Epirubicin dose and sequential hormonal therapy – mature results of the HMFEC randomised phase III trial in premenopausal patients with node positive early breast cancer.

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Abstract

Background

The HMFEC trial was developed at a time of uncertainty around the dose intensity of chemotherapy given to premenopausal patients with node positive breast cancer and to the benefits of tailored endocrine therapy in such patients.

Patients and methods

HMFEC was a multi-centre, phase III, open label, randomised controlled trial with a 2x2 factorial design. Eligible patients were premenopausalwith node positive early breast cancer; significant cardiac disease or uncontrolled hypertension were exclusion criteria. Patients were allocated to receive either 8 cycles of $FE_{50}C$ or $FE_{75}C$ (given 3 weekly) with or without hormone manipulation (HM) (tamoxifen or LHRH agonists according to residual hormone levels at end of chemotherapy) irrespective of ER status. The primary endpoint was disease free survival (DFS). Principal analyses were by ITT; however, to reflect contemporary practice, subgroup analyses according to ER status were also conducted. The mature follow-up now available from this modest sized trial enables presentation of definitive results.

Results

Between 1992-2000 a total of 785 patients were randomised into the HMFEC trial (203 $FE_{50}C$-HM, 191 $FE_{50}C$+HM, 198 $FE_{75}C$-HM, 193 $FE_{75}C$+HM).At a median follow-up of 7.4 years, 245 DFS events have been reported (92 ER-, 153 ER+/unknown). The effects on DFS were not statistically significantly different according to epirubicin dose (HR=0.82, 95%CI: 0.63-1.06; p=0.13 $FE_{75}C$ vs $FE_{50}C$); however, $FE_{75}C$ appeared to induce more alopecia and

neutropenia. No statistically significant evidence was observed to support an improvement in DFS in patients allocated HM either overall (HR=0.88, 95%CI: 0.68-1.13; p=0.32) or in patients with ER+/unknown disease (HR=0.85, 95%CI: 0.62-1.17; p=0.32) although effect sizes are consistent with worthwhile clinical effects. Overall, there was no evidence of a difference in survival between any of the four treatment groups of the trial.

Conclusion

Higher doses of epirubicin cause more adverse events in the absence of clear improvement in overall survival. Endocrine therapy with either tamoxifen or goserelin provided no significant added benefit to cytotoxic chemotherapy in this group of patients.

Trial Registration Number: ISRCTN98335268

Introduction

In 1990, at the inception of the HMFEC trial, there was uncertainty surrounding the optimal dose of anthracycline chemotherapy in patients with early breast cancer (EBC). Previously, Bonnadonna et al had reported the success of CMF in delaying recurrence (1) and early EBCTCG overview results had begun to characterise effects of tamoxifen and cytotoxic therapy on breast cancer recurrence and mortality, disclosing an unequivocal benefit for premenopausal patients receiving chemotherapy. At that time, the benefit for tamoxifen alone (i.e. without chemotherapy) was only evident in postmenopausal women (2). Further, the concept of substituting an anthracycline for methotrexate in the CMF regimen was being evaluated by our group, amongst others, in premenopausal patients with node positive EBC and early results suggested a possible benefit for FEC compared with CMF in terms of disease free survival (DFS) (3, 4). However, this trial, as well as others in the adjuvant setting (5) and experience in patients with metastatic breast cancer, had disclosed additional toxicity, especially cardiac toxicity (6). However this was largely considered to occur after relatively high cumulative doses of anthracyclines and more commonly with doxorubicin than with epirubicin. Thus, clinicians were uncertain as to the ultimate worth of anthracycline substitution as well as the optimal anthracycline dosage.

In view of the EBCTCG 1988 meta-analysis, many clinicians argued that adding either tamoxifen or ovarian ablation to chemotherapy in premenopausal patients was both toxic and unnecessary following chemotherapy, especially since cytotoxic chemotherapy often resulted in

amenorrhoea, which itself could have the potential to improve survival (7). A study to assess the effects of adjuvant medical ovariectomy in those who had retained ovarian function after chemotherapy and of tamoxifen in those who had become amenorrhoeic was warranted.

We therefore proposed to assess a 3 weekly schedule of FEC using 50mg/m^2 of epirubicin ($FE_{50}C$), a standard dose at the time, versus FEC using 75mg/m^2 of epirubicin ($FE_{75}C$) followed by hormonal manipulation (HM) or not in premenopausal women with node positive breast carcinoma.

