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► To cite this version:

J.P. van Damme, S. Schmitz, J.P. Machiels, C. Galant, V. Grégoire, et al.. Prognostic factors and assessment of staging systems for head and neck soft tissue sarcomas in adults. *EJSO - European Journal of Surgical Oncology*, 2010, 36 (7), pp.684. 10.1016/j.ejso.2010.05.020 . hal-00603541

HAL Id: hal-00603541

<https://hal.science/hal-00603541v1>

Submitted on 26 Jun 2011

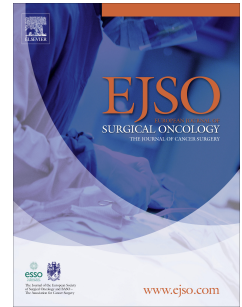
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Accepted Manuscript

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PII: S0748-7983(10)00128-9

DOI: [10.1016/j.ejso.2010.05.020](https://doi.org/10.1016/j.ejso.2010.05.020)

Reference: YEJSO 2982

To appear in: *European Journal of Surgical Oncology*

Received Date: 3 December 2009

Revised Date: 22 April 2010

Accepted Date: 17 May 2010

Please cite this article as: Van Damme JP, Schmitz S, Machiels JP, Galant C, Grégoire V, Lengelé B, Hamoir M. Prognostic factors and assessment of staging systems for head and neck soft tissue sarcomas in adults, *European Journal of Surgical Oncology* (2010), doi: 10.1016/j.ejso.2010.05.020

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Prognostic factors and assessment of staging systems for head and neck soft tissue sarcomas in adults.

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Prognostic factors of adult HNSTS (Head and Neck Soft Tissue Sarcomas)

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Abstract:***Objectives:***

The primary objectives of this study were to analyse the outcome of patients diagnosed with head and neck soft tissue sarcomas (HNSTS) and to identify relevant prognostic factors. As well as this, we compared the prognostic value of two staging systems proposed by the American Joint Committee on Cancer (AJCC) and the Memorial Sloan-Kettering Cancer Center (MSKCC).

Methods:

From 07/1988 to 01/2008, the charts of 42 adult patients were retrospectively reviewed. Potential prognostic factors were analysed according to overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS).

Results:

At 5 years, OS was 57%, DFS 47% and DSS 72%. On univariate analysis, statistically significant prognostic factors were for OS, distant or lymph node metastasis at diagnosis ($p=0.032$), for DFS, margins after surgery ($p=0.007$), for DSS, regional or distant metastasis at diagnosis ($p=0.002$), initial AJCC and MSKCC stage ($p=0.018$ and $p=0.048$) and margins after surgery ($p=0.042$). On multivariate analysis, margins remained statistically significant for DFS ($p=0.039$) when there was a trend with the initial AJCC stage ($p=0.054$) for OS. The AJCC staging system was of more prognostic value than the MSKCC staging system.

Conclusions:

Achieving clear margins after surgery is vital for improved local control and the best chance of survival. Adjuvant chemotherapy and radiotherapy were not shown to provide additional benefit. To better identify prognostic factors, it seems essential to set up national and international databases allowing multicenter registration for those patients.

Keywords: Soft tissue sarcoma; head and neck cancer; prognostic factors; staging system

Introduction

Sarcomas are rare tumours (3 to 4.5 cases/100.000 persons per year) belonging to the family of non-epithelial malignant tumours.^{1,2} They are divided into two types: sarcomas from soft tissues and sarcomas from bone or cartilaginous tissues. The management and outcomes of these two types of tumour are very different.³ Only 5-10 % of sarcomas from soft tissue are located in the head and neck region where they represent less than 1% of all head and neck tumours.^{4,5}

In Belgium (population of 10,4 million people), the theoretical annual incidence of head and neck soft tissue sarcomas (HNSTS) is around 30 cases. There are seven tertiary referral centers and the lack of a centralised public health policy explains the difficulty in gathering a high number of patients in referral centres. To the best of our knowledge, this article is the first to analyse data on a series of Belgian patients diagnosed with HNSTS. The primary objective of this study was to analyse the outcome of HNSTS in our institution and to determine the most relevant prognostic factors.

