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Interpreting adjuvant breast cancer data in 2006 and beyond

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Abstract

Substantial progress has been made in the multidisciplinary management of early stage breast cancer since the introduction of combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil in the 1970s. Adjuvant chemotherapy significantly reduces the risk of cancer recurrence and death, and these effects persist for up to 20 years post surgery. Numerous attempts have been made to further improve survival outcomes by varying the dose, dose intensity and sequencing of drug delivery. The Cancer and Leukemia Group B (CALGB) conducted a series of trials examining these variations in adjuvant chemotherapy for the treatment of node-positive breast cancer patients. In this report, we discuss the major findings from some of these studies and highlight the role of oestrogen-receptor status on survival outcomes of modern chemotherapy.

Keywords: Breast cancer; Adjuvant therapy; Node-positive; Oestrogen-receptor status

1. Introduction

The pivotal trial of adjuvant combination chemotherapy by Bonadonna and colleagues in the 1970s clearly demonstrated a better rate of relapse-free survival with cyclophosphamide, methotrexate, and fluorouracil (CMF) compared to no treatment following radical mastectomy in primary breast cancer patients with positive axillary lymph nodes [1]. A high rate of relapse-free survival was evident in the first year following mastectomy and this rate continued through year 2. A long-term, follow-up study of these patients indicated that the efficacy of CMF was maintained for up to 20 years post surgery [2]. The probability of relapse-free survival was remarkably consistent and remarkably low from 2 to 20 years, with the best rates already being observed shortly after 2 years. These findings suggested that the benefit of this particular chemotherapy was greatest in the first 2 years after surgery, and beyond that, survival seems to be unaffected by initial chemotherapy. The good news, of course, is that there has been no apparent rebound in the later years, suggesting that some patients may have been cured by CMF and that its effect may not be restricted to slowing the course of the disease.

2. The US Intergroup node-positive trials

Once it had been established that adjuvant chemotherapy could improve the survival of patients with breast cancer, attempts were made to extend the benefit by utilising variations in drug dose and intensity. The Cancer and Leukemia Group B (CALGB), more recently on behalf of the National Cancer Institute's Breast Intergroup (Int), developed a programme in the early 1980s to examine whether different levels of doses or dose intensity of adjuvant chemotherapy or the introduction of a taxane was a critical determinant of outcome in women with node-positive breast cancer (Figure 1) [3–6].

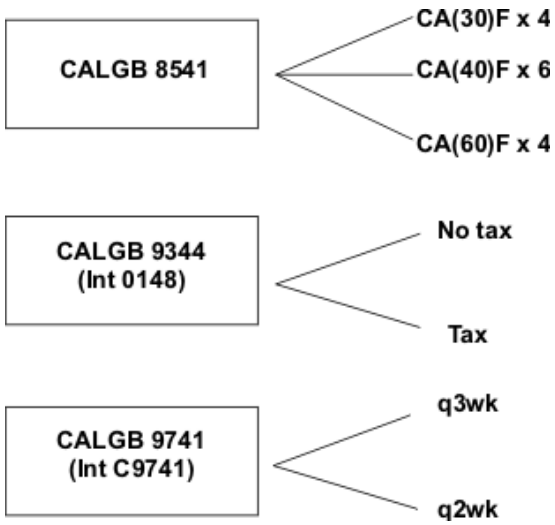

Fig. 1. Design of the three US National Cancer Institute's Breast Intergroup (Int) trials of patients with node-positive breast cancer: CALGB 8541, CALGB 9344 (Int 0148), and CALGB 9741 (Int C9741). C, cyclophosphamide; A, doxorubicin; F, fluorouracil; Tax, taxane (paclitaxel) [3,4,5,6].

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The CALGB 8541 trial examined the effect of dose and dose intensity on survival outcomes of 1572 women with node-positive breast cancer. Patients were randomised to either high-, moderate- or low-dose intensity chemotherapy with cyclophosphamide, doxorubicin and fluorouracil (CAF) [3,4]. The high-dose arm received twice the dose intensity and twice the drug dose as the low-dose arm. The moderate-dose arm received two-thirds the dose intensity as the high-dose arm but the same total drug dose [3,4]. At a median follow-up of 9 years, the differences in disease-free survival and overall survival between the high- and intermediate-dose arms were not significantly different, but both arms were significantly superior to the low-dose arm [4].

