# Tumour characteristics and survival in familial breast cancer prospectively diagnosed by annual mammography.

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PM, TH, AIH and DGE designed the project,
PM, KT and DGE computed the results
PM and DGE wrote the manuscript.
All: Contributed to design of the project, interpretation of the results, commented upon the manuscript and approved the final manuscript.

## Abstract

~~At risk w~~Women ~~in~~ from breast cancer families without a demonstrable *BRCA1/2* mutation were subjected to annual mammography from age 30 years onwards. One-hundred and ninety-eight patients were ~~prospectively~~ diagnosed prospectively with invasive breast cancer and followed for a total of 15,513 years. Overall 10-~~-~~year~~s~~ survival was 88%. Together with our previous report that women in such kindreds had about twice the population risk of breast cancer, the combined conclusion was that the overall chances of ~~contracting~~ developing ~~an incurable~~ breast cancer causing death within 10 years before 50 years of age was 1% or less when subjected to annual mammography and current treatment. These are empirical prospective observations which may be used for genetic counselling.

The majority (160/194=84%) of patients had ER+ and/or low grade tumours with 92% 10-year~~s~~ survival. One~~A~~ minor group~~fraction~~ of the patients had ER- ~~and/or high grade~~ tumours, another ~~minor~~small group had high grade tumours with nodal spread, both groups ~~which~~ were ~~both~~ associated with worse prognosis, but the two groups were not mutually associated. ~~but possibly through independent carcinogenetic pathways.~~


## Introduction

Family history has been used to identify women at increased risk ~~for~~ of developing breast cancer [1]. Women at increased breast cancer risk ~~for breast cancer~~ have been subjected to annual mammography for early diagnosis aiming ~~at~~ for early treatment with the hope of improving prognosis [2-5]. The two collaborating centres issuing this report initiated clinical activities more than 20 years ago ~~their clinical activities~~ as open prospective trials, referring all women at appropriate risk to undergo annual mammography (Mx). Follow up has been actively sought effectively making the study an open prospective observational trial. We have tested all breast cancer kindreds seen throughout these years for *BRCA1/2* mutations [6-10], and we have reported risk for breast cancer in healthy women in breast cancer kindreds without a demonstrable *BRCA1/2* mutation [11]. The results were that women having one young (mother or sister) with breast cancer before 50 years of age, had no increased risk for breast cancer before 50 years of age, while those with two or more close relative with breast

cancer had twice population risk of breast cancer. The latter implied that women with two or more close relatives with breast cancer had 4% risk for breast cancer before 50 years of age. We here report survival when breast cancer was diagnosed prospectively ~~diagnosed~~ in kindreds without a demonstrable *BRCA1/2* mutation.

## Methods

The series include all cases subjected to annual mammography having increased risk for breast cancer due to family history from the outpatient cancer genetic clinics in Manchester (UK) and Oslo (Norway). The Norwegian series included 3,161 patients and was censored September 2013. The UK series included 9,500 patients and was censored ~~……~~in October 2013. ~~At risk w~~Women at increased breast cancer risk ~~in~~from families without a demonstrable *BRCA1/2* mutation were subjected to annual mammography from age 30-35 years onwards. The annual examinations were performed in dedicated breast cancer diagnostic centres. Examination did not routinely include ultrasound, ~~clinical breast examination~~ or MRI, although clinical breast examination was carried out in Manchester. ~~, but~~However, USS and occasionally MRI ~~such~~ were ~~done~~performed with low ~~a~~ threshold if indicated by the results of the mammographic examination. How the Norwegian and Manchester series were ascertained and genetically tested to exclude causative *BRCA1/2* mutations, has previously been described in detail [11-12]. In short, a) all available breast and ovarian cancer cases, b)and/or obligate carriers in the families, and c)all prospectively diagnosed cases were examined by sequencing and MLPA methods, additionally in Norway - if none such were available - d) healthy women at risk themselves were tested. All families where one or more persons with causative mutation(s) were found, were excluded from the present study.