In the literature, there are usually two staging systems described for use with sarcoma patients. The first, proposed by the American Joint Committee on Cancer (AJCC), and by the International Union Against Cancer (UICC) is the most frequently used.⁶ The second, proposed by the Memorial Sloan-Kettering Cancer Center (MSKCC), was described by their authors as easier to use (Table 1).⁷⁻⁸ Using our data, we compared the two staging systems, to better assess which was the most relevant for the prognostic value of patients with HNSTS.

Materials and methods

The medical records of 42 patients over 18 years old, with HNSTS diagnosed at St-Luc University Hospital, a tertiary referral centre, between 07/1988 and 01/2008 were retrospectively reviewed.

Prognostic factors

The following variables of potential prognostic value were collected: gender, age at diagnosis, radiation history (sarcomas were labelled as radiation-induced based on the criteria of Arlen: histological confirmation of sarcoma, a different histology in relation to the previous cancer, tumour in or in the burden of the radiation field and a minimum interval of 3 years⁹), symptoms, anatomical site, dates of the consecutive treatments, surgical margins (In the head and neck, wide margins are not always easy to achieve because of anatomical limitations. In our study, margin status was considered as follows: Margins were defined as negative when at least 1cm free or less than 1 cm when wider margins were not possible to achieve because of anatomical factors, but when the surgeon believed he had performed a complete resection or with a well encapsulated tumour on the pathological report; margins were defined as close when less than 1 cm and the surgeon believed he had performed a borderline resection, peroperative extracapsular spread or with histological evidence of extracapsular spread; margins were defined as positive when they were macroscopically or microscopically invaded), radiation therapy (total dose), chemotherapy (type of cytotoxic agents and number of treatment courses), the presence of lymph nodes or distant metastasis at diagnosis, size of the tumour (≤ 5 cm vs. > 5 cm), extension (superficial or deep compared to the superficial fascia), histological type and subtype (with the exclusion of dermatofibrosarcoma protuberans and angiosarcoma which are excluded by the AJCC staging system⁶), grade according to the National Cancer Institute (NCI) (all the tumours which could be graded I to III according to

NCI were reviewed by the same pathologist C.G.), TNM classification and staging relating to AJCC and MSKCC staging systems.^{6,8}

The files of 29 patients with insufficient medical records or follow up were excluded from the study.

End points:

The end points of this study were overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS). OS was defined as the time interval between the date of the first treatment and death or last follow-up, DFS was defined as the time interval between the date of first treatment and death or disease progression, DSS was defined as the time interval between the date of first treatment and death related to sarcoma. OS, DFS and DSS were analysed for all possible prognostic factors.

The average follow-up after treatment was 54 months (range: 1 – 240 months).

Statistics:

Survival probability was calculated using the Kaplan Meier method.¹⁰ Median OS, DFS and DSS were calculated for each prognostic variable.

Univariate analysis was carried out with the LOG-RANK test. Multivariate analysis of each prognostic factor significantly affecting the survival in univariate analysis was carried out using the COX model (proportional hazards model). The survival differences were considered as statistically significant when the p value was < 0.05 .

Results

Patient's characteristics

The male/female ratio was 1/1.1 (20 males and 22 females). Median age at diagnosis was 50 (range 18 – 91 years). Localizations of HNSTS were at the paranasal sinus in 17 patients, in the neck, including parotid gland area in 10 patients, the scalp and face in 9 patients, and the upper aerodigestive tract (oral cavity, larynx, superior oesophagus) in 6 patients. The most frequent histological subtypes were undifferentiated sarcoma in 7 patients, leiomyosarcoma in 6 patients, malignant peripheral nerve sheath tumour (MPNST) in 5 patients and rhabdomyosarcoma in 5 patients. The most frequent clinical manifestation was progressive developing of a painless mass in half of the patients and less frequently nasal obstruction with or without epistaxis and dysphonia. Most tumours were ≤ 5 cm (30/42) and deep infiltration through the superficial fascia was mentioned on pathology or imaging reports in 35/42 patients. Three patients were staged as N1 and one patient was staged as M1 at time of diagnosis.

