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Clinical benefit and risk of death with endocrine therapy in ovarian cancer: A comprehensive review and meta-analysis

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HIGHLIGHTS

- Hormone therapy is used in pretreated EOC but the magnitude of activity is unknown.
- This is the most comprehensive meta-analysis on endocrine treatment in advanced EOC.
- Our findings show that endocrine therapy has a reasonable activity in advanced EOC.
- Our data are hampered by the heterogeneity of trials encompassing nearly 40 years.
- RCTs in the first line treatment of advanced hormone receptor +ve EOC are warranted.

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ABSTRACT

Background. Steroid hormones promote epithelial ovarian cancer (EOC) growth and their receptor expression is associated with disease outcome. Hormone therapy is frequently used in pretreated EOC, but the magnitude of activity overall and by specific agents or tumor characteristics is unknown.

Methods. Clinical Benefit Rates (CBR) and deaths from clinical trials of endocrine agents were meta-analyzed. Summary estimates of CBR (SCBR) and Odd Ratio for death (SOR) were calculated according with type of drug, ER and PgR status, platinum resistance, line of therapy, tumor grade and tamoxifen dose.

Results. Fifty-three trials in 2490 patients were analyzed. Overall, SCBR was 41% (95%CI, 0.34–0.48) for any endocrine treatment, 43% (95%CI, 0.30–0.56) for tamoxifen, 39% (95%CI, 0.29–0.50) for aromatase inhibitors and 37% (95%CI, 0.26–0.48) for progestins. The SCBR for ER+ and/or PgR+ tumors was 46% (95%CI, 0.34–0.57) versus 37% (95%CI, 0.27–0.48) in tumors with unknown receptors and 55% in platinum sensitive (95%CI, 0.28–0.80) versus 40% (95%CI, 0.29–0.51) in platinum resistant tumors The SOR for death calculated from 6 out of 9 randomized clinical trials (RCTs) showed a reduced mortality with endocrine therapy (SOR = 0.69, 95%CI, 0.50–0.97), with a possible tendency for a greater effect in first line and low grade tumors. The overall quality of the RCTs was low.

Conclusions. The activity of endocrine therapy in advanced EOC is worth considering and seems to support large properly designed randomized trials in the first treatment of hormone sensitive EOC.

1. Introduction

Epithelial ovarian cancer (EOC) is the fifth most common female cancer and the sixth most lethal cancer in developed countries. >60% of women have advanced-stage disease (stage III–IV) at diagnosis, which accounts for the high mortality rate in the US [1]. The disease prognosis is poor also in Europe with a mean age-standardized 5-year

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OS of only 37.6% after surgical cytoreduction and platinum-based chemotherapy [2]. Recently, two phase III trials [3,4] have shown the efficacy of bevacizumab in combination with chemotherapy in prolonging progression free survival (PFS) overall and in overall survival (OS) in one study [4] in the subgroup of high-risk patients. However, concerns about the cost effectiveness of bevacizumab have been raised [5].

Identifying prognostic and predictive factors for advanced EOC is also an important challenge. A putative direct action of gonadal steroids on ovarian carcinogenesis has been shown in both normal ovarian tissue and malignant ovarian tumors. Mechanistically, ovarian cancer growth, progression and metastasis can be explained through different molecular pathways related to estrogen, including: (i) tumor production of vascular endothelial growth factor via estrogen receptor (ER) signaling (direct pathway); (ii) increased tumor-endothelial cell migration via mitogen-activated protein kinase signaling (indirect pathway) [6]. Progesterone receptor (PgR) can induce apoptosis, cell cycle arrest and senescence in ovarian cancer cells, suggesting modulation of PgR levels and/or activity as a form of endocrine treatment of EOC [7].

A recent study by Sieh et al. [8] examined 2.933 women with invasive EOC to assess whether tumor expression of ER and PgR was associated with subtype-specific survival. Positivity for PgR was highest for endometrioid carcinoma and low-grade serous carcinoma, intermediate for high-grade serous carcinoma and lowest for mucinous carcinoma and clear-cell carcinoma. Strong PgR expression (≥50%) was associated with significantly improved HGSC survival independent of site, age, stage, and grade and both ER and PgR expression were associated with significantly improved survival in EOC. Further studies have confirmed the prognostic effect of ER and PgR in EOC [9,10].

