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LETTER TO THE EDITOR



# Female gender in the hormonally active age group plays a major role in high-grade chondrosarcoma survival

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## Introduction

Chondrosarcoma (CS) is a rare malignant neoplasm with cartilage differentiation and is the second most common primary bone malignancy [1,2]. The clinical behaviour and prognosis of these tumours depend upon many variables, of which histological grade is one of the most crucial [3,4]. Women have been shown to have a survival advantage for most cancers [5]. Studies in the literature have mainly focussed on more common malignancies like lung, renal and colorectal carcinoma [5–8]. In sarcomas, the role of oestrogen has mainly been studied in sarcomas affecting female organs. Expression of hormone receptors has been associated with favourable survival outcome in endometrial stromal sarcoma [9] and uterine sarcomas [10]. Literature describing the role of hormones on bone sarcomas in scarce, although the beneficial role of female gender in CS has been reported in some large nationwide studies [2,11] but studies have failed to identify any influence of gender on the disease-free survival [12–14].

Sex hormones, especially oestrogen, are important in the regulation of bone development. Mutations in oestrogen specific receptor 1 (ESR1) have demonstrated an important role for oestrogen in the proliferation and differentiation of chondrocytes in the physeal growth plate [15]. Components involved in the oestrogen signalling pathway, have been found in CS, although their exact role remains unclear [16–18].

The purpose of this study was to investigate the role of gender on disease-specific survival (DSS) and local recurrence (LR) in a large cohort of primary CS. Moreover, we aimed to study the role of gender in hormonally active age and compare it to different grades of CS.

## Material and methods

This retrospective study included 702 patients, identified from prospectively maintained databases, who had been diagnosed with a primary CS in the pelvis or extremity between 1990 and 2015, at three tertiary sarcoma units; the Royal Orthopaedic Hospital, Birmingham, UK, Helsinki University Hospital, Helsinki, Finland and Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. All patients were diagnosed and treated at the referral hospital. Those who were primarily treated elsewhere and referred for the management of a recurrence were excluded. A minimum of 2 years' follow-up for survivors was required. Resection specimens were examined by specialised bone sarcoma pathologists, for grade and margin of resection. The highest grade seen on histology was taken as the definitive grade, even when this higher grade comprised only a small number of cells. The margin was quantified by specialist bone sarcoma pathologist and classified according to the system described by Enneking [19].

### *Statistical analysis*

DSS and local recurrence-free survival (LRFS) rates including 95% confidence intervals (CIs) were assessed using the Kaplan–Meier method. Survival rates were calculated from the date of surgery to the most recent follow-up, confirmation of an LR or death due to sarcoma or the treatment of sarcoma. Between-group comparisons were performed using the log-rank test. The Cox regression model was used to identify independent factors affecting DSS and LRFS. Continuous variables were reported as mean and 95% CI. Differences in proportions were assessed using Fisher's exact test. We calculated the CI for relative risks. All analyses were performed using SPSS Statistics version 24.0 (IBM, New York, NY, USA), and a $p$ value of $<.05$ was considered significant.

## Results

The mean age was 52 years (range 10–95 years) in male patients and 53 years (range 7–91 years) in female patients ($p = .425$). About 50.2% of the patients were younger than 55 years and 49.8% were older than 55 years. Mean size was 11 cm in males and 10 cm in females ($p=.1$). There was female prominence for tumours in the proximal humerus

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Supplemental data for this article can be accessed here.