Patients, material and methods

HMFEC was a multi-centre, phase III, randomised controlled trial with a 2x2 factorial design. Patients were randomised to either receive $FE_{50}C$ or $FE_{75}C$ with or without sequential HM. To enter a patient centres faxed the ICCG Data Centre where randomisation was centrally and independently managed. Allocation utilised computer-generated permuted blocks stratified by centre and using a 1:1:1:1 treatment allocation.

Patients with histologically confirmed invasive primary breast cancer were eligible if they were premenopausal (defined as either last menstrual period within one year of randomisation, or circulating oestrogen (E2) and FSH/LH levels compatible with ovarian function)and had 1-5 histologically involved axillary lymph nodes. Patients were to have had either mastectomy or conservation surgery with radiation planned to the breast and axilla. Patients

had to have adequate bone marrow (WBC $\geq 3.5 \times 10^9$/l, platelet count$\geq 100 \times 10^9$/l), renal and hepatic function (creatinine $\leq 120\mu$mol/l, bilirubin $\leq 30\mu$mol/l), be accessible for follow-up, and have given informed consent according to the rules of the participating institution. Patients with significant cardiac disease or uncontrolled hypertension were ineligible.

All treatments administered in the trial were open label. Chemotherapy doses wereeither 5-fluorouracil 600mg/m^2, epirubicin 50mg/m^2, and cyclophosphamide 600mg/m^2 ($FE_{50}C$) or the same regimen but with epirubicin 75mg/m^2 ($FE_{75}C$). The regimen was administered in three-weekly cycles for a total of 8 cycles. Dose modifications and/or delays for chemotherapy were based on treatment day haematological and liver toxicity. Weekly blood counts were performed until recovery at which time chemotherapy could be resumed. In addition, a 25% dose reduction for all drugs at subsequent cycles was recommended for unresolved mouth ulceration. Chemotherapy was discontinued for any patient whose nadir WBC dropped below 1.0×10^9/l or whose platelet count dropped below 25×10^9/l, patients who had appearance of congestive heart failure or persistent arrhythmia, or patients who had a >2 month break in treatment for any reason.

HM was scheduled to start once chemotherapy had been completed. On completion of chemotherapy FSH/LH levels were assessed to evaluate extent of continuing ovarian function and thus to classify whether or not patients remained premenopausal (defined as persistent menstruations and/or low level of FSH/LH, measured once, at the end of chemotherapy). Those

patients previously allocated HM were prescribed a long-acting GnRH agonist (goserelin or equivalent) given subcutaneously every 28 days for 3 years if they remained premenopausal and tamoxifen (20mg daily) for a total of 5 years if they did not. If the GnRH agonist was discontinued for any reason the patient was to receive tamoxifen up to the end of the planned period of hormonal therapy. Routine testing of hormone receptor (HR) status was not yet in place in centres at the time of trial initiation and thus allocation to HM was irrespective of HR status.

The primary endpoint was DFS defined as time to local-regional recurrence, (ipsilateral breast or axillary node relapse), distant recurrence, new primary breast cancer or death from any cause; patients who remained alive and disease-free at their last follow-up were censored at that date. Secondary endpoints were breast cancer free survival (BCFS), defined as time to local-regional recurrence, distant recurrence, new primary breast cancer or breast cancer death prior to confirmation of relapse; DFS using the STEEP definition (8); metastasis-free survival (MFS) defined as time to occurrence of metastases or breast cancer death prior to confirmation of relapse; and overall survival (OS). All time-to-event endpoints were measured from date of randomisation. Where cause of death was unknown, these events were classed conservatively as breast cancer deaths. Treatment-related deaths were classified as any death occurring within 30 days of receiving trial treatment. Relative dose intensity (RDI) was used as a measure of treatment compliance.

HMFEC was designed to test the effect on DFS of two separate treatment comparisons; $FE_{50}C$ versus $FE_{75}C$ and adjuvant chemotherapy +/- sequential HM. Assuming a five year DFS of 60%, 720 patients (180 per group) would enable detection of an absolute difference of 10% (improvement from 60% to 70%) with a 5% significance level and 80% power. To allow for possible non-compliance with follow-up, the trial aimed to recruit 800 patients. Efficacy analyses were conducted using the intention-to-treat population, stratified by ER status and, for the chemotherapy comparison, by the HM randomisation, and for HM, by the chemotherapy randomisation. Evidence subsequent to that available at trial initiation confirmed the restriction of hormone therapy to patients with ER-positive disease. Therefore, it was agreed, a-priori, that patients with ER-positive or ER-negative disease would also be analysed separately due to the differential effect of endocrine therapy according to ER status and the likelihood of confounding due to different time dependent risk profiles for these two patient groups (i.e. ER-negative=high early risk of relapse, ER-positive=lower but prolonged risk of relapse). Time to event analyses were conducted with Kaplan-Meier plots graphically depicting survival functions and log-rank tests providing a comparison between treatment groups. Hazard ratios (HR) were determined with Cox proportional hazards regression analysis both univariately and following adjustment for BMI, age at randomisation, nodal status, tumour grade and size with values <1 favouring $FE_{75}C$ for the chemotherapy comparison and favouring sequential chemotherapy+HM for the HM comparison. This analysis includes all data received and processed by 13 March 2012.