In the Norwegian series, ~~at risk~~ women at high and moderate breast cancer risk as described in the previous report [11] as well as women with a male ~~person~~ relative between the breast cancer case and themselves were initially selected. In the UK series, all women at high or moderate risk (lifetime risk of 1 in 6 or higher [2,4] based on family history were selected. All cases with breast cancer prior to inclusion or at first prospective~~ly~~ Mx were excluded. All breast cancer cases, irrespective of mode of detection, after first prospectively planned Mx were assessed. Survival after first diagnosed breast cancer was calculated, any possible second cancer in any organ was not considered besides for cause of death as described below.

The following observations were used for this study: Age at diagnosis, age at last follow-up/age at death if dead, tumour size, histopathological grade (grade) scored as low (1), intermediate (2) or high (3), estrogen receptor (ER) positive(+) or negative(-) , carcinoma in situ (CIS)/invasive carcinoma without nodal spread at diagnosis (N-)/nodal spread at diagnosis (N+), and the cancers were scored as ductal (D) or lobular (L). Mode of ~~diagnosing~~ the breast cancer diagnosis was not included as a variable in the present study. Only a few tumours had been tested for HER2 as this was not routine until recently, therefore, HER2 status was not included in the analyses.

Associations between categorized variables were considered by chi-square tests. Differences in distributions for continuous variables were assessed by two-sample t-tests. Survival was estimated by the Kaplan-Meier algorithm as time from diagnosis to last follow-up/death. Each patient was scored as alive or dead when censored. Causes of death were identified from the medical files and cancer registry (UK) and patients having died of causes other than breast cancer and not having had spread from breast cancer when dying, were censored as alive to derive a disease-specific survival. Univariate and multivariate hazard rates (HR) for death were calculated by using the Cox proportional hazard method.

Ethics

All patients had consented to genetic testing according to national legislation for health care, and all patients had consented to the current research as approved by national ethical committees

Results

Forty-three cases (18%) had CIS (39 DCIS and 4 LCIS) and were excluded from further analyses.

Out of 198 cases with infiltrating breast cancer, 194 had been examined once or more after diagnosis and were included in the survival analyses. Mean and median ages at diagnoses were 49.5 and 49.0 years, respectively. They had been observed for a total of 15,513 person years, with a mean of 7.6 years~~,~~ and median 7.1 years.

Fifty-four percent of the cases were aged less than 50 years at diagnosis. Eighty-seven percent of the cancers were ductal, 75% were N-, 78% were ER+ and 63% ~~had~~ were Grades 1 or 2.

Median and mean tumour size at diagnosis was 13mm and 15.7mm, respectively. Nineteen (10%) had died. See Table 1 for details.

Table 2 shows ~~the results of t-tests~~ mean tumour sizes and ages at diagnosis, and differences as judged by two-sample t-tests. Lobular cancers were larger and diagnosed at an earlier age than ductal cancers. Grade 3 tumours were larger than grade 1 tumours (p=0.000), cases with~~and~~ N+ had larger tumours ~~cancers were larger then Grade 1 and~~ than with N- cases~~cancers~~, while there was no difference in size between ER- and ER+ tumours. There was an insignificant trend that those having died had larger tumours at diagnosis than those still alive.

Survival in different groups is given in Table 3. Five- and ten-years survival in all cases were 93% and 88%, respectively, and there were no difference in survival between the UK and the Norwegian series (Fig 1). Survival in ductal and lobular cases was similar. Survival was similar in patients aged less than 50 versus more than 50 years at diagnosis (Fig 2). No case with a Grade 1 tumour~~s~~ had died. Cases with ER+ ~~and~~ grade 2 tumours also had good prognosis. Eighty-two percent had grade 1~~,~~ or grade 2 or ER+ tumours and as a combined group had 92% 10-years survival. ER- , and N+ (Fig 3) and Grade 3 (Fig 4) were associated with a higher likelihood of death (p=0.000). ER- tumours ~~was~~ were associated with ~~death~~ increased mortality ~~also~~ even when node negative cases were considered separately (Fig 5), while tumour grade was not significantly associated with death in node negative cases (Fig 6).