Using a 2×3 factorial design, Study 9344 (Int 0148) evaluated the effects of adding sequential paclitaxel and also of escalating doxorubicin dose [5]. Time to recurrence and survival were assessed in 3121 patients who received a combination of cyclophosphamide (600 mg/m^2) with one of three doses of doxorubicin (60, 75 or 90 mg/m^2) for 4 cycles followed by either no treatment or paclitaxel (175 mg/m^2) for 4 cycles. Dose escalation with doxorubicin failed to improve disease-free and overall survival at 5 years compared with standard doxorubicin dose. However, the addition of paclitaxel significantly reduced the risk of disease recurrence by 17% ($P = 0.0023$) and the risk of death by 18% ($P = 0.0064$). The benefit, however, appeared to be confined to the subgroup of ER-negative patients. The hazard ratio for disease-free survival in the ER-positive patients was 0.91 (95% CI 0.78–1.07) and in the ER-negative patients it was 0.72 (95% CI 0.59–0.86). The safety profile of adding 4 cycles of paclitaxel to a standard course of cyclophosphamide/doxorubicin was consistent with the known safety profile of single-agent paclitaxel [5].

The 9741 (Int C9741) trial was designed to compare concurrent doxorubicin and cyclophosphamide followed by paclitaxel versus sequential doxorubicin, paclitaxel and cyclophosphamide either in a 2-weekly dose-dense schedule or in a 3-weekly conventional schedule [6]. Overall, 2005 women were randomised to adjuvant chemotherapy using a 2×2 factorial design. After 4 years of follow-up, disease-free survival in the dose-dense treatment arms (both concurrent and sequential) was 82% compared with 75% among those in the standard-dose treatment arms (concurrent and sequential). The 3-year overall survival was 92% and 90% for the dose-dense and 3-weekly regimens, respectively, representing a 31% improvement favouring the dose-dense treatment. The incidence of grade 4 neutropenia was substantially higher among patients treated in the standard-dose than those in the dose-dense arms [6].

To summarise the findings from these trials of patients with node-positive breast cancer, the primary outcome measures of disease-free and overall survival were significantly improved by: high-dose (within the conventional dose range) compared with low-dose chemotherapy in the 8541 trial; the addition of paclitaxel to a standard adjuvant chemotherapy regimen in the 9344 trial; and by dose-dense chemotherapy in the 9741 trial [3–6].

3. Oestrogen-receptor status and outcomes of chemotherapy

Accumulating evidence suggests that the survival benefits of chemotherapy may differ according to oestrogen-receptor status. In particular, patients with ER-negative tumours seem to benefit more from additional or more intensive chemotherapy than do those with ER-positive tumours [7,8]. To address this issue further, we performed a retrospective subset analysis of the three US Intergroup trials of node-positive breast cancer patients to examine whether those with ER-negative disease would benefit more from adjuvant chemotherapy than those with ER-positive tumours treated with tamoxifen [9]. The majority of patients in both the 9344 and 9741 trials, and approximately 50% of those in the 8541 trial received treatment with tamoxifen for a recommended 5 years after chemotherapy.

3.1. Disease-free survival and absolute benefit

For patients with ER-negative disease, the differences in disease-free survival by treatment were significant (Figure 2) [9]. High-dose CAF was associated with a hazard reduction of 36% compared with lose-dose CAF (CALGB 8541) (Figure 2A) [3,4]; the addition of paclitaxel to a standard adjuvant chemotherapy regimen was associated with a hazard reduction of 25% at 10 years (CALGB 9344) (Figure 2B) [5], and 6-year data for the CALBG 9741 trial demonstrated a hazard reduction of 24% with dose-dense chemotherapy, as shown by the early separation of the curves. Based on our understanding of this disease and its treatment, this benefit will most likely persist as follow-up continues (Figure 2C).

For ER-positive patients who received tamoxifen, comparable survival curves to those of ER-negative patients were observed. However, unlike the pattern for ER-negative patients, there were no significant differences in outcome by treatment. Overall, the absolute improvements in disease-free and overall survival rates were substantially greater in the ER-negative group than in the ER-positive group. These benefits are demonstrated by Figure 3, which compares disease-free and overall survival rates for patients in the low-dose regimen of CAF in the 8541 study with the same patients modelled as though they were receiving biweekly doxorubicin, cyclophosphamide and paclitaxel as in study 9741. The cumulative overall risk reduction due to the intervening improvements in chemotherapy for patients with ER-negative disease was 55%. This estimate and its standard error incorporates the uncertainty associated with the estimates from each study, with each study having essentially the same control arm as the previous study's 'best' result. For ER-positive patients, the risk of