Further details on Materials and Methods are available in the Supplementary Patients and Methods (web appendix – Data A1).

Results

Between 1992-2000 a total of 785 patients from 16 centres in 7 European countries (web appendix-List A1) were randomised (203 $FE_{50}C$-HM, 191 $FE_{50}C$+HM, 198 $FE_{75}C$-HM, 193 $FE_{75}C$+HM) (web appendix-Figure A1). The median observed follow-up was 7.4 years (IQR 4.8-10.1) in all surviving patients. Baseline clinic-pathological characteristics of patients were evenly balanced between treatment groups (web-appendix-table A1).

Chemotherapy compliance was good overall with 706 (89.9%) receiving all 8 cycles of chemotherapy ($FE_{50}C$=363 (92.1%), $FE_{75}C$=343 (87.7%), (web appendix–table A2). The principal reasons for early discontinuation were toxicity and patient choice. Twenty four patients (3.1%) did not start allocated chemotherapy (2 $FE_{50}C$-HM, 5 $FE_{50}C$+HM, 4 $FE_{75}C$-HM, 13 $FE_{75}C$+HM). However, of these, nine patients received alternative anthracycline treatment. These patients were analysed according to randomised treatment. RDI in the ITT population was slightly lower in $FE_{75}C$ patients, with 301 (77.0%) receiving at least 85% of their planned dose intensity compared with 328 (83.2%) of patients allocated $FE_{50}C$.

A total of 756 (96.3%) patients (365 (95.1%) allocated HM, 391 (97.5%) allocated no HM) completed chemotherapy treatment and remained disease-free and could therefore be assessed for menopausal status. In patients

allocated to no HM, 119 (30.4%) were classified as premenopausal post-chemotherapy, 245 (62.7%) were postmenopausal post-chemotherapy and 27 (6.9%) had unassessed menopausal status post-chemotherapy; for those allocated HM, there figures were 79 (21.6%), 275 (75.3%) and 11 (3.0%) respectively. In patients allocated HM, 47 (59.5%) were prescribed GNRH aloneand249 (90.5%) patients received tamoxifen alone as per protocol. 47 (12.0%) patients allocated not to receive HM received either GNRH or tamoxifen (web appendix-table A3).

In total, 245 DFS events have been reported ($FE_{50}C$=133, $FE_{75}C$=112; HM+=114, HM-=131; ER+=153, ER-=92) (web appendix-table A4).There was no evidence that $FE_{75}C$ was significantly better than $FE_{50}C$ for DFS (HR(unadjusted)=0.83, 95%CI:0.65-1.07; p=0.15) – Figure 1a, (HR(adjusted)=0.82, 95%CI:0.63-1.06; p=0.13). However, the effect size for the improvement of DFS for $FE_{75}C$ was consistent with a clinically worthwhile effect compared with $FE_{50}C$ for patients with ER- disease (HR(unadjusted)=0.66, 95%CI:0.44-1.01; p=0.05 – Figure 1b, HR(adjusted)=0.71, 95%CI:0.46-1.12; p=0.14). In addition, for patients with ER+/unknown disease randomised to receive HM,$FE_{75}C$ appeared significantly better than $FE_{50}C$ in terms of DFS (HR(unadjusted)=0.59, 95%CI:0.36-0.95; p=0.03 – Figure 1c, HR(adjusted)=0.54, 95%CI:0.32-0.89; p=0.02). There was no evidence of a difference between $FE_{50}C$ and $FE_{75}C$ for DFS in patients with ER+/unknown disease randomised to receive no HM (HR(unadjusted)=1.44, 95%CI:0.93-2.23; p=0.10) – Figure 1d, HR(adjusted) =1.44, 95%CI:0.92-2.27; p=0.11).