Grade and nodal status were highly associated (p=0.000), but ~~-~~ER and nodal status at diagnosis were ***not*** associated, p=0.25 ~~-~~(Table 4).

By univariate Cox proportional hazard, ER, Grade and Nodal status were associated with death, while age at diagnosis and tumour size at diagnosis were not associated with death (Table 5).

By multivariate Cox proportional hazard ER, Grade and Nodal status were associated with ~~death~~ increased mortality ~~while~~ whilst age and size were not. (Table 6).

Discussion

Overall 10--years survival in initially healthy women from *BRCA1/2* negative familial breast cancer families, and who had with cancers prospectively detected cancers when subjected to annual Mx, was 88%.

In our previous report on breast cancer risk for cancer in healthy women in breast cancer kindreds where no *BRCA* mutation was demonstrable [11], we noted that there was no increased risk of early onset breast cancer in those having had only one relative with early breast cancer.only if no other breast cancer cases in the family, while theThe overall risk of breast cancer was about twice the population rate if two or more breast cancer cases had been diagnosed in the family. The latter included a 4% risk for early onset breast cancer before 50 years of age. Considering that the previous and the current findings together,Combined with our previous report risk for breast cancer in these families is approximately twice the population risk, this means that the risk for contractingof developing a an incurable breast cancer before 50 years of age wasis about 2%0.02, which multiplied with by a 12% risk of dying from that breast cancer within 10 years, x 2 x 0.11 < 1% when subjected to annual Mx from 30 years of age, givinges a combined risk of less than 1% to contract an early breast cancer causing death within 10 years. Or – vice versa - the probability to **not** have an early breast cancer **or** being cured from a breast cancer before 50 years of agecausing death within 10 years was > 99%. If stratifying according to family history of breast cancer [11] there was no increased risk of dying from breast cancer before 50 years of age if only one breast cancer case was known in the family (= young affected mother or sister only), while the risk was about 1% if many breast cancer cases had been diagnosed in the family. These were our combined empirical observations in patients from breast cancer kindreds without demonstrable *BRCA* mutations subjected to annual Mx from 30 years of age and with current breast cancer treatment if breast cancer. These data, and which maycould be used for genetic counsellingcounseling of women at moderate breast cancer risk.

With the increasing availability and reduced cost of genetic testing, one may consider testing a healthy woman with a family history of breast cancer directly and not – as has been done so far – test affected relatives initially. If doing so, the question of risk for breast cancer in *BRCA1/2* carrying kindreds in women not having the family's *BRCA* mutation will become an issue to clarify [13], as will the biology of such breast cancers. There is a possibility that some families with highly penetrant *BRCA1/2* mutations may have additional (genetic) factors

causing breast cancer (independently or modifiers of *BRCA1/2* penetrance). Studies are ongoing to address this.

~~What we~~We have reported ~~is~~ the outcome of our health service as applied since the start of the activity. The scope of our study was survival ~~after~~from breast cancer in those accepting our offer of annual mammography from 30 years onwards and current treatment ~~when~~once cancer was diagnosed. The examinations were part of the health care system, and both patient compliance and capacity problems in the diagnostic outpatient clinics might ha~~d~~ve postponed some examinations for some time. We did not focus on screen detected versus interval cancers (which anyway is difficult when some patients because of the frequent examinations felt a lump but did not ~~tell~~inform us until the next scheduled mammography). If considering details on time between examination, screen detected versus interval cancers, and compared those with tumour characteristics ~~like~~such as grade, ER, nodal status and size, the strata would be too many for meaningful calculations in our limited series. The results were that most patients in this highly selected series had low grade and/or ER+ tumours which was associated with very good survival. Survival was so good that stratification of this group with respect to survival ~~had no~~is of little interest. In contrast two infrequent subgroups (ER- and high grade) had worse outcome, and numbers did not allow meaningful substratification of these two groups. These patients are now being subjected to sequencing for many more genes known to be associated with breast cancer in search of biological causative factors.