Thus, EOC is an endocrine-related neoplasm and hormone receptor status has prognostic significance. It is still unclear, however, whether the use of molecular therapeutic targets such as ER and PgR may predict tumor response and provide a significant outcome benefit in specific patient subgroups. Several studies have shown good objective responses with hormonal treatment of advanced EOC but the magnitude of activity overall and by specific agents and tumor characteristics is unknown [11–63]. Since the addition of hormone therapy may become a viable and extremely cost effective option for the treatment of advanced EOC, we performed a comprehensive review and meta-analysis of clinical trials to assess the effect of hormonal treatments on EOC outcome overall and by specific subgroups.

2. Material and methods

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All analyses were based on previous published studies, thus no ethical approval and patient consent required.

The primary endpoint was the Clinical Benefit Rate (CBR) defined as the proportion of patients who have achieved Complete Response (CR), Partial Response (PR) or Stable Disease (SD) or the proportion of patients with no disease progression within the study period.

Hormonal treatments included the following drug categories: tamoxifen; aromatase inhibitor such as anastrozole, letrozole or exemestane; ethinyl estradiol plus progestins or progestins alone such as medroxyprogesterone acetate or megestrol acetate; LHRH analogs; flutamide; fulvestrant. Additional subgroup analyses included the following covariates: steroid receptor status, platinum sensitivity, tamoxifen dose, prior line of therapy and tumor grade.

2.1. Search strategy

We identified studies by searching Medline, ISI Web Science (Science Citation Index Expanded), Embase, Cochrane Library; by examining the reference list of published trials, reviews articles and editorials and by hand-searched references in identified trials and symposia reports from the major cancer associations. Any clinical trial that examined the relationship between the use of endocrine therapies and objective response rate in ovarian cancer patients was eligible for inclusion in our revision. For database search we used [((“Endocrine therapy” [Mesh]) OR (“hormone therapy”) OR (“aromatase inhibitor”) OR (“tamoxifen”) OR (“anastrozole”) OR (“letrozole”) OR (“exemestane”) AND (“ovarian cancer” [Supplementary Concept] OR “epithelial ovarian cancer [Supplementary Concept]” OR “EOC” OR “OC”)] as the search terms. The literature search was independently carried out by 2 independent reviewers (LP and NP) with a standardized approach and discrepancies were resolved by consensus. The databases were searched for papers published through March 21, 2017.

2.2. Inclusion and exclusion criteria

All published resources (as full paper or as conference abstract) were eligible for inclusion in our analyses but they had to fulfill the following criteria: 1) to report data to calculate Clinical Benefit Rates (CBR) among EOC patients receiving endocrine drugs; 2) to be independent studies. Observational studies were excluded.

2.3. Data extraction

Two independent reviewers undertook the literature search and extracted the data using standardized data collection forms. Data retrieved from the reports included publication details, methodological components, study characteristics such as sample size, interventions, follow-up duration, outcome measures, features of patients (e.g. hormonal receptors status), information on drugs used (e.g. type of drugs, dose), total number of CR, PR, SD and disease progressions among patients receiving endocrine drugs, the total number included in the trial as well as the number of evaluable patients and the number of deaths by trial arms in randomized trials. When the total number of progressions was not available, it was sometimes possible to extract the number of events from the Log-rank curves. All data were checked for internal consistency and the principal investigators of the studies were contacted, if needed, to recover missing information, up-date outcome measures, or to clarify inconsistency.

2.4. Statistical analysis

To calculate the Summary clinical benefit (SCBR) we used the random effects modeling as described by van Houwelingen et al. [Stat Med 21(4):589-624, 2002] with summary estimate obtained from maximum likelihood estimation, with a hierarchical model when two estimates were extracted from a single study. We used transformation of proportions (relative frequencies of responses) into quantities suitable for the usual random effects summaries. The summary proportion is calculated as the back-transformation of the weighted mean of the transformed proportions, using inverse arcsine variance weights. We used the Freeman-Tukey arcsine transformation in order to stabilize variances.

We also extracted the number of deaths or the hazard ratio from randomized trials to calculate the Summary OR for the risk of death comparing the arm with endocrine drugs versus the control arm.