Overall, there was no evidence of a benefit of HM for DFS (HR(unadjusted)=0.88, 95%CI:0.68-1.13; p=0.32)– Figure 2a, (HR(adjusted)=0.85, 95%CI:0.66-1.10; p=0.22), For patients with ER- disease the results, as now expected, suggested little effect (HR(unadjusted)=0.93, 95%CI:0.62-1.40; p=0.72) – Figure 2b, (HR(adjusted) =1.06, 95%CI:0.69-1.63; p=0.80) however for patients with ER+/unknown disease, the effects were consistent with worthwhile clinical effects (HR(unadjusted)=0.85, 95%CI:0.62-1.17; p=0.32) – Figure 2c, (HR(adjusted) =0.74, 95%CI:0.53-1.04; p=0.08).

BCFS, DFS-STEEP and MFS show similar results to those reported for DFS (web appendix–table A4).

At a median follow-up of 7.4 years, deaths have been reported for a total of 131 (16.7%) patients ($FE_{50}C$-HM=34, $FE_{50}C$+HM=36, $FE_{75}C$-HM=29, $FE_{75}C$+HM=32).Overall, there was no evidence of a difference in survival between any of the four treatment groups. Thus, no difference in OS was seen between $FE_{50}C$ and $FE_{75}C$ (HR(unadjusted)=0.90, 95%CI:0.64-1.28; p=0.58 – Figure 3a). Results are similar for the FEC dose comparison when considering the clinically relevant subgroups, i.e. for patients with either ER-disease (all ER- patients) (HR (unadjusted)=0.76, 95%CI:0.45-1.28; p=0.29 – Figure 3b), ER+/unknown disease (with HM) (HR=0.66, 95%CI:0.36-1.23; p=0.19 – Figure 3c) and ER+/unknown disease (without HM) (HR=1.96, 95%CI:0.94-4.10; p=0.07 – Figure 3d).

Similarly, there was no evidence of a difference according to whether patients were prescribed HM either overall (HR=1.11, 95%CI:0.79-1.56; p=0.55 – Figure 4a) or specifically for those patients with ER- disease (HR=0.83, 95%CI:0.49, 1.39; p=0.48 – Figure 4b) or ER+/unknown disease (HR=1.40, 95%CI:0.88, 2.23; p=0.15 – Figure 4c).

Four (3.1%) patients died of non-breast cancer causes in the absence of a reported metastatic relapse; one patient died following a pulmonary embolism (allocated to $FE_{50}C$-HM) 3.8 years after randomisation and having received tamoxifen off protocol. One had a myocardial infarction ($FE_{50}C$-HM) 7.9 years after randomisation, one died of septic shock associated with pancytopenia ($FE_{75}C$+HM) 3.6 years after randomisation and therefore not related to chemotherapy allocated as part of the trial and one died from ovarian cancer ($FE_{75}C$+HM) 10.7 years after randomisation.

A total of 770 (98.1%) patients received at least one cycle of chemotherapy. Of the pre-specified toxicities, all but leucopenia were numerically more common in patients receiving $FE_{75}C$ compared with $FE_{50}C$ (web appendix-Table A5). However, only grade 3 and 4 alopecia was statistically significantly more frequently reported for $FE_{75}C$ ($FE_{50}C$=142 (36.5%), $FE_{75}C$=205 (53.8%); p<0.001). In addition, the reported incidence of grade 3 and 4 neutropenia (non-febrile), a toxicity that was not pre-specified, was statistically significantly increased in patients receiving $FE_{75}C$ ($FE_{50}C$=5 (1.3%), $FE_{75}C$=17 (4.5%); p=0.008).

Discussion

The results of this trial suggest benefit from chemotherapy in premenopausal patients with EBC may be increased by using a higher dose of epirubicin in the FEC regimen, although the improvement in DFS did not meet statistical significance. Increasing anthracycline dose however, comes at the cost of greater toxicity, in particular, neutropenia and alopecia. Since the initiation of HMFEC the adjuvant treatment of premenopausal patients with EBC has evolved considerably. The recent EBCTCG meta-analyses demonstrated that lower doses of chemotherapy per cycle appear less effective than higher doses, consistent with the findings in this study. In practice, epirubicin doses still vary, and while $FE_{50}C$ may be considered to contain an insufficient dose of epirubicin today, $FE_{75}C$ remains a commonly used regimen, often given followed by a taxane, following reported benefits of this sequence (9). Taxanes have also been evaluated as a replacement to anthracycline-containg regimens since the initiation of our trial (10). The 2015 St Gallen statement on the issue of taxanes concluded that, for Luminal B-like patients deemed to require chemotherapy, taxanes should be considered for patients with more extensive disease burden, in contrast to Luminal A-like patients, where anthracycline regimens or CMF could be used. In triple-negative disease, the Panel considered that the chemotherapy should include an anthracycline and a taxane. (11). FEC100 has also since been shown by others to be more effective than FEC 50, for both DFS and overall survival.(12) In addition, the meta-analyses reported that, in premenopausal patients who had ER-positive EBC, the beneficial effect of chemotherapy could not simply be ascribed to the effect on ovarian function.

