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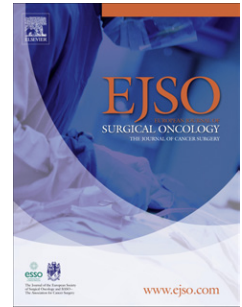
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Authors: Tim Pencavel, MB BS Christopher P. Allan, MPhil, FRACS J. Meirion Thomas, MS MRCP FRCS Andrew Hayes, PhD FRCS



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Title Page

Treatment for breast sarcoma: a large, single-centre series.

Tim Pencavel MB BS^{*+}

Christopher P Allan MPhil FRACS^{*}

J Meirion Thomas MS MRCP FRCS^{*}

Andrew Hayes PhD FRCS^{*}

^{*}Sarcoma/Melanoma Unit, Dept of Academic Surgery, Royal Marsden Hospital, and

⁺Targeted Therapy Team, The Institute of Cancer Research

The results of this series have been presented at the British Sarcoma Group annual conference 2008.

2,301 words.

3 Figures.

3 Tables.

Corresponding author:

Timothy Pencavel
Sarcoma/Melanoma Unit,
Royal Marsden Hospital NHS Foundation Trust,
Fulham Road,
London.
SW3 6JJ
tim.pencavel@icr.ac.uk

Ph: 020 7153 5157

Title:

Treatment for breast sarcoma: a large, single-centre series.

Running Head:

Breast sarcoma.

Conflict of Interest:

The authors are not aware of any competing or conflicting interest in the preparation of this manuscript.

Synopsis:

Breast sarcoma is a rare condition. This large series evaluates prognostic factors from the standpoint of a large tertiary referral centre. Previous breast irradiation emerges as the factor most strongly associated with poorer prognosis; other factors are also discussed.

Abstract

Background

Breast sarcoma is a rare cancer. We report a major series from a tertiary referral centre.

Methods

Retrospective analysis was performed on patients with histologically-proven breast sarcoma treated between 1996 and 2006. Kaplan-Meier survival curves were constructed and differences assessed by Log-Rank and Wilcoxon tests.

Results

63 patients were identified; 57 underwent treatment with curative intent. 24 patients had undergone previous radiotherapy

36 patients who underwent primary surgery elsewhere were referred for further treatment, of which 22 had at least one involved margin from primary resection. Surgery performed and margins status varied between patients undergoing primary surgery at this institution (n=21; WLE=8, mastectomy=12, chest wall resection=1, involved margins=2 [10%]) or at a referring institution (n=36; lumpectomy=25, mastectomy=11, involved margins=22 [61%]), although there was no difference in tumour size or previous radiotherapy status.

Previous irradiation was associated with poor prognosis. A greater proportion of these patients required primary mastectomy to ensure adequate clearance; the majority of the post-irradiation tumours were angiosarcomas (15/19) and significantly more relapsed locally ($P<0.001$).

All patient disease-free survival (DFS) rates were 71% at 2 and 42% at 5 years. DFS improved when primary surgery was undertaken at a high-volume sarcoma unit; 2-yr 84% vs 75%; 5-yr 58% vs 37%. There was a trend towards worse DFS with increasing size and increasing grade of tumour but this did not attain significance.

Conclusions

Radiation-induced breast sarcoma has worse local recurrence rates compared to primary breast sarcoma. Involved margins were fewer at a specialist unit, which may translate into improved outcome.

Key words

Breast sarcoma, survival, surgical margins, radiotherapy.

Introduction

Sarcoma of the breast is a rare condition, accounting for less than 1% of all primary breast malignancies^{1, 2}. Accordingly the biological behaviour and treatment factors affecting outcome are less commonly reported than breast malignancies of epithelial origin³. Furthermore there are a great number of varying histopathological subtypes that can affect the breast⁴, the commonest histopathological subtypes being malignant phyllodes tumour^{5, 6} and angiosarcoma⁷. Most previous series of breast sarcomas have either comprised a small number of patients or have included patients over a very long study period (up to 90 years, summarised in table 1). In these studies the two commonest variables that impact on outcome are the size of the primary tumour and the margin status of the primary resected specimen. Multiple other factors have sporadically been shown to affect prognosis, including grade and margin status, although the size of previous studies has made the drawing of definitive conclusions difficult. The major aetiological factor that is implicated in the development of breast sarcoma is previous irradiation of the breast after treatment for a prior malignancy⁸⁻¹¹.