The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-square statistic. Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the $P = 0.10$ level of association. We considered I^2 as a further measure of heterogeneity among studies. A threshold of I^2 below 50% is considered an acceptable level of between studies heterogeneity. When between-study heterogeneity is below 50% fixed effects models were considered. Sub-group analyses and meta-regressions were carried out to investigate between-study heterogeneity focusing on drugs used, hormonal receptors status, and tamoxifen dose. Publication bias was evaluated graphically with a funnel plot and the Macaskill test, which is more powerful when <20 estimates are included in the

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analysis. Two investigators (LP, SG) conducted the search independently, and the quality of randomized clinical trials was also evaluated [Cochrane Handbook for systematic reviews of interventions. The Cochrane Collaboration, 2011]. All the statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC; version 9.2) and R software, version 2.12.2 (http://www.r-project.org).

3. Results

We retrieved 416 papers and 53 met the inclusion criteria [11–63]. Two were excluded because they were observational studies [64,65]. For Emons et al. [42] we were able to extract data for deaths but not for number of progressions, from Li et al. 2012 [66] we were not able to extract data on responses nor reliable data on mortality/survival. The search strategy is illustrated in Fig. 1.

3.1. Characteristics of included studies

We included in the analyses 53 clinical studies, nine of them were two-arms randomized trials (See Supplementary Tables 1 and 2 for characteristics). Overall from 49 studies we were able to extract information to calculate the clinical benefit and among them eight were randomized trials [28,30,39,59–63], from six two-arms randomized trials we were able to retrieve data to compare mortality in the hormonal treatment arm versus a comparator arm (controls, placebo or chemotherapy) [30,42,58,60,62,63].

The 41 original selected articles and 12 abstracts presenting the results of phase II studies were published between 1982 and 2015 [11–63]. The sample size of the included studies ranged from 9 to 155 subjects. The CBRs were assessed by RECIST criteria in 29 studies [11,13,14,19–21,23–28,30,38,42,43,45,49,53,56,59,60], CA125 serum levels in 11 studies [15–17,39,40,44,46,48,50,52,63], not reported in 6 studies [12,22,29,41,61,62] and both in 7 studies [18,47,51,54,55,57,58]. Five studies included cohorts with only ER + tumors [16,20,54,56,57], whereas 17 studies had receptor positivity for ER and/or PgR [11–13,15,17,18,21,22,25,27,31,32,34,36,47,49,51]. Twenty seven studies encompassed subjects resistant to platinum chemotherapy [12,17,19–21,25,32,34–40,43–46,48,50–52,55,56,58,60,61]. According to the hormonal agents, 10 studies used aromatase inhibitors [15–18,34,47,49,51,54], 26 the selective estrogen receptor modulator tamoxifen [11–14,19–24,27,29,31,34,35,38–41,43,45,46,52,53,55,59], twelve estroprogestins [25,28,32,34–37,44,58,60,62,63], 3 tamoxifen *plus* progestins