HMFEC also looked at the effect of HM in patients following chemotherapy. There was no evidence to suggest that HM improved DFS in either patients with ER- negative or ER-positive EBC. However, while this result is expected for ER-negative disease (as has been shown in another trial in which tamoxifen was found to be ineffective in ER negative premenopausal patients (13), the inconclusive result seen for ER-positive patients in this study is likely due to small numbers and insufficient power rather than a lack of effect of HM, given the recent results of large randomised trials showing the benefit of adjuvant endocrine therapy in these patients. (14) Recent results from the SOFT trial suggest that, for a subgroup of patients with ER-positive breast cancer who remain premenopausal post-chemotherapy, ovarian suppression in addition to tamoxifen reduced the risk of breast cancer recurrence compared with tamoxifen alone (15) and suggest this is weighted towards patients <35 years of age at breast cancer diagnosis. In our study, analogous to this, the patients who became amenorrhoeic and subsequently received tamoxifen would perhaps have benefitted more than those patients who received goserelin alone (15). In addition, the SOFT/TEXT trial further suggests that, at least in some patients, the addition of an aromatase inhibitor to ovarian suppression may be more efficacious than tamoxifen (14). In contrast, the ABC trial, that randomised pre- and perimenopausal patients with EBC who were receiving five years tamoxifen treatment with or without chemotherapy, to ovarian ablation or suppression (OAS) versus no OAS concluded that OAS gave no added benefit to either tamoxifen alone or tamoxifen and chemotherapy in premenopausal women (16). However ABC

did not pre-select patients on the basis of them remaining premenopausal following chemotherapy and whereas the median age in this subgroup in SOFT was 40 years, less than a quarter of patients in ABC were <40 at trial entry. Irrespective of effects of ovarian suppression however one would expect to observe an improvement due to the sequential addition of tamoxifen.

There are some aspects of this study which fall short of current practice: principally, the small sample size; however, at the time of study conception trialists often anticipated larger treatment effects explaining the smaller number of patients required. This deficiency is, to some extent, ameliorated by the long follow-up duration, a consideration which contributed to the delayed publication of results from this trial. Secondly, we allocated endocrine therapy to ER-negative patients, who nowadays would not be expected to benefit from such treatment, because of uncertainty around the predictive ability of ER at that time (17). Finally, in patients who became amenorrhoeic, we assessed ovarian status by a single estimation of estradiol, FSH and LH; it is increasingly recognised that younger patients can regain ovarian function some time after the completion of chemotherapy and for this reason contemporary practice is to measure hormones on more than one occasion.

In conclusion, we have observed a modest improvement in DFS in patients who received $FE_{75}C$ compared with $FE_{50}C$ chemotherapy, but this is associated with more severe neutropenia and alopecia, and in view of the lack

of effect on survival, we cannot recommend the higher dose of FEC in this subgroup of breast cancer patients. No conclusive benefit of additional HM therapy was observed, although the magnitude of effect observed was consistent with that seen elsewhere in the literature and it is likely that such treatment plays an important role in patients ER-positive breast cancer.

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Disclaimers: No potential conflicts of interest.