**Table 1.** Patient demographics.

| Eligible patients | Total 702 | Female 305 (43.3%) | Male 397 (56.6%) | *p* Value |
|---|---|---|---|---|
| Grade | | | | .001 |
| Grade 1 | 228 (32.8%) | 120 (39.5%) | 108 (27.5%) | |
| Grade 2 | 257 (36.9%) | 103 (33.9%) | 154 (39.3%) | |
| Grade 3 | 115 (16.5%) | 36 (11.8%) | 79 (20.2%) | |
| Dedifferentiated | 96 (13.8%) | 45 (14.8%) | 51 (13.0%) | |
| Site | | | | .001 |
| Pelvis | 193 (27.5%) | 55 (18.0%) | 138 (34.8%) | |
| Proximal humerus | 106 (16.7%) | 64 (25.5%) | 42 (11.0%) | |
| Proximal femur | 92 (11.4%) | 34 (13.5%) | 58 (15.2%) | |
| Distal femur | 72 (11.4%) | 32 (12.7%) | 40 (10.5%) | |
| Scapula | 44 (7.0%) | 22 (8.8%) | 22 (5.8%) | |
| Local recurrence | 165 (23.6%) | 61 (20.1%) | 104 (26.3%) | .053 |
| Metastases at any time | 138 (19.7%) | 46 (15.1%) | 92 (23.2%) | .007 |
| Mean size in cm | 10.6 | 10.1 | 11.0 | .100 |
| Mean age in years | 53 | 54 | 52 | .425 |
| Under 55years | 352 (50.2%) | 143 (47.0%) | 209 (52.6%) | .148 |
| Over 55 years | 349 (49.8%) | 161 (53.0%) | 188 (47.4%) | |
| Margins | | | | .270 |
| Intralesional | 168 (23.9%) | 84 (27.5%) | 84 (21.2%) | |
| Marginal | 208 (29.6%) | 86 (28.2%) | 122 (30.7%) | |
| Wide | 292 (41.6%) | 124 (40.7%) | 168 (42.3%) | |
| Extracorporeal irradiation and reimplantation | 6 (0.9%) | 1 (0.3%) | 5 (1.3%) | |
| NA | 28 (3.9%) | 18 (4.6%) | 10 (3.3%) | |
| Margins grade 2 | | | | .676 |
| Intralesional | 49 (11.3%) | 16 (15.5%) | 33 (21.4%) | |
| Marginal | 72 (28.0%) | 29 (28.2%) | 43 (27.9%) | |
| Wide | 126 (49.0%) | 55 (53.4%) | 71 (46.1%) | |
| Extracorporeal irradiation and reimplantation | 1 (0.4%) | – | 1 (0.6%) | |
| NA | 8 (3.1%) | 3 (2.9%) | 6 (3.8%) | |
| Margins grade 3 | | | | .364 |
| Intralesional | 13 (11.3%) | 6 (16.7%) | 7 (8.9%) | |
| Marginal | 42 (36.5%) | 13 (36.1%) | 29 (36.7%) | |
| Wide | 56 (48.7%) | 17 (47.2%) | 39 (49.2%) | |
| NA | 4 (3.5%) | – | 4 (5.1%) | |

(64% female and 36% male) and a male prominence for pelvic tumours (29% female and 71% male). All other tumour locations showed similar distribution between male and female patients. The rate of LR was 23.6%, 26.3% in male and 20.1% in female ($p = .053$). Among male patients the histological grade was 1 in 27.5%, 2 in 39.3%, 3 in 20.2% and dedifferentiated (DD) in 13.0%. In female patients, the grade was 1 in 39.5%, 2 in 33.9%, 3 in 11.8% and DD in 14.8% ($p = .001$). There was no difference in margins achieved in terms of the proportion of intralesional, marginal or wide excisions between male and female patients ($p = .270$) (Table 1).

After univariable analysis, the overall survival for female patients at 5-years was 78.0% and at 10-years was 74.1%. For male patients, the overall survival at 5-years was 68.2% and at 10-years was 59.5% ($p < .001$). In addition to gender, the univariable analysis identified significant factors affecting DSS to be LR ($p \leq .001$), metastases at diagnosis ($p \leq .001$) and grade ($p \leq .001$).

After multivariable analysis, increasing size (HR 1.028, 95%CI 1.001–1.057, $p = .046$), increasing age (HR 1.035, 95%CI 1.031–1.078, $p = .000$), male gender (HR 1.982, 95%CI 1.399–2.808, $p = .000$), LR (HR 1.766, 95%CI 1.210–2.577, $p = .003$) and increasing grade (HR 3.793, 95%CI 3.150–4.568, $p = .000$) were statistically significant factors worsening DDS.

