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Indications and results of sternal allograft transplantation: learning from a worldwide experience

Running head: allograft sternochondral transplantation

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Abstract

Background: Reconstruction of the anterior chest wall defect after sternectomy is a challenge for cardiothoracic surgeons. In 2010 the Padua group published the first case of cadaveric sternum transplantation after sternectomy. This multi-center study reports the clinical indications, early and long-term results of sternal chondral allograft transplantation.

Methods: This is a retrospective multicentre-study from seven Academic-Centres. Demographic data, surgical indications, technical details, early postoperative results were collected. The complications, long-term stability and tolerance of the allografts were also analysed.

Results: Between January 2008 and December 2019 58-patients underwent sternectomy followed by reconstruction using cadaveric-cryopreserved sterno-chondral allografts. Thirty-two patients were males, with a median age of 63.5 years(IQR50-72). Indications for sternectomy were secondary sternal tumors(n=13), primary sternal tumors(n=15) and non-neoplastic disease(30). Thirty patients underwent total sternectomy, 16 lower-body sternectomy and 12 upper-body-manubrium resection. The 30-days mortality was 5%. The overall morbidity was 31%. Six early reoperations were necessary because of bleeding(n=1), titanium-plates dislocation(n=1) and re-suture of the skin in the lower part of the incision(n=4). Overall, the 5-year survival was 74%. The surviving patient's reconstructions are stable and free from mechanical or infective complications.

Conclusions: The main indications for sternal allograft implantation were complex post sternotomy dehiscence followed by primary or secondary tumor involvement of the sternum. The collected results demonstrate that sterno-chondral allograft transplantation is a safe and effective method in reconstructing the anterior chest wall after sternectomy. Further studies to demonstrate the integration of the bone grafts into the patient's sternal wall will be made.

Keywords

Chest-wall, sternum, bone allograft, sternal transplantation, sternal tumor, post-sternotomy complications.

Sternal surgery requires a complex and multilevel approach. The problems faced by the surgeons include re-establishment of the mechanical properties of the chest wall, sustaining the ability to support respiratory efforts. Stability is a requisite to prevent resultant seroma, and infection, and maximize bone incorporation into the surrounding structures[1]. Different materials and techniques have been used for sternal reconstruction and replacement, but a gold standard technique and an ideal material have still to be identified[2,3]. In 2010 the group of Padua[4] published the first case of cadaveric sternal replacement after sternectomy for a large chondrosarcoma. Since these first successful experiences, diverse groups from all over the world have utilized this technique[5,6,7,8,9]. This multi-center study collects many of the known cases of sternal allograft transplantation performed throughout the world. Its goal is to delineate the indications and discuss the operative, perioperative, and long-term results.

Material and Methods

Between January 2008 and December 2019, 58-patients underwent sternal substitution or reconstruction using cadaveric cryopreserved sternal allograft at seven academic centers. Among them, 4 centers are general-thoracic units, 1 center is a cardiac surgery unit, 1 center is a cardiothoracic surgery unit and 1 center is a plastic surgery unit. The median number of allograft implantations for each center was 8 (range1-18,mean8.29±7,IQR2-17). A median number of 5 cases per year were performed during the 12-year study period (IQR4-6mean 4.8±1.6,range1-7). The distribution of allograft implantation over the indicated time period is shown in figure.1. The medical records of all patients were examined retrospectively. The preoperative data collected included patient demographics, comorbidities, previous surgical interventions or medical treatment. We obtained the surgical data from operative reports. Peri-operative morbidity was considered within 30-

days from surgery. All specific complications related to the chest wall reconstructions were included. The process of allograft procurement and the surgical techniques have been previously detailed in papers describing the surgical procedure[10,11]. Patients who underwent sternal reconstruction for neoplastic disease were followed with outpatient visits and computed tomography(CT)-scan at 3,6 and 12-months for the first year and then once a year for at least 5-years. Patients that underwent reconstruction for non-neoplastic disease were followed for 3-years.

Statistical Analysis

Categorical variables were presented as counts and percentages, and comparison were conducted using Fisher’s exact test. Continuous variables were presented as median with interquartile range(IQR) and/or mean±standard-deviation(SD), and comparisons were conducted using the Mann-Whitney-u-test. We used the Kaplan-Meier method for survival analysis and the long rank-test was used to compare groups. $P<0.05$ was considered statistically significant. All the statistical analyses were performed using SPSS.20.0 for windows.