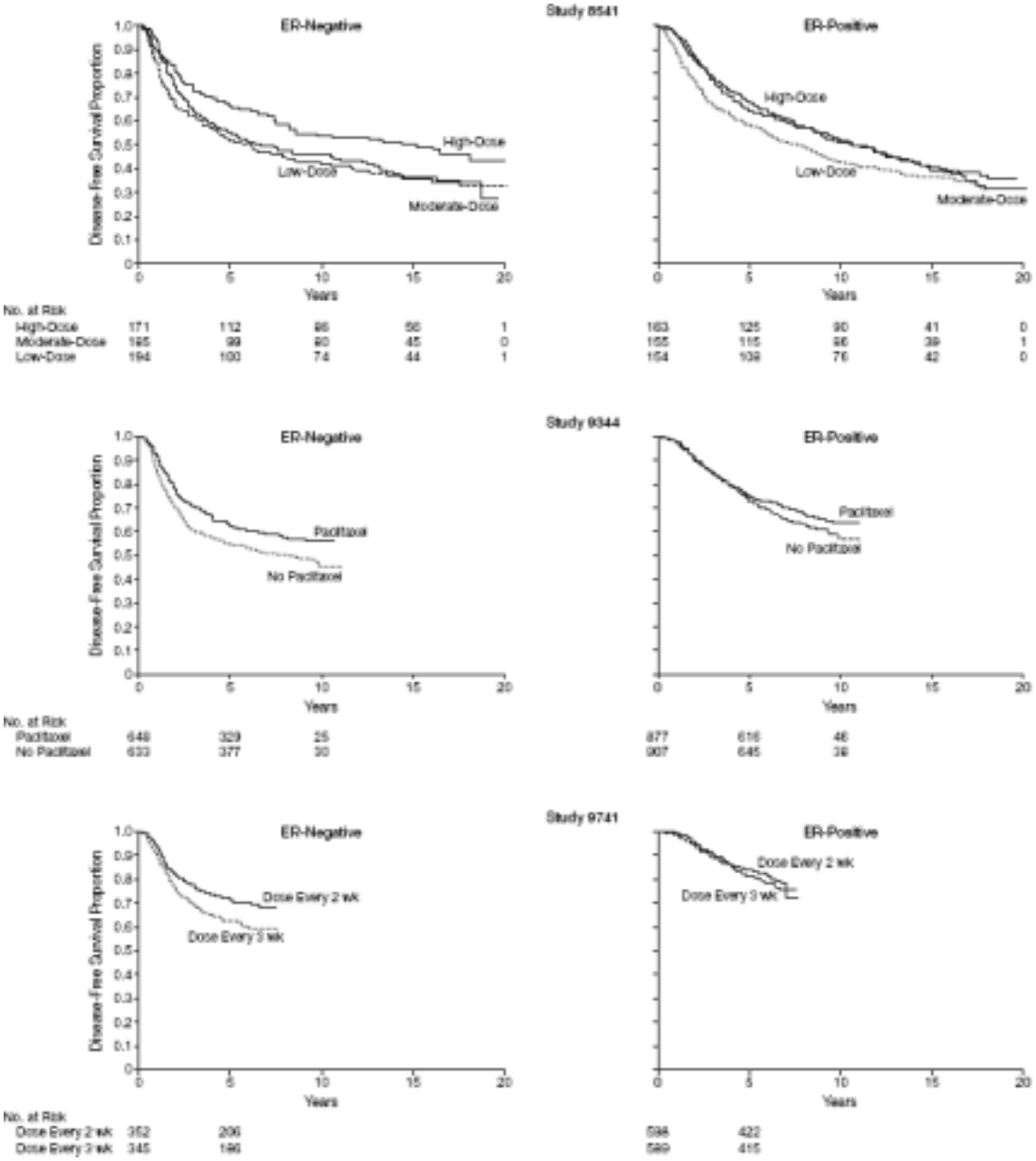

Fig. 2. Kaplan–Meier curves for disease-free survival of node-positive breast cancer patients with oestrogen receptor (ER)-negative or -positive tumours in the CALGB 8541 (upper panel); 9344 (middle panel); and 9741 (lower panel) trials. Reprinted with permission from *J Am Med Assoc* 2006, **295**, 1658–67.

recurrence was 26% and the reduction in risk of death was 23%, neither of which was statistically significant. The absolute improvement in 5-year disease-free survival was 22.8% for ER-negative patients compared with 7.0% for ER-positive patients. The corresponding improvements for overall survival were 16.7% versus 4.0%.