To more accurately define the role of female gender and by extrapolation, the effect of female hormones on overall and DSS, patients were stratified according to age and gender, with a cut-off of 55 years. This age was chosen as the effect of female hormones diminishes after the menopause and was the mid-point for age distribution. For grade 1 CS and dedifferentiated CS, age stratification or gender did not have a significant effect on DSS. In grades 2 and 3 CS, however, stratifying groups by age (greater or younger than 55 years) and gender, resulted in a statistically significant difference between the groups. Female patients, with grades 2 or 3 CS, less than 55 years had significantly improved DSS when compared to male patients less than 55 years. However, after 55 years, no difference was seen between male and female patients in terms of DSS. Results are summarised in Figure 1 and Supplementary Appendix Figure 2 and Table 2.

LR developed in 165 patients (23.6%); 104 male patients (26.3%) and 61 female patients (20.1%). The univariate analysis identifies significant predictors of LR as gender ($p = .011$) and margin ($p \leq .001$). After multivariable analysis, increasing age (HR 1.017, 95%CI 1.003–1.030, $p = .013$), male gender (HR 1.628, 95%CI 1.079–2.456, $p = .020$), margin (HR 0.485 95%CI 0.372–0.632, $p = .000$ and grade (HR 1.641, 95%CI 1.338–2.012, $p = .000$) were statistically significant factors affecting LRFS.

## Discussion

The beneficial effect of female gender on survival in a number of diseases is well established [20,21]. In cancer, some