Results

Patients

There were 32-male patients(55%) and 26-female patients(45%). The median age was 63.5years(IQR50-72,range5-81)(table.1). The indications for allograft sternal reconstruction were: primary sternal tumors in 15-patients(26%), secondary sternal tumors in 13-patients(22%)(table.2), other non-neoplastic conditions in 30-patients(52%), in particular post sternotomy dehiscence in 25-patients(table.3). Among them 13 had at least a previous sternal revision, and in 6 Robicsek procedures requiring more complex sternal reconstructions. A total of 23 patients(77%) had documented preoperative wound infections. Nineteen of these patients(63) were treated preoperatively with a vacuum-assisted closure device(VAC) for a median of of 8-days(IQR6-12).

There was a distinct difference between the preoperative characteristics of the group of patients that had non-neoplastic pathology requiring sternal reconstruction and the patient population who had neoplastic disease. The patient group without neoplasm was older(p=0.02), and more obese(p=0.01) than the patients who were known to have neoplastic disease. The most common symptoms in the patients who had neoplastic disease were pain and swelling 93%vs63%. Instability and pain were the most frequent presenting signs in the case of non-neoplastic conditions (90%vs0%)(table1).

In the neoplastic group, 97% of the patients had a preoperative pathological diagnosis achieved by needle biopsy in 20 patients(72%) and by open biopsy in 6 patients(21%). Prior pre-operative therapy was given to 25-patients: 12 received chemotherapy, 9 radiotherapy and 4 chemo/radiotherapy. At pathological analysis, the median tumour dimension was 6.25 cm(range3-43). The most common histology for primary sternal tumors was chondrosarcoma(53%). Metastatic breast cancer represented the large percentage of secondary sternal tumors(46%).

Surgical data

We report the details of the procedures in table.4. A total sternal replacement/reconstruction with allograft was performed in 30-patients: 25-had post sternotomy complex dehiscence;2 had neoplastic involvement of manubrium and the sternal body; 1-patient had a post radiation necrosis; 1-patient, drug-addicted, had a

sternal osteomyelitis; in 1-patient, with a very small chest, a full sternal allograft was used to enlarge the chest cavity to fit a Cardiowest-Artificial-Heart[12].

A subtotal reconstruction of the sternum was performed in 28-patients: 12 underwent reconstruction of the manubrium and partial sternal body(21%) and 16 received a partial sternal body reconstruction(28%). Subtotal sternectomy and partial allograft reconstruction was performed in 26-patients with localized neoplastic involvement of the sternum and in 2-patients with other benign conditions. By comparing the two groups we have seen how in the case of neoplastic pathologies a subtotal replacement of the sternum was used more frequently(94%), while in the case of non-neoplastic pathologies the replacement of the sternum was total in 93% of cases, in particular in post-sternotomy dehiscence. The median operative time was 154-minutes(IQR111-162), the sternal allografts were fixed to the recipient chest wall with a median of 4 titanium bars/pts(range2-8) without statistical difference between groups(figure.2A). The removal of other thoracic structures as well as the sternum was more frequent in the group of patients with neoplastic pathologies(p=0.001). The ribs were the most frequent structure resected with a median of 4-ribs/pts(range1-12), followed by clavicles in six patients that underwent manubrium resection. Other resected structures were thymus, brachiocephalic and caval vein, pericardium, breast, and lung parenchyma. In oncologic patients, we report 2 R+ resection(1-R1,1-R2). In 50-patients(86%), the sternal reconstruction was covered with vital tissue represented by pectoralis major muscle flaps in 78% of the cases, latissimus dorsi flap 5%, rectus abdominis 7%, pectoralis minor 2%. Seven patients completed the reconstruction with a fascio-cutaneous flap. The use of a muscle flap has been more frequent in patients with non-neoplastic diseases(100%vs71% P=0.04). Omental transposition was used in two patients with post sternotomy sternal destruction with associated mediastinitis.

Post-operative results

Fifty-one patients(88%) spent at least one night in the intensive care unit(ICU) after surgery. The median ICU-time was 3-days(IQR1-9.5), the median hospital-stay was 11-days(IQR8-18). The group of patients with non-neoplastic diseases showed a longer duration of ICU stay(p=0.001), mechanical ventilation time(p=0.002) and hospital stay(p=0.03)(Table.5). Twenty-one major complications occurred in 18-patients(31%) within the post-operative period. The group of patients who had suffered a post-sternotomy dehiscence had a statistically higher incidence of post-operative complications (47%vs14%,p=0.01).