Histological grade I was diagnosed in 9 tumours and grade II-III in 33 tumours. Sixteen patients had a medical history of cancer (other than sarcoma) and 10 had been previously treated with radiotherapy. Eight of those 10 patients developed a radio-induced sarcoma, according to the Arlen criteria. The median time interval between previous radiotherapy and diagnosis of sarcoma was 252 months (range: 72-480 months). Five-year OS of radio-induced HNSTS patients was 58%, which compared with a 5-year OS rate of 56% in the group of non radio-induced HNSTS patients.

Treatment characteristics

Thirty-nine patients were treated with primary curative-intent surgery. Margins were negative in 10, close in 17, positive in 10 and unspecified in 2. Three patients had a non-resectable paranasal sinus sarcoma and were primarily treated with chemotherapy and radiotherapy. Radiotherapy was used in 18 patients : pre or postoperative in 16 patients with curative intent and alone or combined with chemotherapy in 2 patients with non-resectable tumours. The mean total dose was 58 Gy (range: 22 – 72 Gy). Chemotherapy was used in 10 patients, as adjuvant in 8 patients and exclusive or combined with radiotherapy in 2 patients (table 2).

AJCC and MSKCC staging systems

Excluding 6 patients with a diagnosis of dermatofibrosarcoma protuberans or angiosarcoma, (not considered by the AJCC staging system), 25 patients were classified T1 (21 as T1b) and 11 were classified T2 (9 as T2b). According to the AJCC staging system, 8 patients were stage I, 19 stage II, 5 stage III and 4 stage IV. According to the MSKCC staging system, 2 patients were staged as stage 0, 7 as stage I, 19 as stage II, 7 stage III and 1 as stage IV (table 2).

The prognostic value of the AJCC staging system was more relevant than the MSKCC staging system. In relation to DSS, the prognostic value was statistically significant in the two systems but was found more significant in the AJCC system ($p=0.018$ vs. $p=0.048$). For OS, the prognostic value reached the level of significance in the AJCC system ($p=0,054$) but was not statistically significant in the MSKCC system ($p=0,198$). For statistical reasons, the 2 patients staged as stage 0 in the MSKCC staging system (not used in the AJCC staging system) were included in the group of patients MSKCC stage I. With a comparable MSKCC or AJCC stage, the median OS was similar. With DSS, the prognostic value of the two

systems for stage was good and statistically significant although the median survival was slightly higher in stage II when compared to stage I. This was probably explained by the limited size of our series.

Prognostic factors – univariate analysis:

Because almost all patients were treated by curative-intent surgery (3 patients with non-resectable tumours were treated palliatively with chemo or radiotherapy), this factor was excluded from statistical analysis.

For OS, the univariate statistical analysis showed that distant metastasis or lymph node metastasis at diagnosis had a statistically significant prognostic value ($p=0.032$) whereas the AJCC staging system showed only a trend ($p=0.054$). Median OS of patient N1 or M1 was 9 months compared with 30 months for the rest of the population.

For DFS, achieving clear margins ($p=0.007$) was a statistically significant prognostic factor (table 2, figure 1) whereas radiotherapy showed only a trend for a better prognosis ($p=0.053$).

In the case of negative margins, the median DFS was 92 months compared to 13 months in the case of positive margins. In the case of close margins, the median DFS was 14 months, comparable to the median DFS of patients with positive margins (figure 1).

For DSS, N1 or M1 at diagnosis ($p=0.002$), AJCC stage ($p=0.018$) (figure 2), MSKCC stage ($p=0.048$) and margins ($p=0.042$) were statistically significant prognostic factors whereas adjuvant radiotherapy showed only a trend for a better survival rate ($p=0.051$). Patients with an early AJCC or MSKCC stage had a median DSS of 56 months for stage I and 66 or 60 months respectively for stage II, whereas patients with an advanced stage had a median DSS of 13 months for stage III and 11 months for stage IV. Patients with MSKCC stage 0 had a median DSS of 98 months, better than that of patients staged AJCC stage I (56 months) or MSKCC stage I (49 months), but the difference was not statistically significant. Patients staged N0 - M0 had a median DSS of 58 months compared to 11 months in patients staged N1

or M1 at diagnosis. In the case of negative margins, the median DSS was 97 months compared with 43 months in the case of close margins and 22 months when margins were invaded.