3.2. Risk of recurrence or death

For patients with ER-negative disease, the pattern of risk of recurrence or death over time was similar in each of the CALGB trials (Figure 4). Namely, the risk of an event was particularly high during the first 2 to 3 years following treatment, just as in the Bonadonna study [2]. The empirical risks show that high-dose chemotherapy is better than low-dose (in CALGB 8541), the addition of paclitaxel to standard adjuvant therapy is better than no paclitaxel (in CALGB 9344), and that 2-weekly dose-dense is better than 3-weekly conventional therapy (in CALGB 9741).

For patients with ER-positive disease, the risk of recurrence or death was similar across all studies, but the pattern differed from that of ER-negative patients in that the risk of an event was very low during the first few years after surgery (Figure 4). When the risks for ER-positive

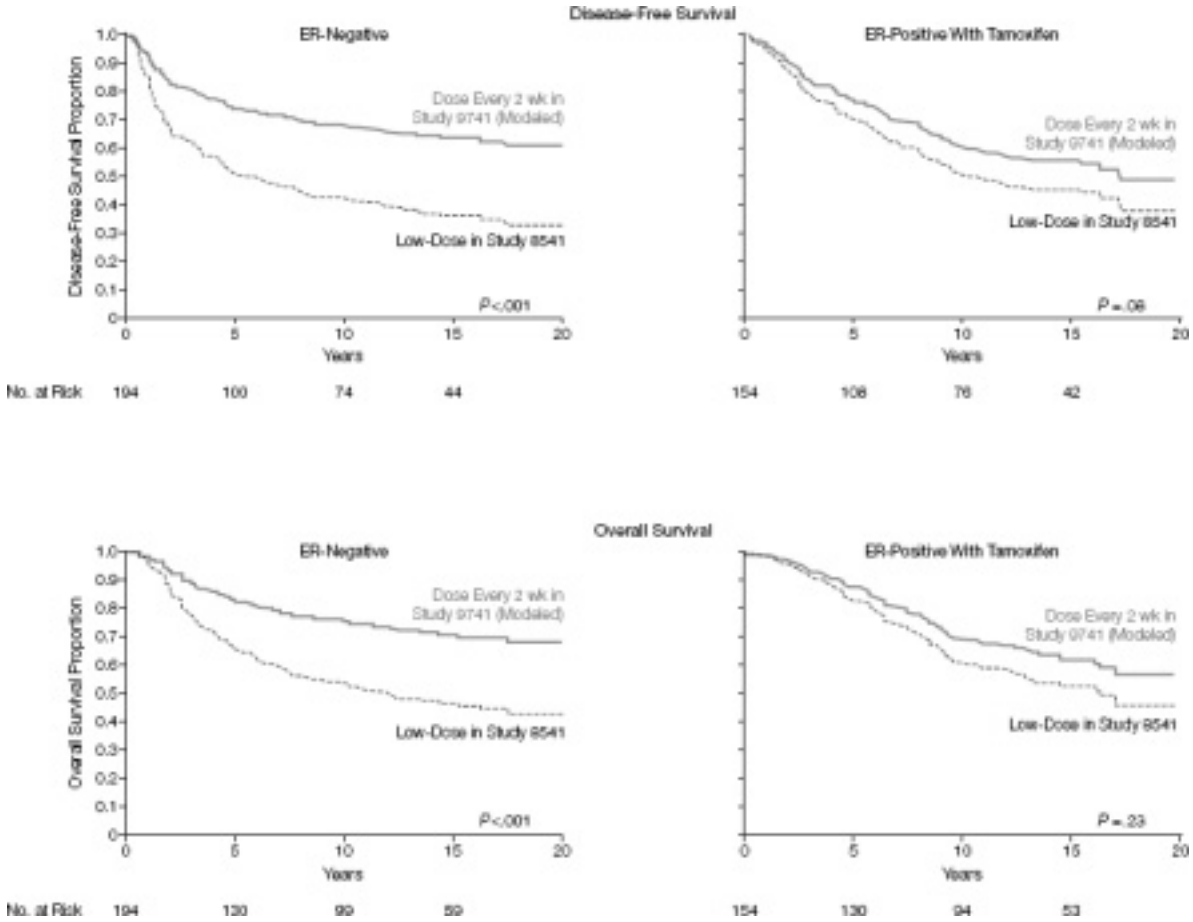

Fig. 3. Disease-free survival (DFS) and overall survival (OS) for node-positive breast cancer patients with oestrogen receptor (ER)-negative tumours or ER-positive tumours treated with tamoxifen. Data compare outcomes for patients in the low-dose cyclophosphamide, doxorubicin and fluorouracil arm of study CALGB 8541 with the same patients modelled as though they were receiving biweekly doxorubicin, cyclophosphamide and paclitaxel in study 9741. Reprinted with permission from *J Am Med Assoc* 2006, **295**, 1658–67. Copyright © 2006, American Medical Association. All Rights reserved.