The most common complication was partial wound dehiscence of the lower pole(7%) treated with VAC-therapy followed by extra re-suture of the soft tissue and skin. Respiratory complications developed in 4-patients(7%). Muscle-flap hematoma due to vascular pedicle leakage requiring reoperation occurred in one patient. One patient felt off the bed hitting the thorax after 23-days from the operation. The titanium plates binding broke loose off the chest bones injuring the underlying soft tissue. During the surgical revision, the broken plates were removed, but the sternal graft was found stable and healed and thus was left in place. The incidence of early reoperation was higher in the non-neoplastic group, mainly related to surgical wound dehiscence (10%)(p=0.02).

The 30-days mortality was 5%(3pts), without statistical difference between groups. One patient with neuroendocrine thymic carcinoma died in the ninth post-operative day because of pulmonary embolism complicated by intravascular disseminated coagulopathy. Two other patients who had a previous cardiac operation complicated with sternal dehiscence and mediastinitis, died because of pneumonia and multiple organs failure.

Follow-up results

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After a median follow-up time of 52-months(IQR36-77), 42-patients were still alive. Overall 5-year survival was 74%; in neoplastic patients 5-year survival was 63% versus 79% for the non-neoplastic group(p=0.1). Nine patients died in the neoplastic group, 8 for disease relapse and 1 because of cerebral vascular accident. Four patients died in the benign conditions group: 3 of cardiovascular complications and 1 of sepsis. Regarding the neoplastic patients 11 received adjuvant therapy(7-chemotherapy,3-radiotherapy,1-chemoradiotherapy), 8-patients had systemic disease relapse (5-patients with previous breast cancer,1-patient with previous hepatocellular carcinoma,1-patient with previous kidney cancer and 1-patient with sarcoma). We documented no local disease relapse. Major complications occurred in 7-patients(13%). The major long-term complication was dislocation of the titanium bars and screws that occurred in 4 cases. Among them, two required re-operation after 21 and 32 months respectively because of complete bars dislocation, a good chest stability was preserved. One patient required the removal of the clavicular titanium plate and screws because of a partial dislocation after 4 months from the operation, with no consequence for the stability of the implant or arm movement. These three patients had undergone a partial sternal reconstruction enlarged to the ribs, thymus and clavicle in one case for neoplastic pathology. Only one patient with previous post sternotomy dehiscence undergoing complete sternal replacement was re-operated 19 months after surgery for partial dislocation of the bars and superficial infection of the surgical wound. He was treated with the removal of the mobile bars, followed by VAC-therapy(16-days) and then reconstruction of the soft tissues with fascio-cutaneous flap. Two patients complained of chronic post-operative pain syndrome requiring long standing analgesic treatment. No patients had respiratory impairment or flail chest. CT-scan reconstruction was performed after 3-months to evaluate the correct position of the bone-graft and titanium bars(Figure.2B). During the follow-up period, in order to evaluate vascularization and new bone formation in the allograft, 7-patients(13%) underwent fluorine-18-sodium-fluoride-positron-emission-tomography([18F]NaF-PET)-scans whereas 6 patients(11%) were studied with Tc-99 bone scintigraphy in two rounds, the first after year 1 and the second after year 2 from surgery. In all patients, we noted a reduction of the osteopaenic defects of the implanted allografts. In all cases the area of tracer accumulation was at the junction between native bone and the grafted bone(Figure.3).

Comment

A correct reconstruction should respect the following rules: respect the anatomy, preserve the function, adequate choice of materials and integration of multidisciplinary competences for complex reconstruction, using the mantra of form and function. Recently, according with the principles of biomimesis[13] the use of biological materials has gained popularity because of the optimal biocompatibility and their complete integration in the human tissue[3,13,14,15]. Marulli et al [16] reported the first multi-centers experience with the use of sternal allograft with good operative and mid-term results, confirming an excellent biocompatibility and a perfect integration of the allograft into the host.

The main indication for allograft transplantation in this series is post sternotomy complex dehiscence followed by primary or secondary tumour involvement of the sternum. In the group of sternotomy complications a full sternal allograft implantation is required because of the almost complete loss of the sternal bone due to degradation of the tissues, in particular if a previous attempts to repair were attempted, and because of the wound infection[5,17]. In the group of neoplastic pathologies a subtotal resection of the sternum was used in most cases but, the need to maintain safe resection margins, in particular in case of primary tumours may lead to the resection of other nearby structures, such as multiple ribs or the clavicles. Pericardium, thymus, lung, vascular structures were other structures that we removed due to oncological reasons.