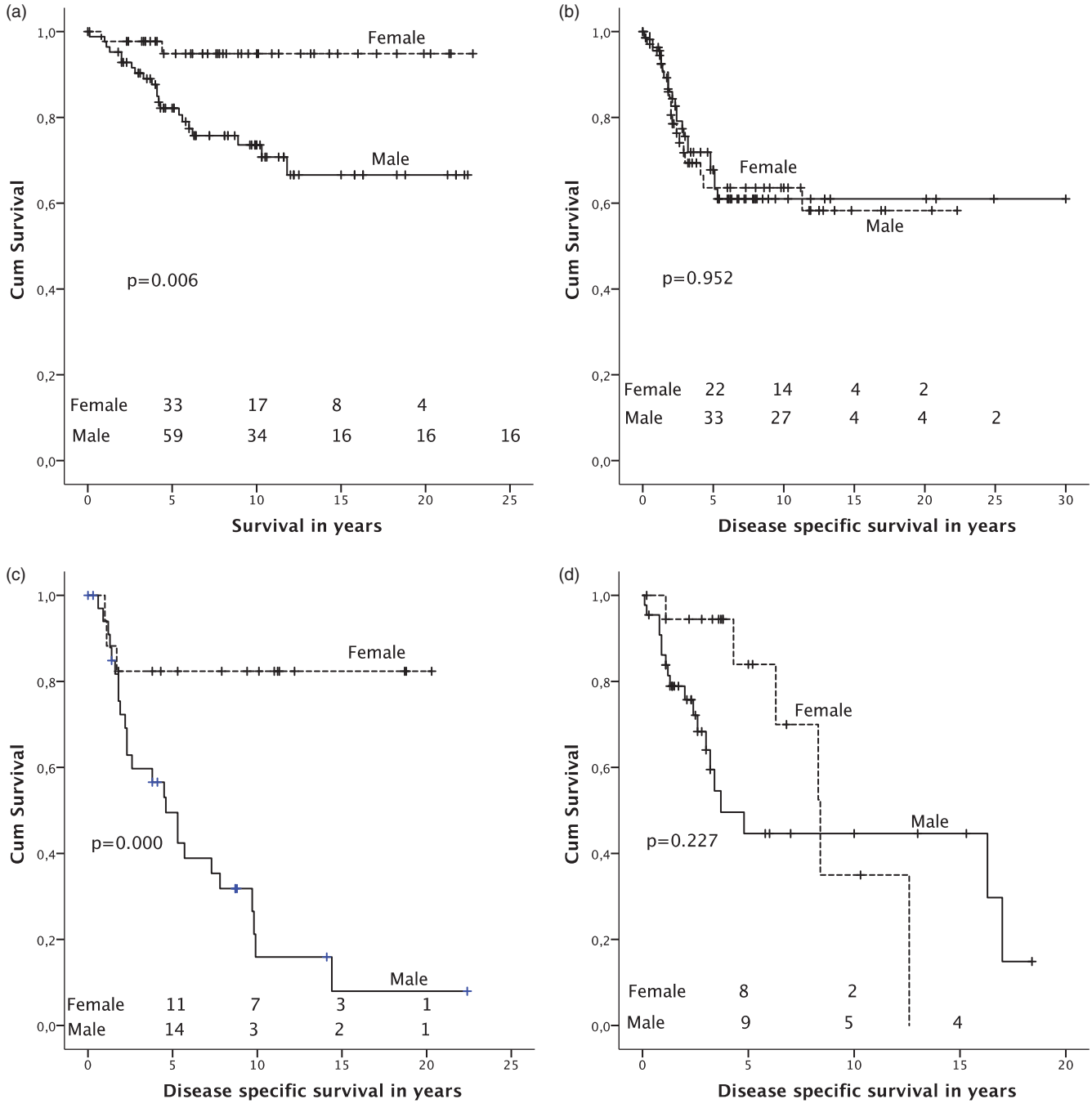


**Figure 1.** (a) Grade 2 chondrosarcoma in patients under 55 years, (b) Grade 2 chondrosarcoma in patients over 55 years, (c) Grade 3 chondrosarcoma in patients under 55 years and (d) Grade 3 chondrosarcoma in patients over 55 years.

**Table 2.** Results from univariate analysis stratified by age 55 years and grade.

| | Under 55 years | | | Over 55 years | | |
|---|---|---|---|---|---|---|
| | DSS at 5-years (95% CI) | DSS at 10-years (95% CI) | *p* Value | DSS at 5-years (95% CI) | DSS at 10-years (95% CI) | *p* Value |
| Grade 1 CS | | | .960 | | | .374 |
| Female | 93.0% (86–100) | 93.0% (86–100) | | 93.4% (86–101) | 93.4% (86–101) | |
| Male | 92.6% (86–100) | 92.6% (86–100) | | 89.1% (79–99) | 89.1% (79–99) | |
| Grade 2 CS | | | .006 | | | .891 |
| Female | 94.9% (88–102) | 94.9% (88–102) | | 63.6% (49–78) | 63.6% (49–78) | |
| Male | 82.2% (75–89) | 73.6% (63–84) | | 67.7% (56–80) | 60.9% (48–74) | |
| Grade 3 CS | | | .001 | | | .239 |
| Female | 82.4% (64–100) | 82.4% (64–100) | | 84.0% (62–106) | 35.0% (−3–73) | |
| Male | 49.3% (32–67) | 15.9% (2–30) | | 49.6% (30–69) | 44.6% (25–64) | |
| Dedifferentiated CS | | | .766 | | | .081 |
| Female | 40.0% (10–70) | 0% (0–0) | | 25.2% (9–41) | 25.2% (9–41) | |
| Male | 38.1% (14–62) | 28.6% (4–53) | | 18.4% (3–34) | 18.2% (3–34) | |

DSS: disease-specific survival; CI: confidence interval; CS: chondrosarcoma.

population-based studies have supported the idea of a protective effect amongst women, though, often these results have been explained by gender differences in site distributions or by the differences in the stages or grades of the tumour [22]. The EUROCARE-2 study analysed survival in 1 million European cancer cases diagnosed between 1985 and 1989. It identified that gender was a predictor of survival, and suggested that women have a biological advantage in surviving cancer [5]. These studies could not find any differences in bone sarcomas, however, all bone sarcomas were pooled into one group, therefore, their results poorly represent the role of gender in different bone sarcomas [22].