Surprisingly, young age at diagnosis was not associated with worse survival as has been previously published for unscreened women [14].(Fig 2)

The associations between the findings lead us to the following speculations:

A ~~minor~~ small proportion of the cases had Grade 3 and/or ER- and/or N+ and carried a worse prognosis, but ER- and N+ were not associated with each other. ~~These findings are in keeping with a notion that there may be two different carcinogenetic pathways leading to death: The one is through ER- without necessarily having detectable nodal spread at the time of diagnosis, the other through high grade leading to early nodal spread. As shown in Table 3~~It is interesting that ~~,~~ the effect~~s~~ on mortality on having a tumour being with both N+ and ~~an~~ ER- ~~tumour~~, ~~were~~was additive (Table 3)~~, which is in keeping with the above notion~~. ~~Because ER- and high grade was strongly associated, both pathways may be caused by the same factor(s).~~

Numbers included were, however, limited, and we look forward to see results from other centres on this specific issue.

Conclusions:

In women at increased familial breast cancer risk without a demonstrable *BRCA1/2* mutation, the overall chances of ~~contracting~~ developing an incurable breast cancer before 50 years of age was less than 1% ~~or less~~ when subjected to annual mammography and current treatment. The majority of patients had ER+ and/or Grade 1 or 2 tumours, and were cured. A minor fraction of the patient had ER- tumours and/or nodal spread at diagnosis~~Grade 3 tumours~~, both of which were associated with worse prognosis~~, but possibly through two different carcinogenetic pathways~~ but ER+ and nodal spread at diagnosis were not associated.

Conflict of interests: The authors declare that they have no conflict of interest.

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Table 1.

Findings in 198 infiltrating breast cancer cases by categorized variables.

| **Scoring** | **Subgroups** | **Number of cases (% of valid cases) in subgroup** |
|---|---|---|
| Type (n*=193) | Ductal | 168(87%) |
| | Lobular | 25 (13%) |
| Age groups (n*=198) | < 50 years | 106(54%) |
| | >= 50 Years | 92 (46%) |
| Nodal status at diagnosis (n*=197) | Node negative | 147(75%) |
| | Nodal spread | 50(25%) |
| ER-status (n*=185) | Negative | 40(22%) |
| | Positive | 145(78%) |
| Grade (n*=192) | Low | 38 (20%) |
| | Intermediate | 83(43%) |
| | High | 71 (37%) |
| Censored (n*=198) | Alive | 179 (90%) |
| | Dead | 19 (10%) |
| Centre (n*=198) | Norway | 69 (35%) |
| | Manchester | 129 (65%) |

n*: number of cases with valid information in selected group.

Table 2
Results of two-sample t-tests for differences between groups.

| **Groups** | **Mean tumour size (mm)** | **p** | | **Mean age at diagnosis (years)** | **p** |
|---|---|---|---|---|---|
| Ductal | 14.9 | 0.03 | | 49.1 | 0.007 |
| Lobular | 23.5 | | | 53.2 | |
| | | | | | |
| Grade 1 | 9.6 | 0.000 | | 49.5 | 0.72 |
| Grade 3 | 18.4 | | | 49.9 | |
| | | | | | |
| Node pos | 22.1 | 0.000 | | 49.6 | 0.97 |
| Node neg | 13.8 | | | 49.5 | |
| | | | | | |
| ER negative | 17.1 | 0.59 | | 48.7 | 0.57 |
| ER positive | 15.8 | | | 49.5 | |
| | | | | | |
| Dead | 22.0 | 0.12 | | 48.7 | 0.67 |
| Alive | 15.4 | | | 49.6 | |

Table 3.
Survival in different groups and results of Mantel tests for differences between groups.