Coverage with muscle flap or other vital tissue is strongly suggested. Sometimes pectoral muscles and subcutaneous and cutaneous island need to be resected en-bloc with the tumour. In these cases a more complex muscle transposition using latissimus dorsi, rectus abdominis with or without fascio-cutaneous flaps is necessary. We always cover the allograft with vascularized tissue in post sternotomy dehiscence cases. We used the pectoralis major in most of the cases, omentum was used to fill the mediastinum in two cases of purulent mediastinitis.

We report an overall surgical mortality of 5%. The reported post-operative mortality of sternal complicated patients after cardiac surgery range between 10% to 40%reflecting the fragility of these patients[5,17]. The literature shows the surgical mortality for chest wall surgery in the case of neoplastic diseases ranged between 2.3% to 7%[1,2,18,20] in line with our results.

Sternal resections and repair represent a subgroup of chest wall surgery in which the risk of post-operative major complications such as respiratory failure and local infection are increased[1,2,18,20]. This multicentre experience using the allograft sternal technique reports good results in terms of post-operative morbidity and mortality. We reported 31% of post-operative complications in 7% of the cases that were mainly related to skin dehiscence followed by respiratory complications such as pneumonia or atelectasis. Respiratory complications following chest wall surgery were described occur in up to 24% of the patients[21]. The post cardiac surgery sternal dehiscence are much more fragile compared to neoplastic patients. Indeed, they are older, more obese, they have more preoperative comorbidities. They represent a subsection of post-surgical complicated patients with an increased requirement of ICU facilities, mechanical ventilation and overall in-hospital stays. Moreover, the use of sternal allograft implantation is reserved to patients with complex sternal dehiscence that frequently had one prior attempt at sternal reconstruction and thus they represent a high-risk sub-population of post sternotomy dehiscence[22]. These considerations could explain the major incidence of post-operative complications and surgical revisions in non-neoplastic patients, however, it does not affect perioperative mortality. Our favourable results may reflect a very stable reconstruction of the sternum with no incidences of post-operative flail chest. In cases of patients with chest instability after sternotomy, a stabilized reconstruction of the chest wall quickly improved the respiratory dynamic.

Specific complications related to the surgical technique were very rare and generally could be considered as minor complications such as seromas(3%) and wound dehiscence(10%). These complications are reported to occur in a range between 7% to 46% of the patients in the major series[19,20,23]. An early implantation failure with the necessity for reoperation was reported as secondary to chest wall trauma after a fall. In particular, in the post sternotomy group preoperative surgical wound infection was documented in (the) 77% of the cases. The postoperative reinfection rate was very low: indeed, two patients were successfully treated with post-operative VAC-therapy after wound dehiscence with positive swabs. In literature the risk of reinfection and reconstruction failure in case of complex post sternotomy cases is well documented[5,17,19,22], confirming that the use of the sternal allograft technique is very effective and safe to treat sternal instability and to reduce the risk of reinfection.

In the literature, in cases of chest wall reconstruction for malignancy, the incidence of implanted material infection is between 3.3% to 23%, but It is much higher in cases of post sternotomy reconstruction and the need to remove the prosthesis ranges from 1.6% for biological materials to 13% in a case of a totally synthetic reconstruction[1,2,3,14,18,20]. In our experience, during the follow-up period, infection of the allograft never occurred and the sternal allograft was never removed.

The possibility of being integrated into the host skeleton and regaining the osteogenesis process and the capacity to grow are important features of bone allografts[24]. However, a

stable anchorage and direct bone to bone contact of the implanted sternum is fundamental to facilitate this process; it can be achieved with a perfect preoperative donor-recipient match facilitated by the use of dedicated imaging software or 3D-printing of the involved bone segment as reported by the Bologna Group[25](figure.4A,b). Similar results can be achieved by the use of crushed spongy bone to fill the gap between the residual edge of the sternum or ribs and the implanted graft as proposed by Kalab et al[5,17](figure.4C). The use of adipose derived stromal vascular fraction cells could be employed to maximize sternal allograft reintegration, as reported by Maliska et al[26]. The insertion of these cells into the allograft will increase the incursion of osteoblast, neutrophils, macrophages and fibroblast[27].