The current study comprises a series of 63 patients undergoing treatment for breast sarcoma over a 10 year period in a single institution, of which 57 patients underwent treatment with curative intent. As such this is the largest series of this condition reported in the literature in a comparable study period. The pathology and biological behaviour of this condition is described and the cohort of patients undergoing treatment with curative intent have been analysed to see what tumour and treatment outcomes impact on local and distant relapse and overall survival.

Patients and Methods

A prospective soft tissue sarcoma database was searched for all patients presenting between January 1996 and December 2006 with breast sarcomas. Only patients with histologically-confirmed sarcomas were included for analysis. All pathological specimens were diagnosed and reported by a single pathologist with dedicated soft tissue sarcoma expertise. Case notes and pathological records were reviewed retrospectively with particular reference to tumour pathology, surgical treatment and margin status, adjuvant treatment and outcome. Tumours were graded as either grade 1, 2, or 3 according to the grading system after Coindre et al¹².

The endpoints of this study were sarcoma specific survival, time to local recurrence, and time to distant metastases in patients who underwent surgical treatment with curative intent. Overall survival was defined as the time from presentation with a breast sarcoma to either death or last follow-up. Time to local recurrence was defined as the time from treatment to radiological or pathological confirmation of local recurrence. Time to distant metastases was defined as the time from treatment of the radiation-induced sarcoma to radiological or pathological confirmation of recurrence. The Kaplan-Meier method was used to calculate survival curves, with curve comparison performed using the Log-Rank test. A p value of less than 0.05 was considered significant. The study protocol was approved by this institution's ethics and research review panel.

Univariate analysis was performed for the following factors: age, grade, size, previous radiotherapy and adjuvant therapy. Histological subtypes were considered for univariate analysis but were not included since, aside from angiosarcoma (the majority of which were radiation-induced), most subtypes included few cases. Multivariate analysis was not performed as only one significant factor was identified.

Results

Patient characteristics and Tumour Pathology

There were 63 patients identified who had histologically confirmed breast sarcomas, 59 female and 4 male. The median age at presentation was 51 years (11 – 85). 24 patients (38%) had a previous history of irradiation to the affected breast. The indications for prior breast irradiation were a previous epithelial breast malignancy in 23, and mantel irradiation for lymphoma in 1 patient.

The baseline characteristics of the patients who underwent surgery are shown in Table 2.

Treatment

There were 6 patients who did not undergo treatment with curative intent, because of the presence of distant metastases at presentation to this institution (1 patient), the presence of severe comorbidities that precluded safe operative intervention (2 patients), or the clear and sustained wishes of the patient not to be treated (3 patients). Therefore, 57 patients underwent primary surgical treatment with curative intent.

Final clear margin status was achieved in 56 of 57 patients (98.2%). In 33 patients, negative margins were achieved after primary surgery; wide local excision in 12/33 and mastectomy in 20/33. One patient required chest wall resection to achieve primary clearance. There were 7 patients who underwent synchronous reconstruction, 3 for oncologic reasons. The remaining 24 patients required at least one re-excision. Significantly more patients who underwent primary surgery away from the specialist unit had positive margins after initial surgery and required further operative intervention (2/21 vs 22/36; $p < 0.001$). Positive margins were seen after both wide local excision (21/24) and mastectomy (3/24), and as expected this rate was significantly higher after wide local excision ($p < 0.001$). The second procedures required to gain negative margins were 10 breast conserving resections, 13 completion mastectomies and 1 chest wall resection. 2

patients had a synchronous reconstruction to gain adequate surgical clearance. Only 1 patient had involved margins after the second resection (a completion mastectomy).

There were 3 patients who underwent axillary lymph node clearance at a non-specialist institution, with no histologically-confirmed nodal disease identified.

Of the 38 patients who had not had prior breast irradiation 47% (18/38) underwent adjuvant radiotherapy. Kaplan-Meier analysis does not reveal any survival advantage for patients receiving adjuvant radiotherapy in this series.