In this large observational study, we have shown the importance of sex in the DSS of high-grade CS. Female gender conferred survival almost twice as long when compared to men in our study for comparable tumour grades. In addition to gender, significant factors were pelvic and proximal humerus locations, grade, age and size, all known factors to affect survival. Tumour size was a significant factor in our multivariate model, in accordance with the available literature [23]. Male patients, in general, tend to have slightly larger tumours, but we were unable to explain the difference seen between male and female patients just by variations in tumour size. We have also demonstrated a variation in tumour location between male and female patients. Women have statistically less pelvic CSs, and more CSs in the proximal humerus. However, we have demonstrated that even taking into account the variations in location and grade between male and female patients, for grades 2 and 3 tumours, the female gender confers a survival advantage when compared to male patients.

We have demonstrated that the protective effect of being female is age-dependent. When patients were stratified by gender and age (over 55 years), both in grade 2 and 3 CSs, female patients under 55 years had a significant survival advantage when compared to male patients under 55 years. Moreover, when women passed the menopause (assumed to be over 55 years of age), the difference in survival when stratified for both gender and age disappeared.

Given the significant difference seen with both age and gender, the logical responsible factor is the change in sex hormone expression caused the menopause with a reduction in the apparent protective effect seen in younger females when compared to males. In the male population, this effect is not seen which again suggests an effect of female sex hormone expression. We have shown the importance of hormone status, as hormonally active females had significantly better survival when compared to men or women having passed the menopause. Oestrogens have been shown to have an important effect on cartilage under physiologic and pathologic conditions. Oestrogen is crucial for normal longitudinal growth, growth plate fusion and on terminating longitudinal growth in adults of both sexes [24,25]. Female patients have been shown to have a significantly higher prevalence of osteoarthritis after the oestrogen decline seen following menopause as compared with male patients during the same time frame [26,27]. The possible inhibitory role of oestrogen in benign bone tumours is shown in osteochondromas. It is well established that osteochondroma increase in size in the peri-pubertal phase and stop growing at the end of puberty. The 17-beta-estradiol, a naturally occurring oestrogen, acts as an inhibitor of chondrogenic differentiation on mesenchymal cells [28]. Oestrogen directly affects chondrocyte proliferation, differentiation and extracellular matrix synthesis and indirectly other hormones and local factors secreted by cells in response to oestrogen stimulation. Oestrogen receptor (ER) $\alpha$ is found in breast cancer cells and endometrium whereas ER$\beta$ is found in bone. It has been shown, that selected CSs have nuclear immunoreactivity for ER$\alpha$ [17,29] and ER$\beta$ [18]. Furthermore, it has been shown that aromatase, the enzyme that mediates the final step in oestrogen synthesis, is expressed in CS and therefore the oestrogen-signalling pathway has been speculated as a potential target for therapy. The conclusion from these studies implies that CS may be susceptible to anti-oestrogen therapy. However, *in vitro* studies with aromatase inhibitors, did not have a significant effect on the proliferation of CS cells [16].

The role of hormones in sarcoma has mostly recently been investigated in gynaecological sarcomas, which are regarded as hormone-responsive tumours [30]. Expression of hormone receptors ER-$\alpha$, PR and AR was associated with favourable survival outcomes in endometrial stromal sarcoma [9] as well as uterine sarcoma [10]. Available evidence on the role of gender in CS is inconsistent. The large national Surveillance, Epidemiology and End Results (SEER) database has reported female gender as a significant factor for survival [2,11]. However, in a comparable nationwide database from the Netherlands looking at survival in CS, no effect of gender was identified, which may reflect variations in diagnosis, particularly in low-grade CS [13]. The role of age has been found to be significant in numerous studies and is probably a significant factor itself [2,11,13,14]. However, this is the first study to identify the variation in survival seen between men and women of younger age, which is not carried forward into the older age group. As CS is the only primary tumour of bone to predominantly affect the adult population, the findings of gender effect that is age dependent, is of even greater significance. The role of the female gender as a positive prognostic factor is of great interest and further work is required to identify the mechanism of action between sex hormones and high-grade CS. However, this study opens new perspectives for the treatment of high-grade CS, which historically has been seen as a surgical disease.

In conclusion, our results show that in high-grade CS, female gender, most likely the expression of oestrogen, has a significant effect on survival as women during their age of fertility, have improved survival when compared men of comparable age, an effect that diminishes after the age of menopause.

## Disclosure statement

The authors report no conflicts of interest.

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