Several studies have demonstrated that 18F-NaF uptake reflects blood flow and bone remodeling after allograft bone implantation[28]. During the follow-up period, [18F]NaF-PET-scan, when available, or TC99-bone-scintigraphy examination were used to measure bone formation and graft incorporation into the existing skeleton and whether or not it was metabolically active. Our patients experienced higher SUVmax at the first PET-scan, this can be explained by the fact that uptake of tracer is higher in new bone formation due to a higher availability of binding sites. In all patients experienced tracer accumulation at the sites where graft and native bone were joined, demonstrating active bone remodeling at those sites. Follow-up complications related to the surgical technique were reported in our experience in four patients, mainly represented by titanium bars dislocation, among them, two patients with complete avulsion of the bars were re-operated. In both cases all the bars and screws were removed, the implanted bone appeared partially reabsorbed and substituted with thick fibrous tissue integrated into the chest wall. Probably, even if no new ossification

takes place in some patients due to unknown causes, the allograft is gradually replaced by dense fibrous tissue that still maintains optimal chest wall stability, but it loses the grip for the titanium screws facilitating bars dislocation. The risk of early reoperation appears greater in the post-sternotomy forms, in the long-term period three of the four re-operated patients underwent a sternal reconstruction enlarged to other mediastinal structures due to neoplastic pathology. The limited numbers of patients and their heterogeneity do not allow a statistically significant analysis, but it is likely that the enlarged resections and partial sternal reconstructions are at greater risk of instability of the titanium implants, perhaps due to a greater devascularisation of contiguous tissues and a greater tensile effort that the bars must sustain when large ribs and/or clavicle are also resected.

In oncologic patients, the use of allograft bone does not exclude the possibility of receiving adjuvant radiotherapy or interfere with radiological follow-up[10,16]. We report an overall 5-year survival of 65% in cancer patients that is comparable with literature data[1,2,18]. A radical resection was obtained in 93% of the cases, one R2-resection owing to residual disease on the aortic arch and one R1-resection of the surgical margin in a large malignant fibrous tumor of the sternum are reported. Recurrence happened in 8-patients. In particular, patients with previous breast cancer tend to relapse systemically more frequently(5/8pts). In this sub-group of patients, the role of surgery remains a matter of debate and should probably be considered only for palliation and local control of the disease[18].

Recently, new patient-customized metallic sternal substitutes have been reported advocating excellent functional and cosmetics results[29]. Nowadays, the main limit of the new sternal substitutes is the cost that ranges between 10.000 to 30.000euros per patient. Another advantage of allograft sternal replacement is the relative low cost, indeed the allograft sternum cost ranges from 800 to 1500euros. The cost of the titanium bars and screws accounts for an additional 1500euros per patient. The ideal material for sternal replacement should be not only biomimetic and safe for patients, but also efficient in terms of cost[5,13,14].

Conclusions

In this series the main indications for sternal allograft implantation were complex post sternotomy dehiscence followed by primary or secondary tumor involvement of the sternum. The results are excellent even in the case of infected surgical sites, with a negligible postoperative reinfection rate. The allograft is biologically tolerated and completely integrated into the host in a short period. In this multicenter experience the sternal allograft can be considered an optimal sternal substitute, it is a very effective technique with low technical morbidity and excellent overall long-term results.

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Table 1: Preoperative characteristics of the population

Characteristics	Tumor (28pz)	Non-neoplastic (30pz)	Overall	p-value
Age	56.5(IQR44-70)	69.5(IQR54-73)	63.5(IQR50-72)	0.02
Gender				0.06
-Male	10(36%)	22(73%)	32(55%)	
-Female	18(64%)	8(27%)	26(45%)	
BMI(kg/m2)	24(IQR21-26)	30(IQR27-37)	26(IQR22-29)	0.01
Comorbidities				0.01
-Hypertension	10(36%)	21(70%)	31(53%)	
-Dislipidemia	4(14%)	18(60%)	22(38%)	
-Diabetes	3(11%)	14(47%)	17(29%)	
-COPD	2(7%)	7(23%)	9(16%)	
-Polivasculopaty	4(14%)	16(53%)	20(34%)	
-Smoking History	8(29%)	19(63%)	27(47%)	
-CRF	-	4(13%)	4(7%)	
-IHD	4(14%)	23(77%)	27(47%)	
-Obesity	1(4%)	13(43%)	14(24%)	
-Hepatitis	1(4%)	2(7%)	3(5%)	
-Previous cancer	16(57%)	6(20%)	22(38%)	
-AF	1(4%)	7(23%)	8(14%)	
-More than 1-comorbidities	12(43%)	28(93%)	40(69%)	
Symptomps				
-pain	21(75%)	19(63%)	40(69%)	
-swelling	5(18%)	-	5(9%)	
-lost mobility	-	6(20%)	6(10%)	
-Chest wall instability	-	27(90%)	27(47%)	
-mediastinal	1(4%)	-	1(2%)	

compression				
-site infection	-	23(77%)	23(40%)	0.001
IQR:interquartile-range:BMI:body-max-index;COPD:chronic-obstructive-pulmonary-disease;CRF:chronic renal failure;IHD:ischemic-heart-disease;AF:atrial-fibrillation.				