Outcome

The 6 patients not treated with curative intent have been excluded from survival analysis – 3 patients died of disease-related complications within 6 months of their first outpatient appointment and the other 3 were only seen once and follow-up data was unavailable.

Median follow-up was 26 (1 – 132) months. 18 patients developed local recurrence, at a median time of 19 (3 – 94) months. 13 patients developed distant recurrence, at a median time of 22 (2 – 64) months. 9 patients died of disease-related complications, at a median time of 41 (10 – 81) months. All patient disease-free survival rates were 71% at 2 years and 42% at 5 years. Local recurrence rates were 23% at 2 years and 48% at 5 years; distant recurrence rates at the same intervals were 17% and 26%, respectively. Sarcoma-specific survival was 93% at 2 years and 78% at 5 years. 2- and 5-year disease-free survival rates were improved when the primary surgical intervention was undertaken at a tertiary referral institute; 2-year 84% vs 75%; 5-year 58% vs 37%. No significant risk factor for decreased survival was identified aside from previous breast irradiation; however, a trend was found for decreased survival with higher grade and larger size (fig 1,2).

Univariate analysis was performed for the following factors: age, grade, size, previous radiotherapy and adjuvant therapy. The outcome measures evaluated were disease-free survival and disease-specific survival. Histological subtypes were considered for univariate analysis but were not included since, aside from angiosarcoma (the majority of

which were radiation-induced), most subtypes included very few cases. Therefore previous radiation, which accounted for the majority of cases in the largest histological subtype group, would have acted as a major confounding factor in the analysis. A summary of the univariate analysis is shown in Table 3.

The only factor to have a significant impact on survival was previous breast irradiation, in which $P=0.037$. The post-irradiation and non-irradiated groups were closely matched in terms of grade and size of tumour at presentation, although the post-irradiation group was significantly older (mean age at presentation, 61.2 vs 45.0 years, $P<0.0001$), presumably as a result of the time interval between treatment for the prior malignancy and development of the radiation-induced sarcoma. In addition, a greater proportion of the post-irradiation group were histologically angiosarcomas (15/19 vs 9/38, $P<0.0001$). In terms of treatment, significantly more of this group required mastectomy as the primary operation (12/18 vs 11/38, $P=0.007$; 1 chest wall resection in radiation group), in order to achieve negative margins. Mean time to recurrence was shorter in the post-irradiation group than the non-irradiated group but this did not achieve significance (20 vs 35 months, $P=0.18$). 26% (5/19) of post-irradiation patients developed distant metastases, compared to 21% (8/38) of non-irradiated patients. Primary sarcomas had improved disease-free survival rates compared with post-irradiation (65% vs 73% at 2 years; 26% vs 55% at 5 years) (Fig 3).

Discussion

This series highlights two main findings. First, sarcoma arising in the post-irradiation breast is associated with significantly worse disease-free survival, with much poorer rates of local and distant relapse. Second, margin status and survival are both worse when primary surgery is carried out away from the setting of a high-volume tertiary sarcoma unit.

The concept of poorer prognosis in radiation-induced sarcomas (RIS) is not new and has been reported in other body sites¹⁰. Whilst the absolute numbers of RIS will remain small compared to the numbers of women treated for breast malignancy, the incidence might be expected to vary with changes in both operative and radiotherapeutic techniques¹¹. The increasing utilisation of breast-conserving therapy, with adjuvant radiotherapy, would be expected to increase incidence. Conversely, however, it may be that reduced normal tissue irradiation by the use of conformal radiotherapy fields results in a lower rise in incidence than might be expected from a change in surgical practice alone.

A greater proportion of the radiation-induced sarcomas were angiosarcomas. This tumour type has diffusely infiltrative margins that are difficult to encompass within a surgical resection margin^{13, 14}, and may account for the worse rates of local relapse seen in our study despite the histopathological evidence of clear margins. In addition, patients in this group are almost universally precluded from further post-operative irradiation following resection of the sarcoma, since surrounding or underlying tissues have already received the maximum tolerated dose. No difference was seen in grade or size, both of which could potentially be confounding factors. Therefore the survival discrepancy noted is likely to be solely due to the cytogenetic and phenotypic changes induced by prior radiation exposure.

The second finding would suggest that it is the familiarity with the sarcomatous disease process, rather than with tumours of the breast *per se*, that is important in defining adequate management of the sarcoma.