| **Selection** | **Subgroups** | **Number of cases included** | **5 years survival (95%CI)** | **10 years survival (95% CI)** | **p** |
|---|---|---|---|---|---|
| All | All | 194 | 93**%** (88-96) | 88**%** (81-92) | |
| | | | | | |
| | Norway | 69 | 94**%** (85-98) | 90**%** (78-95) | 0.85 |
| | Manchester | 125 | 92**%** (84-96) | 88**%** (79-93) | |
| | | | | | |
| | <50 years | 103 | 95**%** (87-98) | 88**%** (77-94) | 0.80 |
| | 50+ years | 91 | 91**%** (82-95) | 87**%** (77-93) | |
| | | | | | |
| | Ductal | 165 | 93% (87-96) | 89% (81-93) | 0.33 |
| | Lobular | 24 | 91% (66-98) | 85% (60-95) | |
| | | | | | |
| | ER neg | 40 | 74% (56-86) | 67% (52-83) | 0.000 |
| | ER pos | 142 | 98% (93-99) | 93% (85-97) | |
| | | | | | |
| | Grade 1 | 38 | 100% | 100% | 0.000 |
| | Grade 2 | 81 | 96% (87-99) | 96% (87-99) | |
| | Grade 3 | 69 | 85% (72-92) | 72% (57-83) | |
| | | | | | |
| | N- | 143 | 96 % (91-98) | 94% (88-97) | 0.000 |
| | N+ | 50 | 83 % (67-91) | 69% (51-82) | |
| | | | | | |
| Grade 1, Grade 2 or ER+ | | 160 | 96% (91-99) | 92% (85-96) | |
| | | | | | |
| N- | Grade 1 | 38 | 100% | 100% | 0.11 |
| | Grade 2 | 64 | 96% (86-99) | 96% (86-99) | |
| | Grade 3 | 38 | 91% (75-97) | 87% (69-95) | |
| | | | | | |
| | ER pos | 107 | 100% | 99% (91-100) | 0.000 |
| | ER neg | 26 | 79% (57-91) | 74% (50-87) | |
| | | | | | |
| Grade 3 and ER- | | 31 | 73% (51-86) | 63% (40-79) | |
| | | | | | |
| N+ and ER- | | 13 | 63% (29-85) | 53% (20-77) | |
| | | | | | |
| N+ and Grade 3 and ER- | | 11 | 55% (18-81) | 41% (10-71) | |

Table 4.

Nodal status at diagnosis versus tumour receptor status and grade.

| | **Node negative** | **Node positive** | **p** |
|---|---|---|---|
| **ER -** | 26 | 13 | p=0.25 |
| **ER+** | 110 | 35 | |
| | | | |
| **Grade 1** | 38 | 0 | p=0.000 |
| **Grade 2** | 66 | 17 | |
| **Grade 3** | 40 | 30 | |

Table 5 Results univariate Cox proportional hazard for death.

| | | Number of cases | Number of deaths | HR (95% CI) | p-value | log-rank p-value |
|---|---|---|---|---|---|---|
| | | | | | | |
| Age | 25-49 | 94 | 7 | 1 | | 0,425 |
| | 50+ | 81 | 10 | 1.48 (0.56 - 3.89) | 0,428 | |
| | | | | | | |
| Size | 0.1 - 1.0 cm | 63 | 4 | 1 | | 0,147 |
| | 1.1 - 2.0 cm | 72 | 6 | 1.28 (0.36 - 4.55) | 0,700 | |
| | 2.1 - 7.0 cm | 40 | 7 | 2.89 (0.85 - 9.86) | 0,091 | |
| | | | | | | |
| ER | Negative (1) | 38 | 10 | 1 | | 0,00016 |
| | Positive (3) | 137 | 7 | 0.19 (0.07 - 0.50) | 0,001 | |
| | | | | | | |
| Grade | Low* or intermediate | 108 | 3 | 1 | | 0,00006 |
| | High | 67 | 14 | 8.38 (2.41 - 29.18) | 0,001 | |
| | | | | | | |
| Nodal status | Negative | 130 | 6 | 1 | | 0,00004 |
| | Positive | 45 | 11 | 6.28 (2.32 - 17.01) | 0,0003 | |

*: No death in cases with low grade.