patients in study 8541 were analysed according to tamoxifen use, the early low risk of recurrence or death was clearly attributable to tamoxifen use and not to ER status alone. For ER-positive patients who did not receive tamoxifen, the risk of recurrence or death was reduced by 67% at year 1 for high-dose CAF compared with low-dose CAF. This risk reduction was similar to that observed for ER-negative patients. Thus, treatment with tamoxifen lowers the empirical risk to such a level that it is difficult or impossible to detect any additional benefit of chemotherapy in these patients.

4. Discussion

The delivery of effective doses and scheduling of chemotherapy is an important issue that may affect overall patient outcomes. The role of dose-dense or dose-intensity rather than conventionally timed or dosed therapy remains controversial, despite many years of clinical trials. In the 8541 trial, disease-free and overall survival were superior with the high- and intermediate-dose arms compared with the low-dose arm, with no significant difference in outcomes between the high- and intermediate-dose arms [3,4]. The higher dose levels used in this trial were considered standard, so it is unclear whether the trial is supportive of dose intensity or the concept that treatment becomes ineffective below a certain dose level.

Other trials have escalated doses beyond the conventional range. In the 9344 trial, dose-escalation with doxorubicin was not beneficial, but the addition of paclitaxel resulted in significant improvements in disease-free and overall survival [5]. The benefits obtained with the dose-dense regimen were limited to the subgroup of ER-positive patients [9]. However, the trial was not powered to make individual comparisons among the treatment arms. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-22 and B-25 trials, the dose of cyclophosphamide was escalated from the standard dose of 600 mg/m^2 to 1200 mg/m^2 (without granulocyte colony-stimulating factor) and 2400 mg/m^2 (with granulocyte colony-stimulating factor) in over 2500 patients and showed no significant survival advantage compared with the standard dose [10].

In the 9741 trial, dose-dense therapy was more effective in prolonging survival than standard-dose chemotherapy [6].