Prognostic factors - multivariate analysis:

After multivariate statistical analysis, the only factor remaining statistically significant was negative margins for DFS ($p=0.039$) when the initial AJCC stage showed only a trend regarding OS ($p=0.054$).

The survival probability curves are shown in figure 3.

Discussion

Comparison with previously reported series

HNSTS are rare tumours. Most recent publications report on series with about 50 patients or fewer, often not being comparable with our study as they mix adult and paediatric populations or report different histological subtypes (e.g. all sarcomas, soft tissues only, or with the exclusion of some histological subtypes).^{1,5,11-13} To date, the two most important published series included no more than one hundred patients.^{4,14} This explains numerous disparities between published series. In our series, the 5-year OS, DFS and DSS are respectively 57%, 47% and 72%. These results are comparable with the data found in the literature reporting a 5-year OS between 32% and 87%, a 5-year DFS between 27% and 74% and a 5-year DSS between 81 and 83%.^{1,3,4,11}

Our series shows a very slight female predominance, confirmed by some authors^{11,15}, but invalidated by others.^{3,16} The median age at diagnosis is 50 years old, comparable to the one found in the literature.^{1,3,11,16,17}

Prognostic factors

In our series, even if the median DSS is clearly better in the case of superficial infiltrations (96 months versus 38 months.), the difference is not statistically significant, -probably because the number of patients in our study was too small. Huber et al. have shown that the absence of deep extension is the best prognostic factor.⁴ Few authors have identified this factor specifically, rather considering the size of the tumour as a poor prognostic factor.^{14,18-21}

In our series, tumour size is not a statistically significant prognostic factor. The histological grade is often identified as a prognostic factor.^{6,14,18,22,23} In our study, even if OS, DSS and DFS are systematically better for patients with grade I sarcoma in comparison with grade II or III, the differences are not statistically significant, again probably due to the limited number of patients studied.

In our series, the presence at diagnosis of lymph node or distant metastasis is rare but has an impact on survival as has been reported by others^{1,11,15} The AJCC recommends staging all patients with no evidence of lymph node metastasis or distant metastasis N0 and M0.

In a review of 1225 patients, Zagars et al. have confirmed that the localization in the head and neck area was a negative prognostic factor for DSS and DFS.²⁴ As our series shows, and in accordance with others, no specific anatomical localization in the head and neck makes an impact on the prognosis.^{4,11} Again, this is probably due to the small number of patients in our series, as in the other studies. In the head and neck region, wide margins after surgery are not always easy to achieve because of anatomical limitations. Negative margins have a major impact on DFS: the median DFS of patients with close margins, is similar to the median DFS of patients with positive margins. These results confirm the major impact of curative surgery with wide clear margins on prognosis.^{1,4,11,13,14,17,18,25} Because of the difficulties in obtaining

negative margins in the head and neck, some authors have reported that the combination of radiotherapy with surgery increased the survival rate and decreased the risk of local recurrence.^{3,22} The trend for a better DFS in our patients treated with postoperative radiotherapy supports the concept of adjuvant radiotherapy in patients with borderline margins. In relation to DSS, radiotherapy seems to be a poor prognostic factor in univariate analysis (36 versus 72 months). These paradoxical results are biased since all patients treated with surgery alone did not have factors of poor prognosis. The role of chemotherapy is generally considered as limited^{3,26,27} but is proposed in advanced stages.²⁸ In our series, use of chemotherapy is not associated with significant survival improvement, mainly because its use was restricted to unresectable or palliative disease.

As reported by others, some prognostic factors are advanced while others, even if recognised in the literature, are not identified.^{4,11,23} Most published series, including ours, report on too limited number of patients or are too heterogeneous. Therefore we feel it essential to set up national and international databases, which could facilitate a prospective multicenter registration for those patients.

