of predominant atypia. In our series, the 5-year survival rates for Grades 1, 2 and 3 were 97, 57, and 39%, respectively, and the grading was a significant predictor of survival. Histological grading was also a significant prognostic factor for distant recurrence: similarly to the Scandinavian experience in which high-grade tumours predicted an increased risk of local recurrence [hazard ratio (HR): 2.8; 95% CI: 2.2–3.5, P < 0.01] and metastasis (HR: 3.4; 95% CI: 2.3–4.5, P < 0.05), also in our patients distant recurrences were significantly more frequent in dedifferentiated tumours with G2/G3 tumours collecting the 90% of total distant metastases. A radical surgery represents the cornerstone in the treatment of PCWC; however, to achieve this goal and to reduce the risk of postoperative complications, resection and reconstruction techniques have to respect some principles: a radical resection should be associated with the maintenance of chest stability, to allow adequate respiratory dynamics without inducing harmful paradoxical movements, and with an acceptable cosmetic result [17]. Consequently, a critical point, particularly in anterior chest wall resections, is a suitable prosthetic replacement, able to restore the rigidity of the chest and to prevent paradoxical motion, and a healthy soft-tissue coverage able to seal the pleural space, to protect the viscera and great vessels and to prevent infection [17–19]. As non-rigid prosthetic materials, the most commonly used are Marlex mesh and ePTFE [17–21]: the choice of prosthetic material is usually based on the surgeon’s preference, and Deschamps et al. [20] have shown no significant difference in the postoperative outcome or in complication rate because of this choice. In our series, Marlex meshes were used in the first experience and lately ePTFE has been preferred for its malleability and above all for its antimicrobial properties. In the case of large anterolateral chest wall defects or in the case of a complete sternectomy, a reconstruction with rigid material is mandatory to restore chest-wall stability, to maintain the geometry of the thoracic cage and to guarantee an adequate protection of the surrounding structures [22, 23]. The use of Marlex-methacrylate prostheses in the first part of our series, improved the geometry of the reconstruction compared with non-rigid reconstruction and afforded three of four ideal characteristics of prosthetic material, according to LeRoux and Shama [24]: rigidity, malleability and radioluency. The fourth ideal, inertness, was still lacking, because rigid shields do not allow ingrowth of fibrous tissue and limit integration of muscle flaps, thus increasing dead spaces and the likelihood of infection. Moreover, in case of wide resections, a large prosthesis enormously increases the rigidity of the chest and, consequently, patient discomfort. On this basis, the centres involved in this study worked on different techniques or used new materials in order to expand the possibility of rigid reconstruction and to improve biocompatibility, overcoming the two major problems of respiratory failure and local infection. The ‘rib-like’ reconstruction, such as the use of titanium bars and the cryopreserved allograft of cadaveric sternum, were technical evolutions developed to obtain a biocompatible prosthesis able to protect the mediastinum and reproduce the best possible tridimensional sternocostal anatomy, together with a certain degree of respiratory movements. Once the chest wall has been stabilized, a soft-tissue coverage may be used to complete the reconstruction and to control infection, obliterate dead space, and cover and separate the synthetic material. A variety of muscles or musculocutaneous flaps have been introduced over the years; in our series, the soft tissue transfer was always performed in close interaction with a plastic surgeon, involved in the preoperative selection of the flap as well as in the surgical procedure. Pectoralis major was the most frequently selected muscle after sternectomy, because of its proximity, reliability and versatility; and as described also by other authors, it was used unilaterally or bilaterally, with skin advancement or as a musculocutaneous flap [22, 23]. Latissimus dorsi flap transposed on thoracodorsal vessels was the preferred choice for anterolateral chest wall defects, because of its length and bulk that provide extensive coverage [17–21, 25].

**CONCLUSION**

Despite the progress in multimodality treatments, PCWCs are still resistant to most medical treatments; therefore a wide surgical resection with tumour-free margins is necessary to minimize local recurrence and to improve long-term survival. In addition to radicality, our experience found the grading of the disease, the dimension and the age as significant prognostic factors. The evolution of the surgical technique and the introduction in clinical practice of new prosthetic materials allowed larger resections, and safe and anatomical reconstruction. Efforts should be continued in the direction of more functional and individually tailored chest wall prostheses and of molecular study for targeted therapy.

**Conflict of interest:** none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr E. Fletcher (Rennes, France): First of all, I would like to apologize for Dr Fadel not being here today for personal reasons, and he asked me to read his comment.

Dr Marulli and his colleagues report a large series of patients who underwent resection and reconstruction for a rare disease, primary chest wall chondrosarcoma. This multicentre and retrospective study covers a period of 26 years. It is well stated in the manuscript that in this disease, chemotherapy and radiation therapy are quite ineffective, and complete of 26 years. It is well stated in the manuscript that in this disease, chemotherapy and radiation therapy are quite ineffective, and complete resection of large primary malignant tumors. Eur J Cardiothorac Surg 1994;8:351–7.

Dr R. Milton (Leeds, UK): I have just a quick practical question, if I may. You did remove the Surgimesh that shapes the intercostal area, so it is a non-rigid prosthesis, and the resin that is used the DualMesh PTFE because there is also the antimicrobial layer.

Dr D. Simansky (Tel Hashomer, Israel): You had a large number of local recurrences, 39, and you speak about wide margins. Did you see any historical development over time, that as your margins got wider, you got less local recurrence, and do you take frozen sections and then continue the excision?

Dr Marulli: Regarding local recurrence, it was not 39 cases. It was 15 cases, mostly related to incomplete surgical resection, particularly on the vertebral area, or, in the past, very big, extensive resections that were considered not safe to reconstruct when we used the Marlex mesh. Now the resections are very large, and probably only the posterior area is the most difficult area to be radical. Finally, only two patients had a local recurrence after macroscopically and microscopically complete resections. We didn’t do frozen section because it is difficult to have a reliable response because sometimes there is bone that is difficult to analyse.

Dr Simansky: And you had two cases of infection. How did you deal with those?

Dr Simansky: You had two cases of infection in the prosthesis.

Dr Marulli: Yes.

Dr Simansky: Did you remove them?

Dr Marulli: Yes. One was a Prolene prosthesis and one was a methylmethacrylate sandwich.

Dr Simansky: How soon after the surgery did you remove the prosthesis?

Dr Marulli: Immediately, and it was not simple, particularly for methylmethacrylate, and in one case we used a new reconstruction with titanium bars only. They did well.

Dr R. Milton: Have you had just a quick practical question, if I may. You did a number of partial sternectomies. What margin do you need in those cases?

Dr Marulli: Usually at least 2 cm.