Table 2: Pathology and oncologic data

Primary sternal tumors(15pts)		**Secondary sternal tumors(13pts)**	
Chondrosarcoma	8(53%)	Breast Cancer	6(46%)
Plasmocitoma	2(13%)	Ovarian Cancer	1(8%)
Malignant solitary fibrous tumor	1(7%)	Thyroid papillary Cancer	1(8%)
Liposarcoma	1(7%)	Clear Cells Cancer	1(8%)
Hemangioma	1(7%)	Hepatocarcinoma	1(8%)
Aneurismal bone cyst	1(7%)	Thymic carcinoma	1(8%)
Preoperative Diagnosis		27(97%)	
- Incisional biopsy		20(72%)	
- Needle biopsy		6(21%)	
Preoperative therapy		25(89%)	
- Chemotherapy		12(43%)	
- Radiotherapy		9(32%)	
- Chemo/Radio		4(14%)	
Median Tumor Dimension(cm)		6.25(Range 3-43;IQR4.8-12.6)	
IQR:interquartile-range.			

Table 3: Clinical data of the non-neoplastic group.

Non-neoplastic conditions(30-pts)	**N(%)**
Post-Sternotomy Dehiscence	25(83%)
Post-radiation necrosis	1(3%)
Poland Syndrome	1(3%)
Failed pectus excavatum repair	1(3%)
Osteomyelitis	1(3%)
Chest wall enlargement for VAD insertion	1(3%)
Previous surgical procedure	
- CABG	18(60%)
- Valvular	3(10%)
- Valve+CABG	2(7%)
- Bentall	1(3%)
- Heart Transplant	1(3%)
- Repair of chest wall deformities	2(7%)
- Sternectomy and reconstruction with marlex mesh	1(3%)
Preoperative surgical site infection	23(77%)
- Staphilo-spp	11(48%)
- Enterobacteriacee	9(39%)
- Pseudomonas-spp	6(26%)
- Klebsiellaspp	5(22%)
- Diphterioides	2(9%)
- Morganella	1(4%)
- Candida	1(4%)
- More than one species	14(61%)
Preoperative VAC-therapy	19(63%)
Days of preoperative VAC-therapy	8(IQR6-12)

VAD:ventricular assist device;CABG coronary-by-pass grafting;VAC:vacuum-assisted-closure IQR:interquartile-range.

Table 4: Operative-data

Variables	**Overall (tot:58pts)**	**Tumor (tot:28pts)**	**Non-neoplastic (tot:30pts)**	**p-value**
Extension of sternal replacement:				0.001
- Total sternal replacement	30(52%)	2(7%)	28(93%)	
- Partial Body and manubrium replacement	12(21%)	10(36%)	2(7%)	
- Partial body replacement	16(28%)	16(57%)	-	
Median operative time(min)	154(IQR111-162) Range 117-429	161(IQR 123-187) Range 117-429	152(IQR 107-159) Range 134-373	0.1
Median number of titanium bars	4(IQR3-4)	4(IQR3-4) Range 2-7	4(IQR3-4) Range 2-6	0.8
Other resected structures:				0.001
- Ribs	18(31%)	14(50%)	4(13%)	
- Clavicle	6(10%)	6(21%)		
- Thymus	1(2%)	1(4%)		
- Brachiocephalic and caval vein	1(2%)	1(4%)		
- Pericardium	1(2%)	1(4%)		
- Breast	3(5%)	3(11%)		
- Wedge lung resection	2(3%)	2(7%)		
Muscle-Flaps:	50(86%)	20(71%)	30(100%)	0.04
- Pectoralis-major	45(78%)	18(64%)	27(90%)	
- Rectus-Abdominis	4(7%)	2(7%)	2(7%)	
- Latissimus-dorsi	3(5%)	4(14%)	1(3%)	
- Pectoralis-minor	1(2%)	1(4%)	-	
- Fascio-cutaneous-flap	7(12%)	7(25%)	-	
Omental-Transposition	2(3%)	-		-
IQR:interquartile-range				