In previous studies, the two most frequently significant prognostic indicators are the size of the primary tumour and the margin status at initial operation (Table 1). Perhaps surprisingly, given its role in the prognosis in soft tissue tumours at other sites, tumour grade has not been consistently shown to be a prognostic factor. The reasons for this are unclear, but it is possible that the published numbers of patients are not sufficient to show a significant difference. Whilst the current series failed to demonstrate an improved survival advantage in tumours related to size or grade, both these factors result in reduced survival at 2 and 5 years. In common with all previous studies, however, the numbers in our study are still relatively small, and a larger experience or multi-institutional study may reveal the impact of those factors, significant in other sites, that are not proven to be important in breast sarcoma at present.

In light of the identification of margin status as a significant prognostic factor in breast sarcoma, it is of concern that there is a marked discrepancy in margin status after primary operative intervention between procedures carried out at a dedicated soft-tissue sarcoma centre and those non-specialist centres where the majority of patients underwent excision. The reason for this discrepancy is unclear but is likely to be multifactorial and include a failure to consider a sarcoma diagnosis on the basis of often equivocal preoperative imaging and fine-needle aspiration samples. Certainly for malignant phyllodes tumours an evaluation of both the stromal and epithelial elements of the tumour, as well as their spatial relationships, is necessary, and such a classification is difficult to achieve on the basis of an FNA. Similarly, ultrasound alone is a poor discriminator of malignant sarcoma lesions from benign lesions or epithelial breast pathology.

The type of operation performed is not dictated by pathology. Clear margins can be adequately gained by wide local excision or mastectomy, such that a sarcoma diagnosis does not necessitate a mastectomy if patient and other factors are amenable to breast conserving therapy. The current series does not show a benefit to adjuvant radiotherapy, albeit in a small cohort of patients, which reinforces the fact that radiotherapy is not a

substitute for sufficiently radical surgery. As with other sarcomas, the aim must be to resect the whole tumour with a margin of normal tissue without ever seeing the tumour itself intraoperatively.

The greatest risk for recurrence is found locally, with a much smaller proportion of patients developing distant metastases. Once again, sarcoma was found to behave differently to epithelial malignancy in this respect¹⁵, with no lymph nodal disease seen in any patient. 5-year sarcoma-specific survival rates were good, with almost 80% of patients surviving 5 years after diagnosis.

Conclusions

We have established that previous radiotherapy is a risk factor for poorer prognosis in breast sarcoma. Higher rates of clear surgical margins are attained when the primary sarcoma resection is performed at a high volume sarcoma unit and this may translate into an improved survival outcome. The timely diagnosis of breast sarcoma requires a high index of suspicion and, as for soft tissue sarcoma at other sites, a definitive histologic diagnosis must be made before embarking on surgical intervention. We thus advocate that patients with a sarcoma of the breast are treated in a facility with expertise in both management of soft tissue sarcoma and disorders of the breast in general.

In addition, surgical and survival advantages are gained at a high-volume tertiary centre. Therefore, a high index of suspicion, coupled with a low threshold for the use of alternative imaging modalities and histological techniques to those used in standard triple assessment is to be recommended to enable rapid and accurate diagnosis. In addition, we strongly advocate early referral to local soft-tissue tumour surgical units.

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Table 1: Previous published breast sarcoma series.

Author	Year of publication	Cases/time in years	Prognostic factors identified
Adem et al ¹	2004	25/90	Size
Barnes and Pietruszka ¹⁶	1977	10/31	Tumour contour, atypia, mitosis
Barrow et al ¹⁷	1999	59/43	Size, margins, subtype
Berg et al ¹⁸	1962	25/?	Margins
Callery et al ⁴	1985	25/33	None
Fields et al ¹⁹	2008	13/20	Size
Gutman et al ²⁰	1994	60/51	Size, multifocality, lymph/vascular/chest wall invasion
Johnstone et al ²¹	1993	10/12	None
Norris and Taylor ²²	1968	32/?	Size, contour, atypia, mitosis
North et al ²³	1998	25/31	Type of surgery
Oberman ²⁴	1965	13/30	Size, type of surgery
Pollard et al ²⁵	1990	25/81	Type of surgery
Sher et al ¹⁴	2007	69/37	Size
Smola et al ¹³	1993	8/23	None
Stanley et al ²⁶	1988	4/?	None
Zelek et al ²⁷	2003	83/37	Grade, size

Table 2: Primary tumour characteristics at presentation (n=57).