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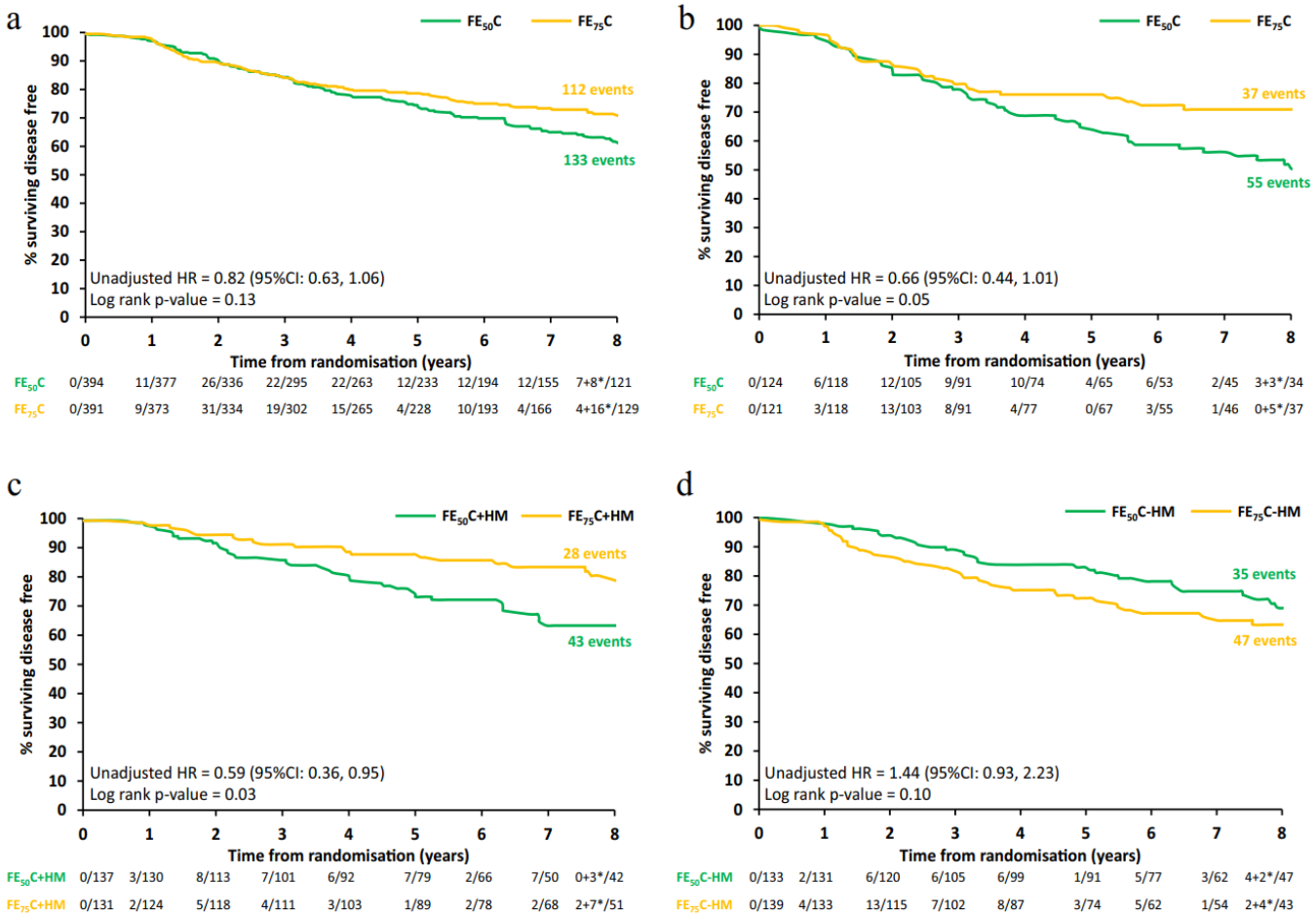

Fig. 1. a: DFS in ITT population−FE50C versus FE75C. b: DFS in patients with ER− disease−FE50C versus FE75C. c: DFS in patients with ER+/unknown disease−FE50C+HM versus FE75C+HM. d: DFS in patients with ER+/unknown disease−FE50C−HM versus FE75C−HM.