Table 6 Results multivariate Cox proportional hazard for death.

| | | Number of cases | HR (95% CI) | p-value |
|---|---|---|---|---|
| Age | 25-49 | 94 | 1 | |
| | 50+ | 81 | 2.45 (0.88 - 6.81) | 0,086 |
| | | | | |
| Size | 0.1 - 1.0 cm | 63 | 1 | |
| | 1.1 - 2.0 cm | 72 | 0.59 (0.15 - 2.25) | 0,438 |
| | 2.1 - 7.0 cm | 40 | 1.23 (0.30 - 5.09) | 0,772 |
| | | | | |
| ER | Negative | 38 | 1 | |
| | Positive | 137 | 0.25 (0.09 - 0.71) | 0,009 |
| | | | | |
| Grade | Low* or intermediate | 108 | 1 | |
| | High | 67 | 4.42 (1.18 - 16.56) | 0,027 |
| | | | | |
| Nodal status | Negative | 130 | 1 | |
| | Positive | 45 | 4.08 (1.28 - 13.06) | 0,018 |

*: No death in cases with low grade.

Fig 1

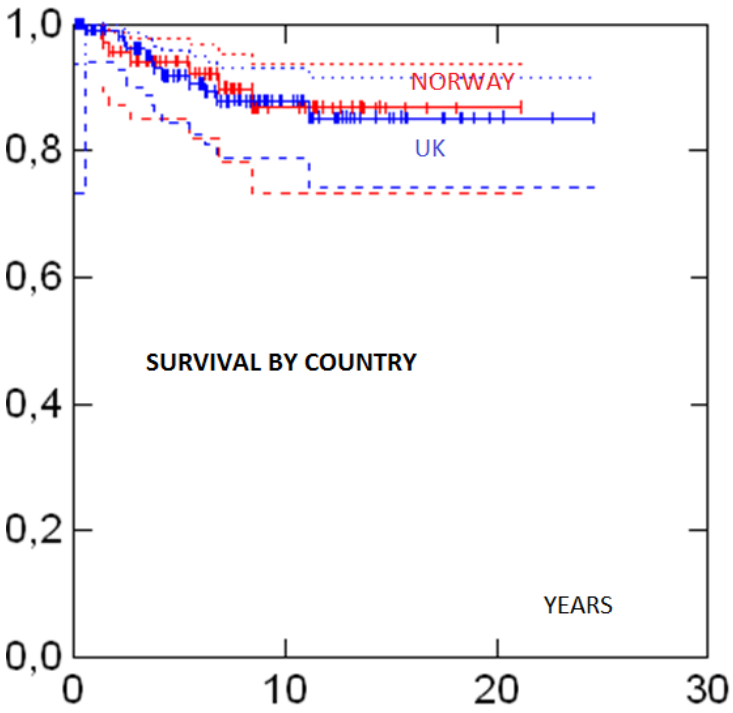
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Fig 2

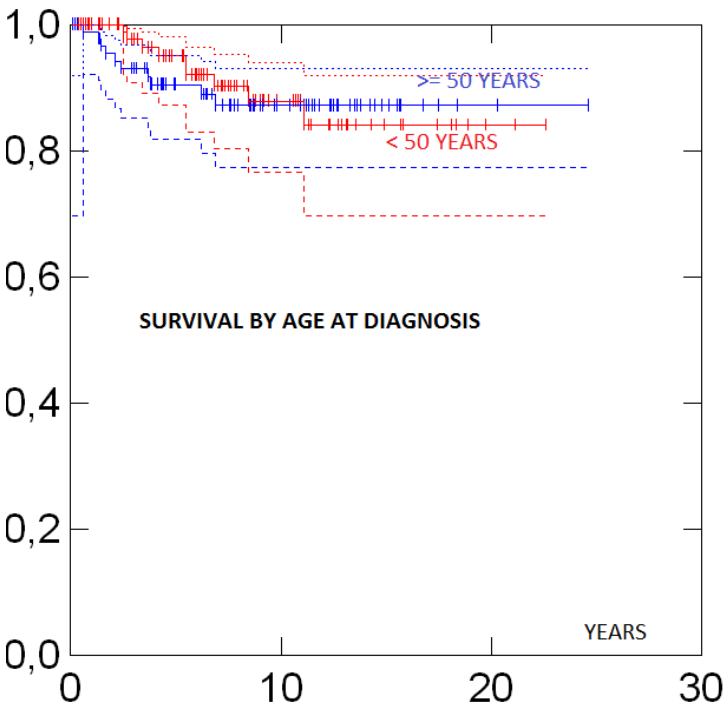
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Fig 3