Characteristic	Number (%/range where applicable)
Median age (years)	49 (11 – 79)
Median size (mm)	47.5 (2 – 235)
Median follow up (months)	26 (1 – 132)
Grade of tumour:	
Grade 1	22 (38.6)
Grade 2	13 (22.8)
Grade 3	19 (33.3)
Unknown	3 (5.3)
Previous irradiation	19/57 (33.3)
Primary sarcoma operation:	
Mastectomy	23/57 (40.4)
Wide Local Excision	33/57 (57.9)
Chest Wall resection	1/57 (1.7)
Involved margins after primary resection	24/57 (42.1)
Adjuvant Radiotherapy	18/57 (31.6)
Chemotherapy	4/57 (7)*
Angiosarcoma	24/57 (42.1)
Phyllodes	8/57 (14.0)
DFSP	5/57 (8.8)
Leiomyosarcoma	4/57 (7.0)
Fibrosarcoma	3/57 (5.3)
Pleomorphic	3/57 (5.3)
MFH	2/57 (3.5)
Synovial	2/57 (3.5)
Others	6/57 (10.5) ⁺

*: 2 further patients given palliative chemotherapy after disease recurrence.

+ : 1 each: Extra-skeletal osteosarcoma, liposarcoma, malignant mesenchymoma, myofibrosarcoma, myxosarcoma, spindle cell sarcoma.

Table 3: Summary of Univariate Analysis

Factor	Associated P value
Age of Patient (>50)	0.28
Grade of tumour	0.063
Size of tumour	0.186
Adjuvant Therapy	0.063
Radiotherapy	0.037

Fig 1: Kaplan-Meier plot of disease-free survival for all tumours sorted into low/intermediate and high grade groups.

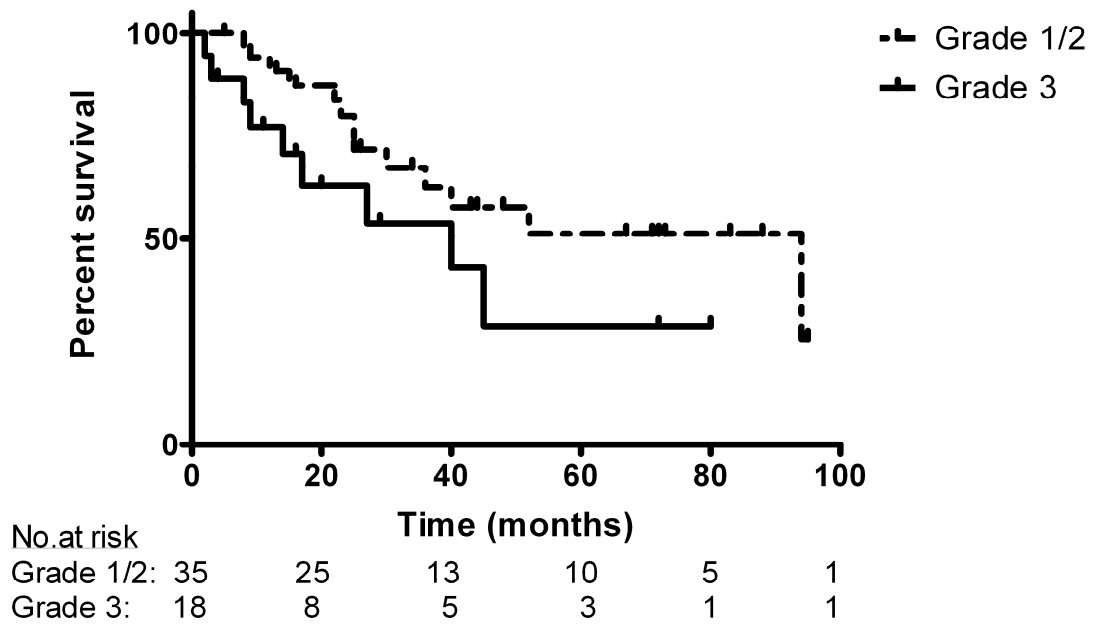
Fig 2: Kaplan-Meier plot of disease-free survival by size of primary tumour at resection.