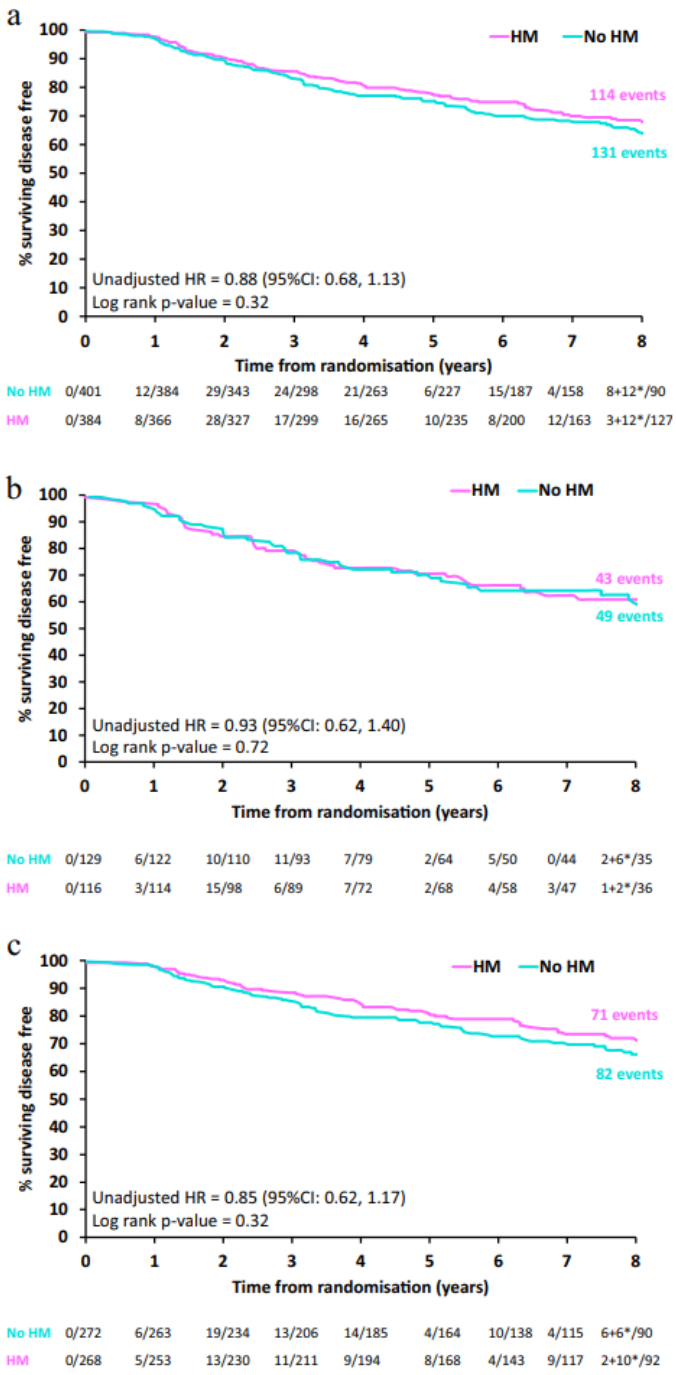

Fig. 2. a: DFS in ITT population sequential chemotherapy þ HM (HM) versus chemotherapy alone (No HM). b: DFS in patients with ER disease sequential chemotherapy þ HM (HM) versus chemotherapy alone (No HM). c:DFS in patients with ERþ/unknown disease sequential chemotherapy þ HM (HM) versus chemotherapy alone (No HM).