Comparison between AJCC and MSKCC staging systems

The value of the AJCC sarcoma staging system is sometimes debated. Nevertheless, it provides the possibility of combining all the studied factors through grade and TNM classification. This is why we staged our patients according to the TNM classification, excluding many patients due to incomplete data or histological types not accepted by the AJCC 6th edition.⁶

In our series, the AJCC staging system's prognostic value is more relevant than the prognostic value of the MSKCC system. This information should be validated in larger multicenter series. The advantages of the MSKCC staging are its simplicity of use and the existence of a

stage 0 for very good prognosis. However, the number of patients staged MSKCC 0 in our series is too small to pass comment on its clinical significance. The weakness of the MSKCC system is that, contrary to the AJCC system, it does not take the lymph node status into account. Interestingly, the prognostic value of the AJCC and MSKCC staging systems become comparable and statistically insignificant when patients staged N1 are excluded from the univariate analysis (data not reported in the article). This explains why, in our series, the prognostic value of staging is higher using the AJCC staging system than using the MSKCC system.

Conclusion

Soft tissue sarcomas are rare tumours in the head and neck. Achieving negative margins after primary surgery is the most important prognostic factor, providing the best chance of local control and survival. In our series, adjuvant radiotherapy and chemotherapy are of limited value. As emphasized by many other authors, we believe that those tumours should exclusively be managed in centers with extensive expertise in head and neck oncology, including surgical teams able to achieve wide tumour resection and to reconstruct large composite surgical defects.^{1,22,25,,27,29}

To better identify prognostic factors, it seems essential to set up national and international databases allowing a prospective registration for those patients.

Acknowledgments.

Mr Nicolas Buyse for the amount and quality of time spent on statistical analysis and for his expertise in this field.

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Table 1. Staging of STHNS according to AJCC and MSKCC.

| Staging relating to UICC and AJCC ¹⁶ | | | | |
|-------------------------------------------------|------------------------------------------|----------------------------------------|----------------------|----|
| Primary tumour | | | | |
| Tx | | Tumour can not be assessed | | |
| T0 | | No evidence of tumour | | |
| T1 | <5cm in greatest dimension | | | |
| | T1a | No spreading to the superficial fascia | | |
| | T1b | Spreading | | |
| T2 | >5cm in greatest dimension | | | |
| | T2a | No spreading to the superficial fascia | | |
| | T2b | Spreading | | |
| Regional lymph nodes | | | | |
| Nx | Regional lymph nodes can not be assessed | | | |
| N0 | No regional lymph nodes metastasis | | | |
| N1 | Regional lymph nodes metastasis | | | |
| Distant metastasis | | | | |
| Mx | Distant metastasis can not be assessed | | | |
| M0 | No distant metastasis | | | |
| M1 | Distant metastasis | | | |
| Stage grouping | | | | |
| Stage I | T1a, T1b, T2a, T2b | Grade I | N0 | M0 |
| Stage II | T1a, T1b, T2a | Grade II-III | N0 | M0 |
| Stage III | T2b | Grade II-III | N0 | M0 |
| Stage IV | Any T | Any G | N1 | M0 |
| | Any T | Any G | N0 | M1 |
| Staging relating to MSKCC ^{3,8} | | | | |
| | Favourable Factors | | Unfavourable Factors | |
| Size | < 5cm | | >5cm | |
| Extension | Superficial | | Deep | |
| Grade | I | | II-III | |
| Stage 0 | 3 favourable factors | | | |
| Stage I | 2 favourable factors | | | |
| Stage II | 1 favourable factor | | | |
| Stage III | 3 unfavourable factors | | | |
| Stage IV | M1 | | | |

Table 2. Univariate analysis of the impact of the different prognostic factors on overall survival, disease-free survival and disease-specific survival (median values in months).