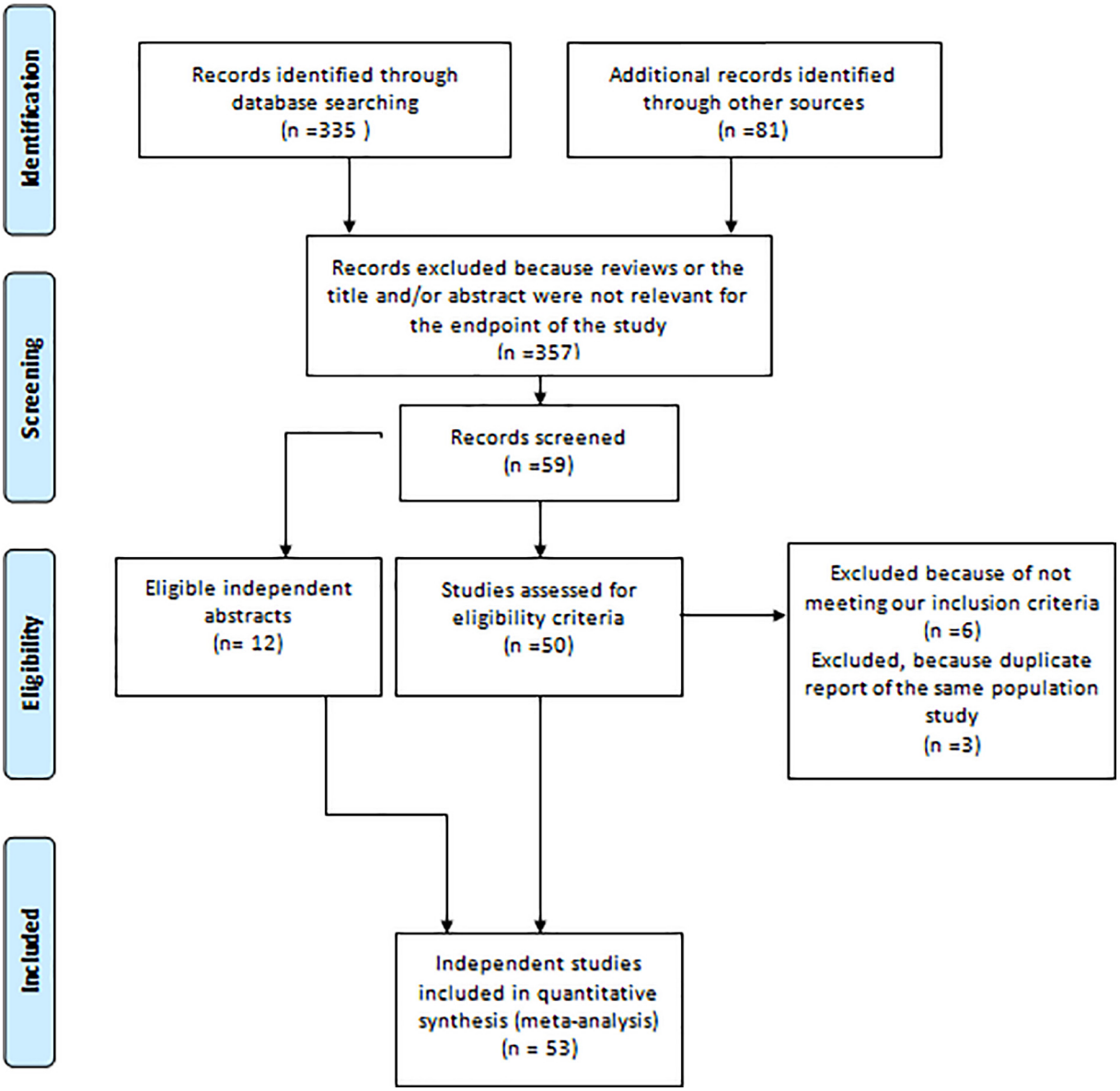

Fig. 1. Flow diagram of study search and selection.

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[26,28,35], 5 LHRH analogs [33,38,48,50,61], one the anti-androgen flutamide [38], and one the ER down-regulator fulvestrant [57]. Overall, the proportion of patients who have been evaluated for CBRs was 83% (n = 2060). The main characteristics of each study are summarized in Supplementary Tables 1 and 2. There was insufficient indication of tumor histology subtype. Drug toxicity is reported in Supplementary Table 2. Grade 3 or higher adverse events were rare (1.3%), mainly consisting of nausea and vomiting in 13 patients, diarrhea in 8 patients, hematological toxicity in 2 patients and rash in 3 patients. The relationship with hormonal treatment was never reported.