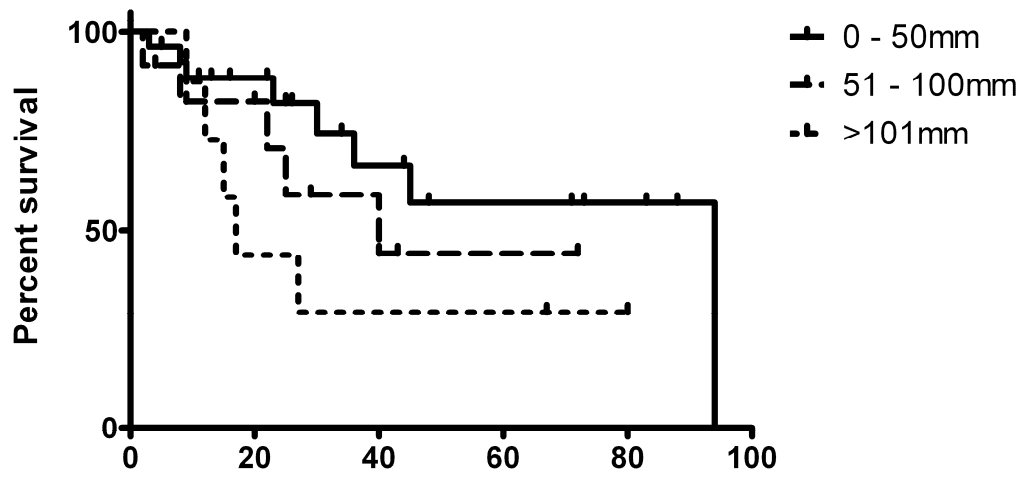
Fig 3: Kaplan-Meier plot of disease-free survival for all tumours, primary and post-irradiation sarcomas.

Conflict of Interest:

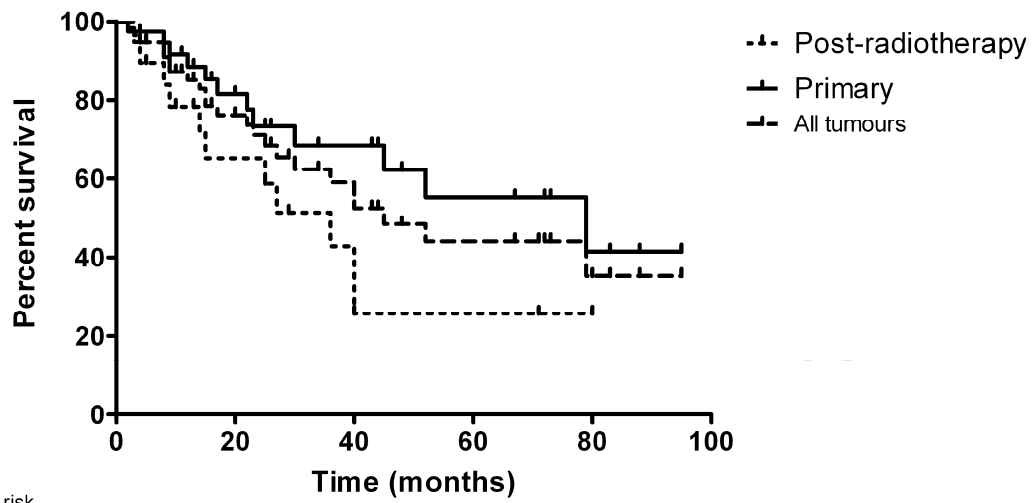
The authors are not aware of any competing or conflicting interest in the preparation of this manuscript.

ACCEPTED MANUSCRIPT





No. at risk:		Time (months)				
0-50mm	27	13	6	4	1	0
51-100mm	12	6	2	1	1	1
>101mm	8	4	3	2	1	1



No. at risk	0	20	40	60	80	100					
All tumours:	57	44	32	21	18	12	10	9	4	2	1
Primary sarcoma:	38	30	22	15	13	10	8	7	3	2	1
Post-irradiation:	19	14	10	6	5	2	2	2	1	0	0