In thick: significant in univariate analysis.

| | n | Overall Survival | | Disease-free | | Disease-specific | |
|-------------------|----|------------------|--------------|--------------|--------------|------------------|--------------|
| | | Median | p-value | Median | p-value | Median | p-value |
| Gender | | | | | | | |
| M | 20 | 43 | 0.760 | 16 | 0.644 | 60 | 0.627 |
| F | 22 | 18 | | 14 | | 44 | |
| Age | | | | | | | |
| <50 | 20 | 38 | 0.188 | 15 | 0.886 | 43 | 0.749 |
| ≥50 | 22 | 20 | | 12 | | 66 | |
| Radiation history | | | | | | | |
| No | 32 | 37 | 0.775 | 15 | 0.628 | 56 | 0.789 |
| Yes | 10 | 11 | | 9 | | 18 | |
| Site | | | | | | | |
| scalp/face | 9 | 18 | 0.674 | 14 | 0.289 | 32 | 0.678 |
| sinonasal tract | 17 | 27 | | 14 | | 42 | |
| parotid/neck | 10 | 31 | | 13 | | 43 | |
| upper airway | 6 | 58 | | 47 | | 60 | |
| Margins | | | | | | | |
| Negative | 10 | 92 | 0.159 | 92 | 0.007 | 97 | 0.042 |
| ≤10 mm | 17 | 32 | | 14 | | 43 | |
| Positive | 10 | 19 | | 13 | | 22 | |
| Radioth. | | | | | | | |
| No | 24 | 37 | 0.551 | 14 | 0.053 | 72 | 0.051 |
| Primary | 2 | 13 | | 1 | | 13 | |
| Adjuvant | 16 | 24 | | 15 | | 36 | |
| Chemoth. | | | | | | | |
| No | 32 | 30 | 0.439 | 15 | 0.527 | 60 | 0.304 |
| Primary | 2 | 9 | | 0 | | 9 | |
| Adjuvant | 8 | 31 | | 15 | | 50 | |
| N1 or M1 | | | | | | | |
| Yes | 4 | 9 | 0.032 | 5 | 0.158 | 11 | 0.002 |
| No | 38 | 30 | | 15 | | 58 | |
| Size | | | | | | | |
| ≤5cm | 30 | 28 | 0.758 | 14 | 0.287 | 56 | 0.584 |
| >5cm | 12 | 28 | | 21 | | 42 | |
| Extension | | | | | | | |
| Superficial | 7 | 45 | 0.237 | 42 | 0.102 | 96 | 0.081 |
| Deep | 35 | 19 | | 14 | | 38 | |
| Grade | | | | | | | |
| I | 9 | 56 | 0.094 | 31 | 0.364 | 76 | 0.171 |
| II ou III | 33 | 18 | | 13 | | 43 | |
| AJCC | | | | | | | |
| I | 8 | 49 | 0.054 | 37 | 0.153 | 56 | 0.018 |
| II | 19 | 28 | | 15 | | 66 | |
| III | 5 | 13 | | 4 | | 13 | |
| IV | 4 | 9 | | 5 | | 11 | |
| MSKCC | | | | | | | |
| 0 + I | 9 | 42 | 0.198 | 27 | 0.517 | 56 | 0.048 |
| II | 19 | 43 | | 18 | | 60 | |
| III | 7 | 12 | | 2 | | 13 | |
| IV | 1 | 11 | | 11 | | 11 | |
| TNM | | | | | | | |
| T1aN0M0 | 4 | 56 | 0.603 | 20 | 0.930 | 91 | 0.151 |
| T1bN0M0 | 20 | 27 | | 17 | | 56 | |
| T1bN1M0 | 1 | 43 | | 9 | | 43 | |
| T2aN0M0 | 2 | 69 | | 69 | | 69 | |
| T2bN0M0 | 6 | 55 | | 18 | | 55 | |
| T2bN1M0 | 2 | 4 | | 1 | | 6 | |
| T2bN0M1 | 1 | 11 | | 11 | | 11 | |

Figure 1. : Disease-free survival (DFS) probability according to the margin status.