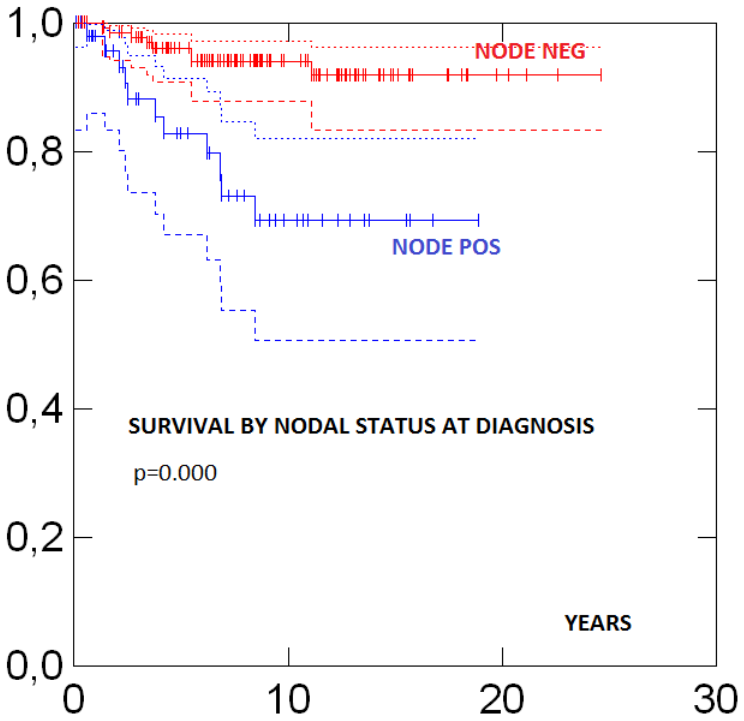
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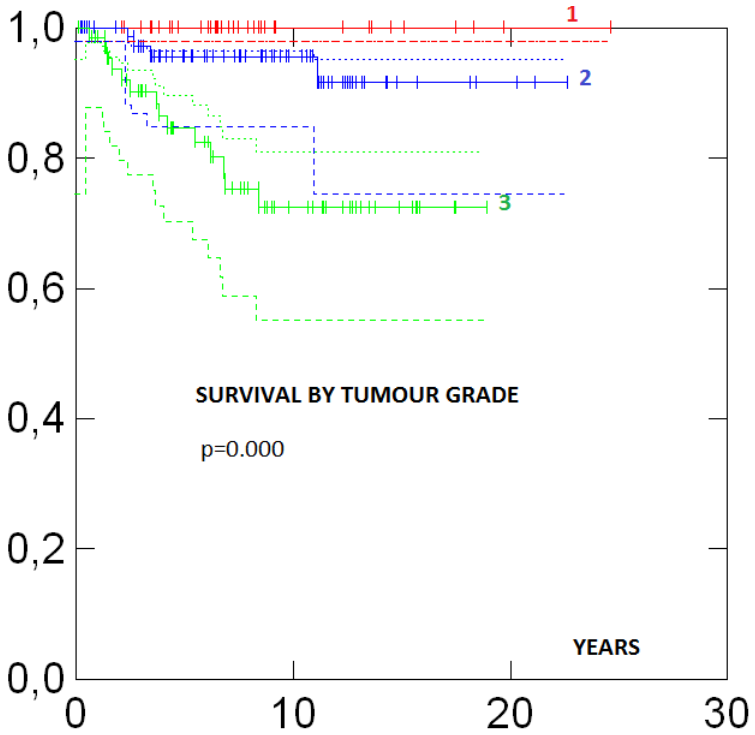
Fig 4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SURVIVAL BY TUMOUR GRADE
p=0.000
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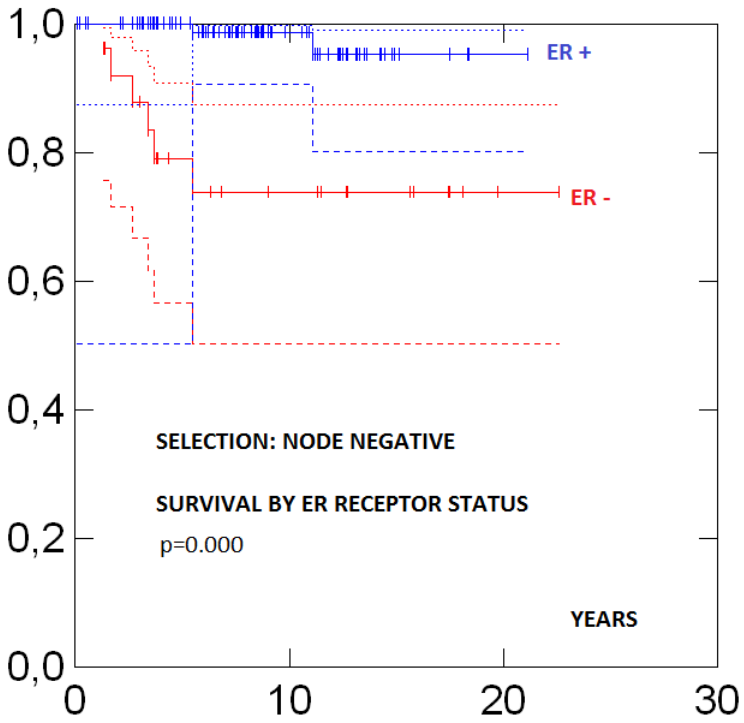