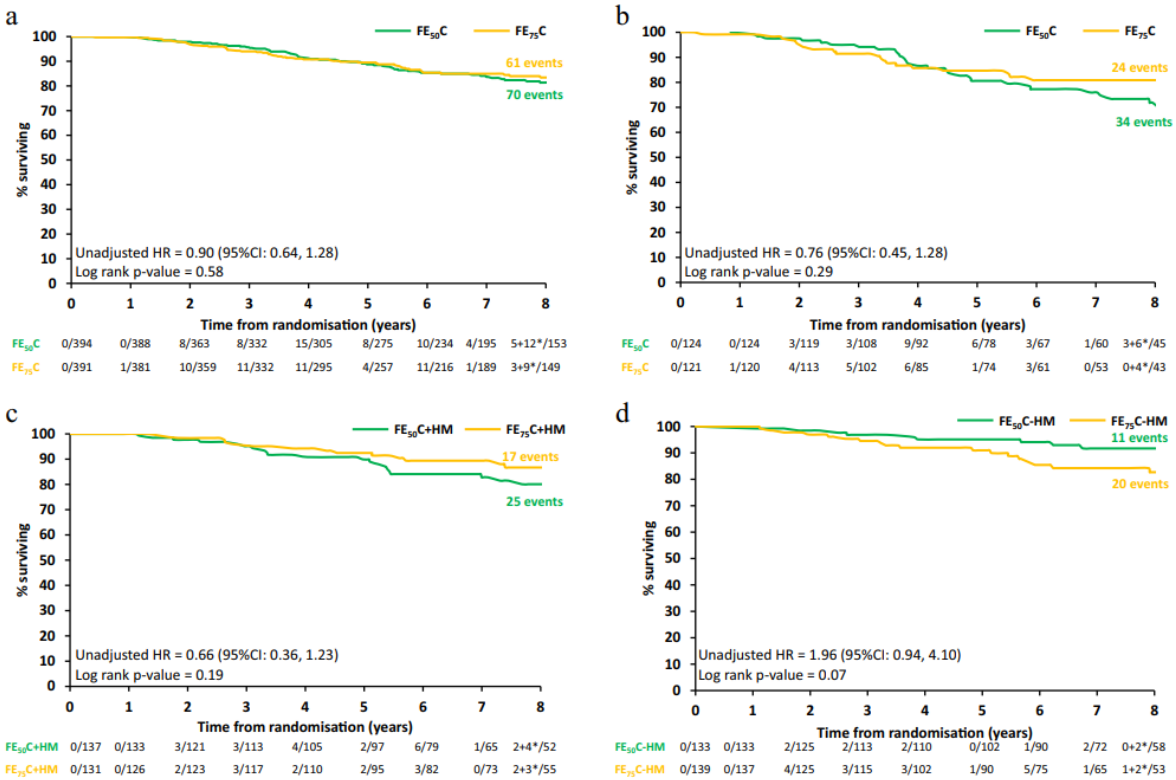

Fig. 3. a: OS in ITT populationeFE50C versus FE75C. b: OS in patients with ER diseaseeFE50C versus FE75C. c: OS in patients with ERþ/unknown diseaseeFE50CþHM versus FE75CþHM. d: OS in patients with ERþ/unknown diseaseeFE50CHM versus FE75CHM.

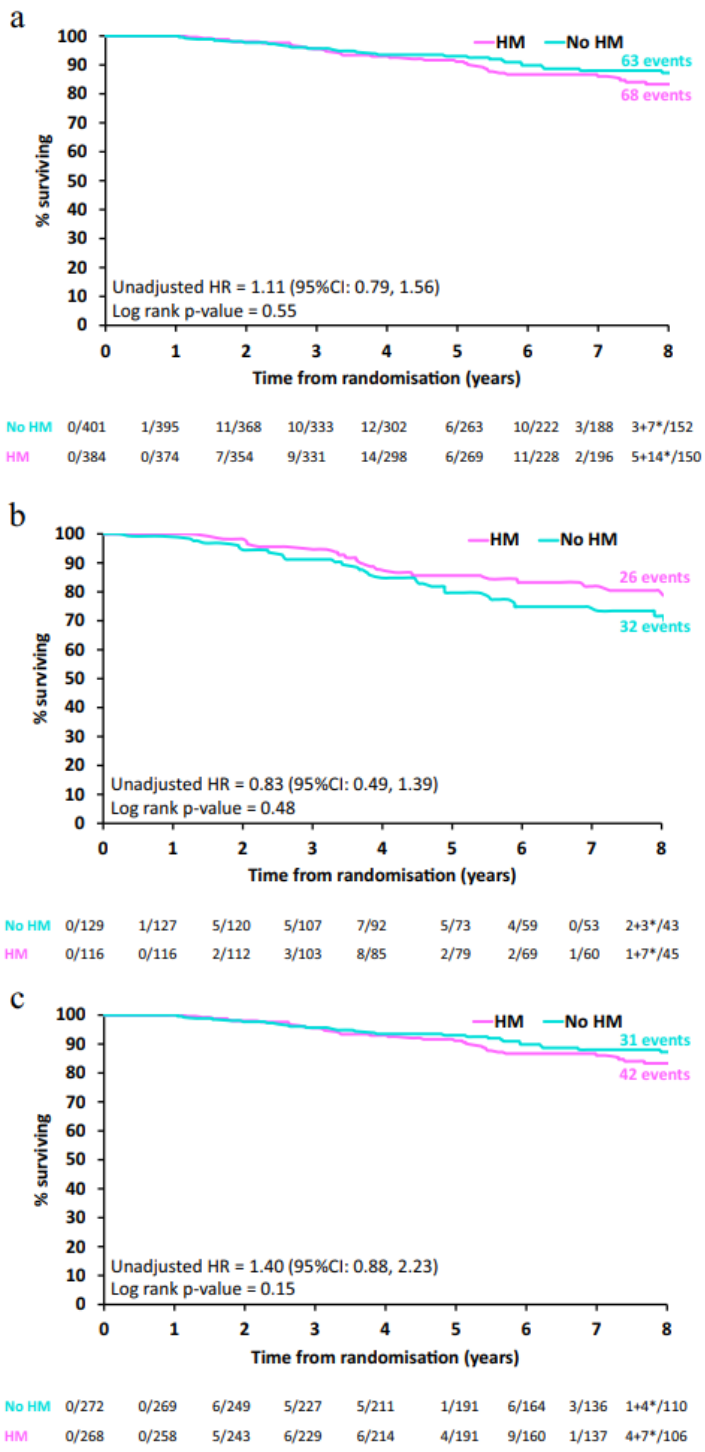

Fig. 4. a: OS in ITT populationesequential chemotherapy þ HM (HM) versus chemotherapy alone (No HM). b: OS in patients with ERþ/unknown diseaseesequential chemotherapy þ HM (HM) versus chemotherapy alone (No HM). c: OS in patients with ER diseaseesequential chemotherapy þ HM (HM) versus chemotherapy alone (No HM).