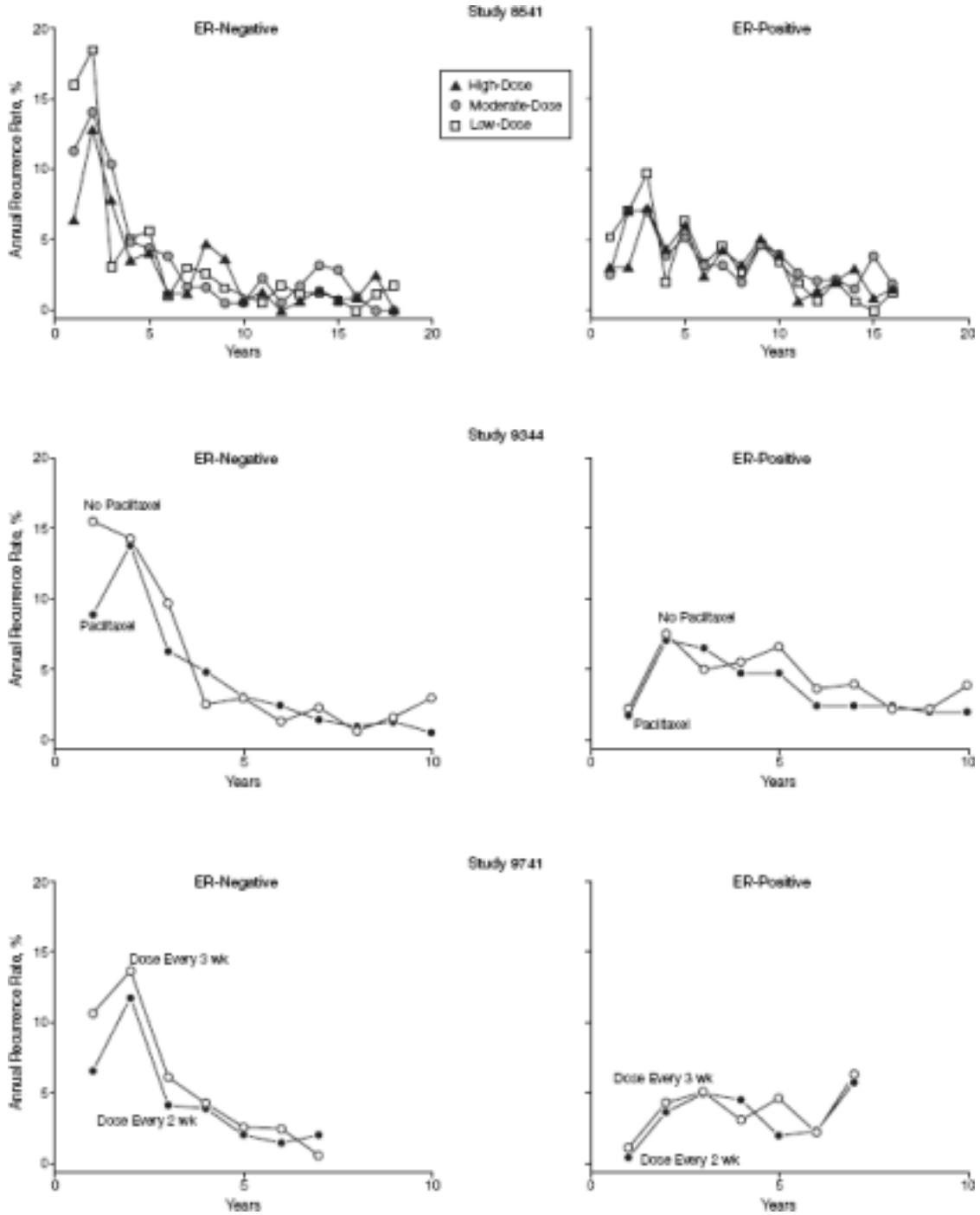

Fig. 4. Empirical risk of recurrence or death over time according to oestrogen-receptor (ER) status in patients with node-positive breast cancer. Reprinted with permission from *J Am Med Assoc* 2006, **295**, 1658–67. Copyright © 2006, American Medical Association. All Rights reserved.

Another prospective, randomised trial comparing dose-dense sequential with conventionally dosed therapy reported similar results after a relatively short follow-up of 28 months [11]. In contrast to these findings, a small randomised study of 216 women with node-positive breast cancer reported that dose-dense sequential chemotherapy with epirubicin/paclitaxel followed by CMF did not significantly improve disease-free or overall survival compared with conventionally dosed therapy [12]. Likewise, survival outcomes were not significantly different between standard fluorouracil/epirubicin/cyclophosphamide (FEC) and accelerated FEC (with granulocyte colony-stimulating factor) at a median follow-up of 6.7 years [13]. However, an unplanned subgroup analysis demonstrated a longer overall survival time with the accelerated versus standard regimen in younger (<50 years) women. Results from the NSABP B-28 trial, which randomised over 3000 women with node-positive breast cancer to 4 cycles of post-operative

doxorubicin/cyclophosphamide (AC) or 4 cycles of AC followed by 4 cycles of paclitaxel, demonstrated superior disease-free survival with the addition of paclitaxel but equivalent overall survival for both treatment arms [14].

Selecting an optimal chemotherapy regimen based on dose, intensity and sequencing, while minimising the risk of potential adverse events, remains a challenge for the practicing clinician. Considering the implications of toxicity as well as costs associated with these strategies, additional research is clearly warranted before such regimens can be accepted outside the clinical trial setting.

5. Conclusion

There is strong evidence that adjuvant chemotherapy can positively impact the natural history of breast cancer by significantly reducing the risk of disease recurrence and death. Data from the three key US Intergroup trials (CALGB 8541, 9344 and 9741) showed survival advantages among node-positive breast cancer patients treated with adjuvant chemotherapy. Several factors were related to outcome, including dose, dose intensity, sequencing of drug delivery, use of paclitaxel, and ER status. The benefit of chemotherapy was substantially better in patients with ER-negative than ER-positive disease, owing at least in part to the early risk reduction provided by tamoxifen in ER-positive patients. Thus, when treated with tamoxifen (and presumably with other hormonal therapies), tumours expressing oestrogen receptors are intrinsically less sensitive to adjuvant polychemotherapy than those not expressing the receptor. Nevertheless, some patients with ER-positive tumours may receive additional benefit from chemotherapy. The challenge lies in identifying them. Overall, our analysis of node-positive patients suggests that hormonal subtype of breast cancer is the strongest predictor of chemotherapy benefit, regardless of the specific dose or schedule.

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