Fig 5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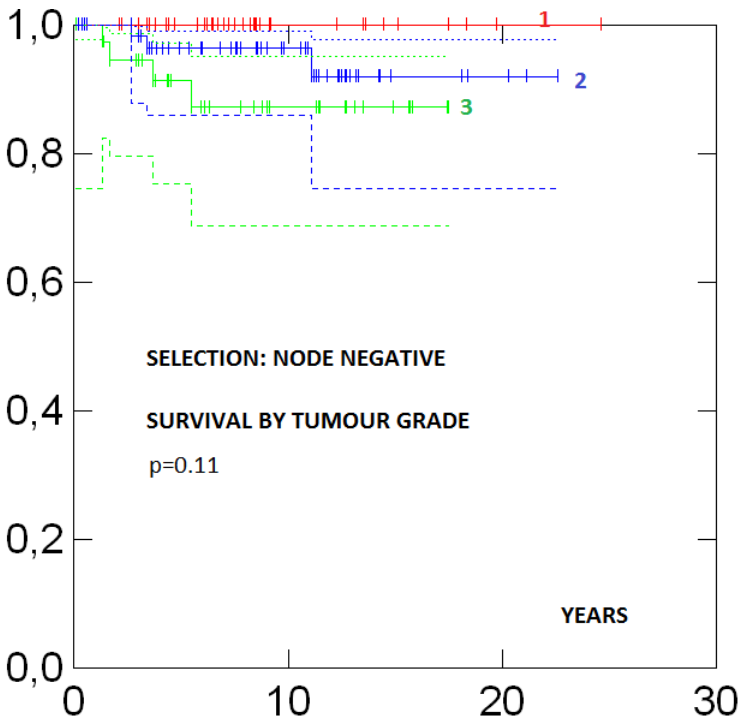
SURVIVAL BY ER RECEPTOR STATUS
p=0.000
YEARS

Fig 6


1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
1
2
3
SELECTION: NODE NEGATIVE
SURVIVAL BY TUMOUR GRADE
p=0.11
YEARS