Table 5: Post-operative results

Variables	**n.pts(%) Median(IQR)**	**Tumor (tot:28pts)**	**Non-neoplastic (tot:30pts)**	**p-value**
Median ICU time(days)	3(IQR1-9.5) Range1-36	1(IQR1-2) Range1-18	5(IQR2-13) Range1-36	0.001
Median Ventilation time(hours)	8(IQR4.7-20.7) Range1-312	3(IQR2-4) Range1-5	13(IQR7-96) Range4-312	0.002
Median Hospital stay(days)	11(IQR8-18)	9(IQR7-16) Range6-61	16(IQR9-21) Range3-37	0.03
Post-Operative Morbidity	18(31%)	4(14%)	14(47%)	0.01
- Pneumonia	4(7%)	-	4(13%)	
- Pleural effusion	3(5%)	1(4%)	2(7%)	
- Wound dehiscence	6(10%)	1(4%)	5(17%)	
- Chest wall seroma	2(3%)	1(4%)	1(3%)	
- Muscle flap Hematoma	2(3%)	-	2(7%)	
- Pneumothorax	4(7%)	-	4(13%)	
- Sepsis	1(2%)	1(4%)	-	
- Melena/gastric ulcer	1(2%)	-	1(3%)	
- Renal failure/hemodialysis	1(2%)	-	1(3%)	
Early Reoperation	6(10%)	1(4%)	5(17%)	0.03
- Wound soft tissue re-suture	4(7%)	1(4%)	3(10%)	
- Bleeding	1(2%)	-	1(3%)	
- Implantation failure after trauma	1(2%)	-	1(3%)	
In-Hospital Mortality	3(5%)	1(4%)	2(7%)	0.6
Causes of Death				
- Pneumonia/sepsis	1	-	1(3%)	
- DIC/pulmonary embolism	1	1(4%)	-	
- Multi-organ-failure	1	-	1(3%)	

IQR:interquartile-range,ICU:intensive-care-unit;DIC:disseminate intravascular coagulation			

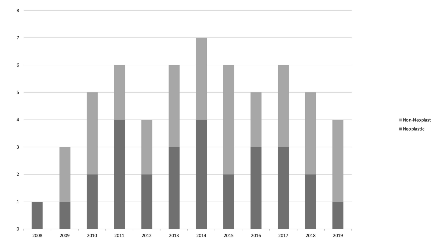
Figure 1: The distribution of the cases during the study period**.**

Figure 2: A)Intraoperative view of a partial(sternal-body) allograft implantation B)Follow-up CT-scan after 3-months from the operation.

Figure 3: A)Tc-99-bone-scintigraphy after 1-year showing tracer accumulation mainly in the contact area between bones. B) Tc-99-bone-scintigraphy after 2-years the tracer is more diffuse into the body of the allograft.C,D) PET-imaging after 2-years showing tracer accumulation into the body of the allograft.

Figure 4: Example of preoperative surgical rendering to plan allograft tailoring(A) and sternal resection for a perfect matching(B). The inter-bone gaps were filled with crushed spongy bone(C).

Journal Pre-proof



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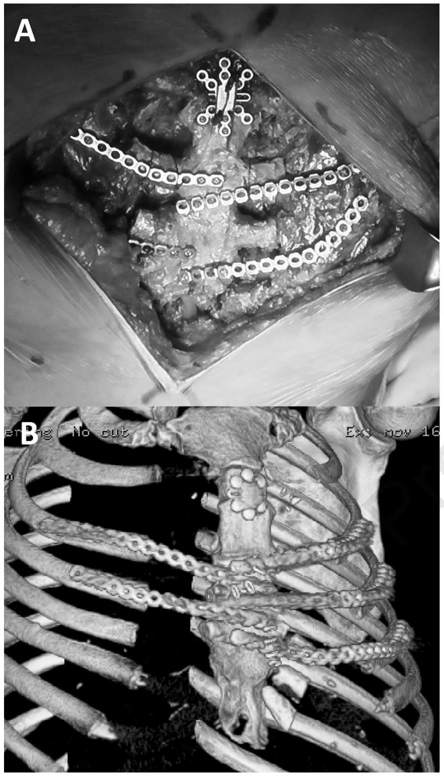