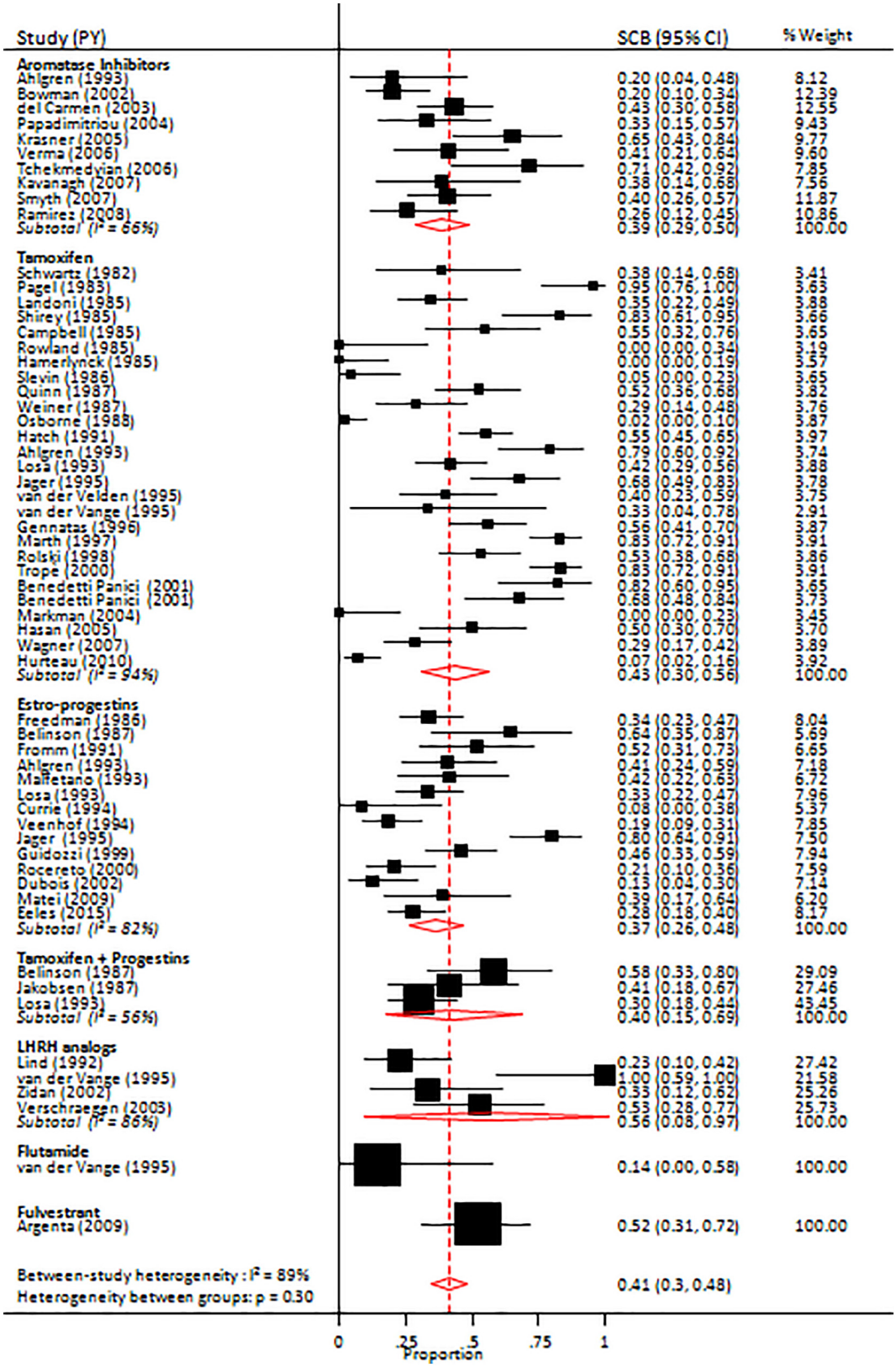

Fig. 2. Forest plot of the association between endocrine therapy by type of drug and summary clinical benefit rate (SCBR) in ovarian cancer.

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3.2. Summary estimates

Overall, the estimates of CBRs involved 2490 patients and revealed that the endocrine therapy was associated with a clinical benefit of 41% (95% CI, 0.34–0.48) in EOC patients, with high between-study heterogeneity ($I^2 = 90\%$). The SCBR by type of drugs is illustrated in Fig. 2. Tamoxifen showed the highest SCBR of 43% (95% CI, 0.30–0.56) based on 23 studies with a high between-study heterogeneity ($I^2 = 94\%$), whereas the SCBR for estro-progestins obtained from 9 studies was 37% (95% CI, 0.26–0.48) ($I^2 = 82\%$). The SCBR for aromatase