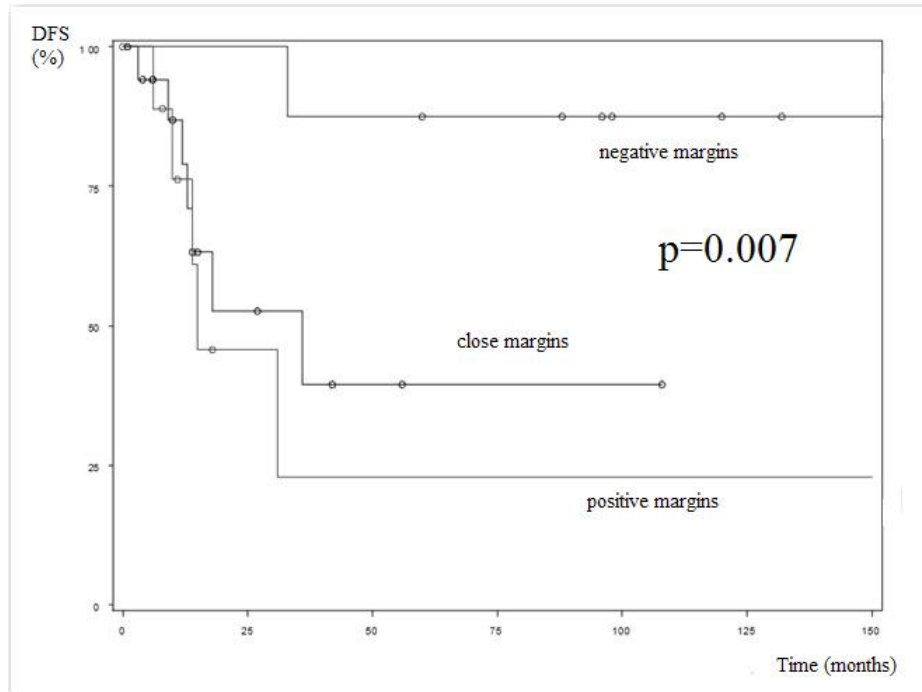


Figure 2.: Disease-specific survival (DSS) probability related to stage grouping according to the AJCC staging system.

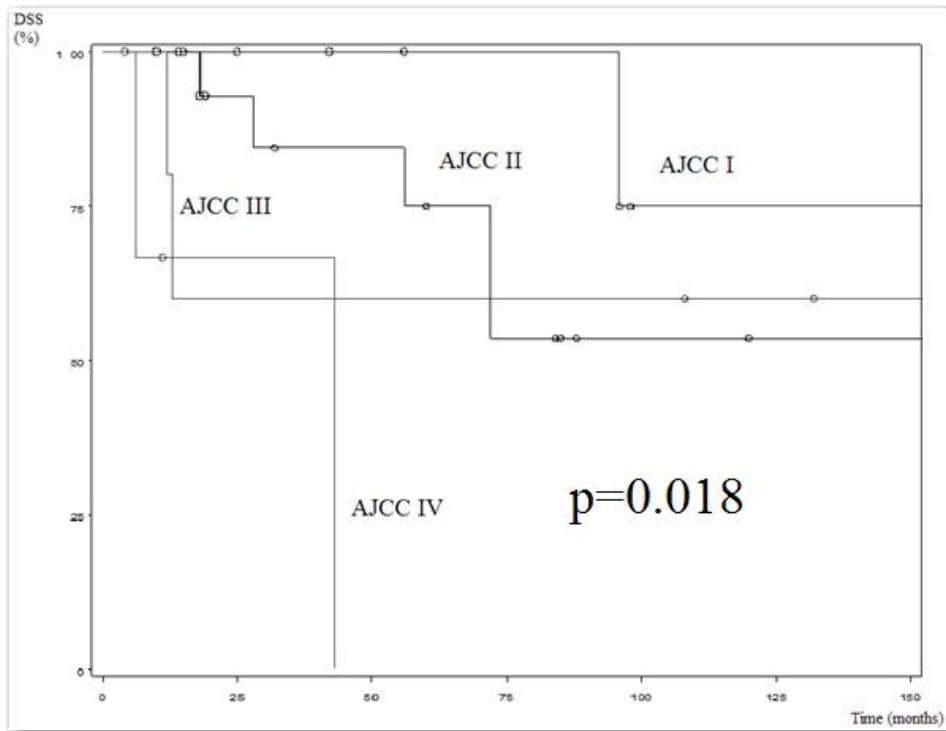


Figure 3. : Overall survival, disease-free survival and disease-specific survival probabilities for the reported series