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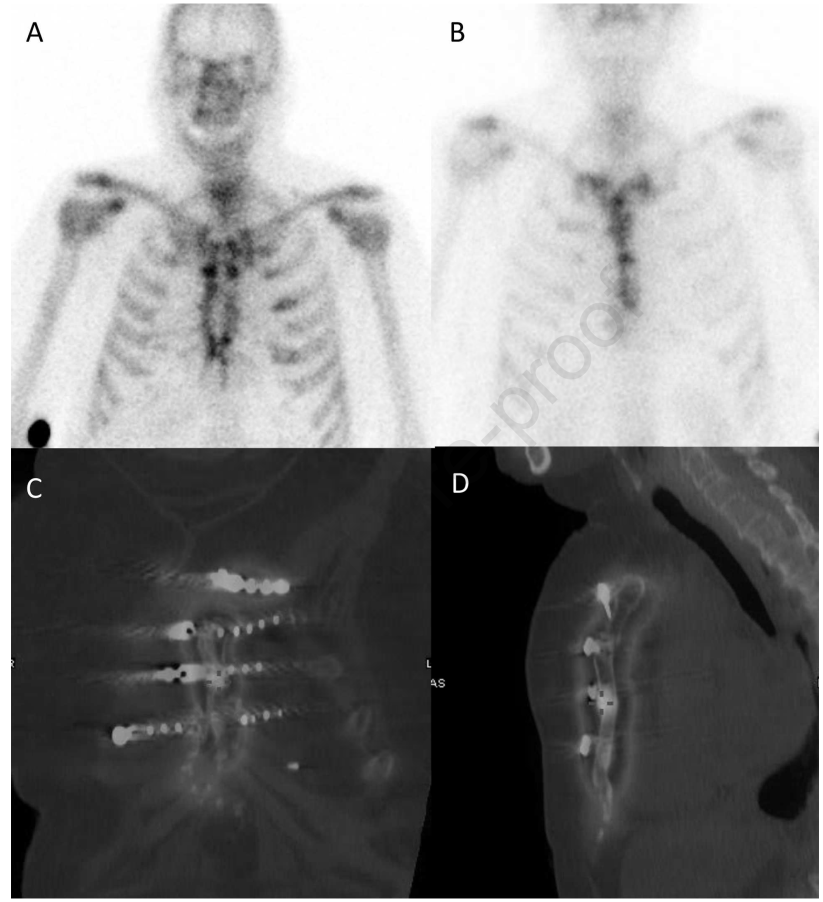

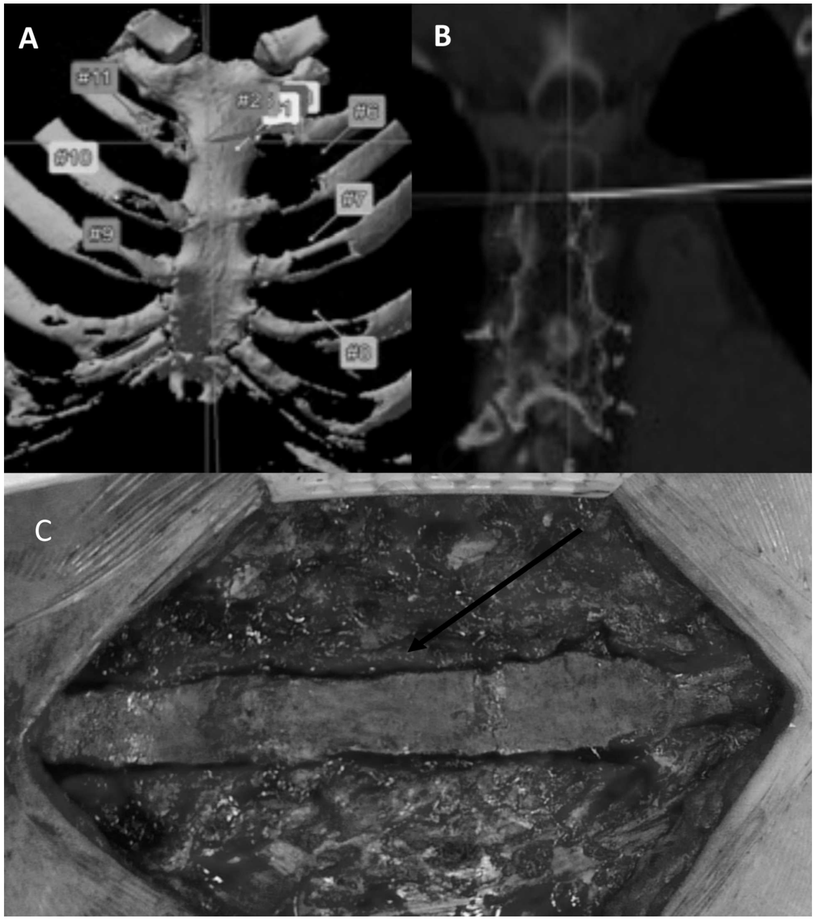
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