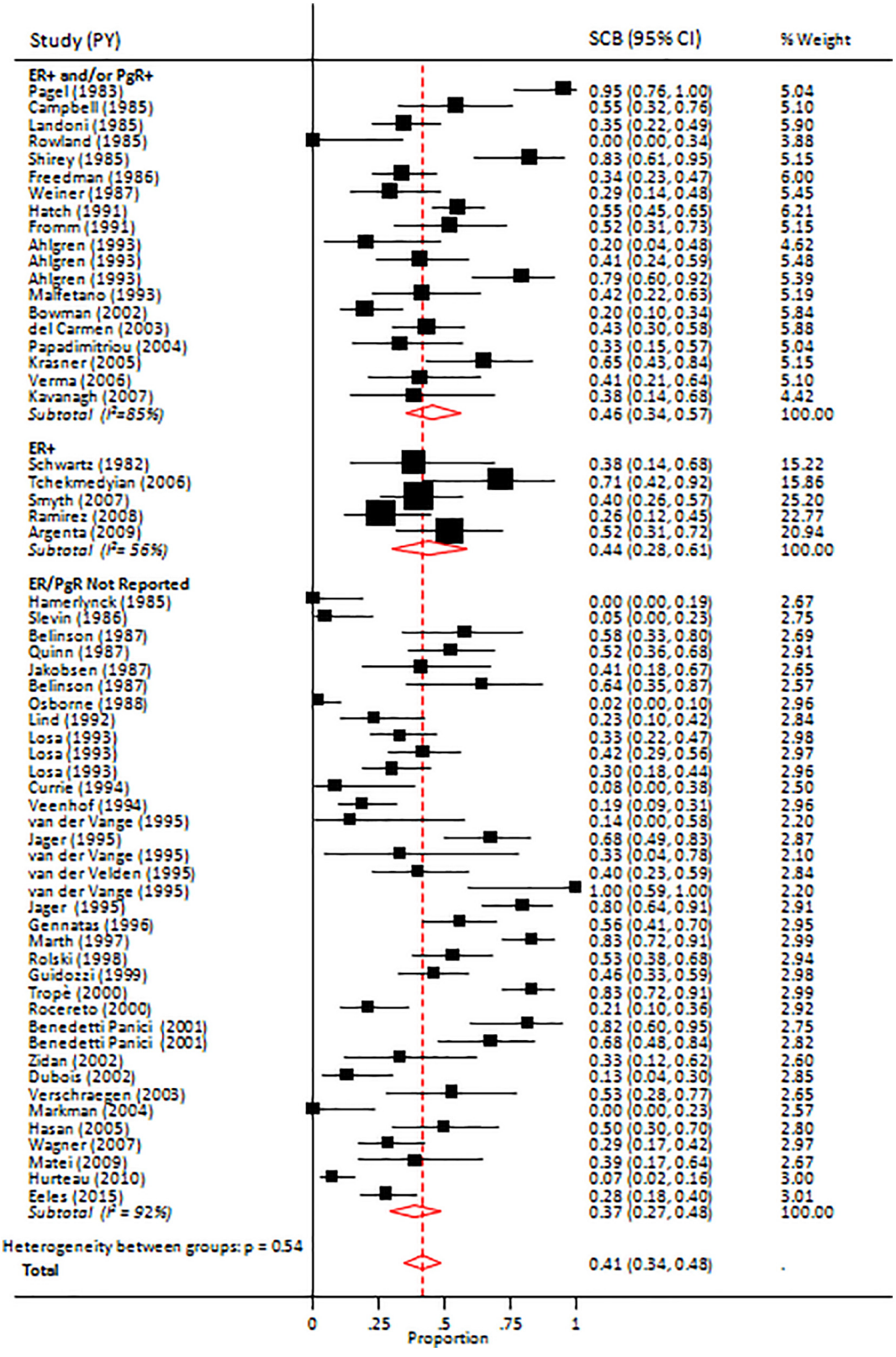

Fig. 3. Forest plot of the association between endocrine therapy by hormone receptors status and summary clinical benefit rate (SCBR) in ovarian cancer.

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inhibitors in 10 studies was 39% (95% CI, 0.29–0.50) with a $I^2 = 65\%$. Three studies of tamoxifen plus progestins gave a SCBR = 40% (95% CI, 0.15–0.69; $I^2 = 56\%$). The SCBR for LHRH analogs in 4 studies was 56% (95% CI, 0.08–0.97) with a large confidence interval and high between-study heterogeneity ($I^2 = 86\%$).

3.3. Between-study heterogeneity

Subgroup analyses by hormone receptor status illustrated in Fig. 3 showed that the SCBR was 46% (95% CI, 0.34–0.57) for the 16 studies including ER + and/or PgR + patients ($I^2 = 84\%$), 44% (95% CI, 0.28–0.61)

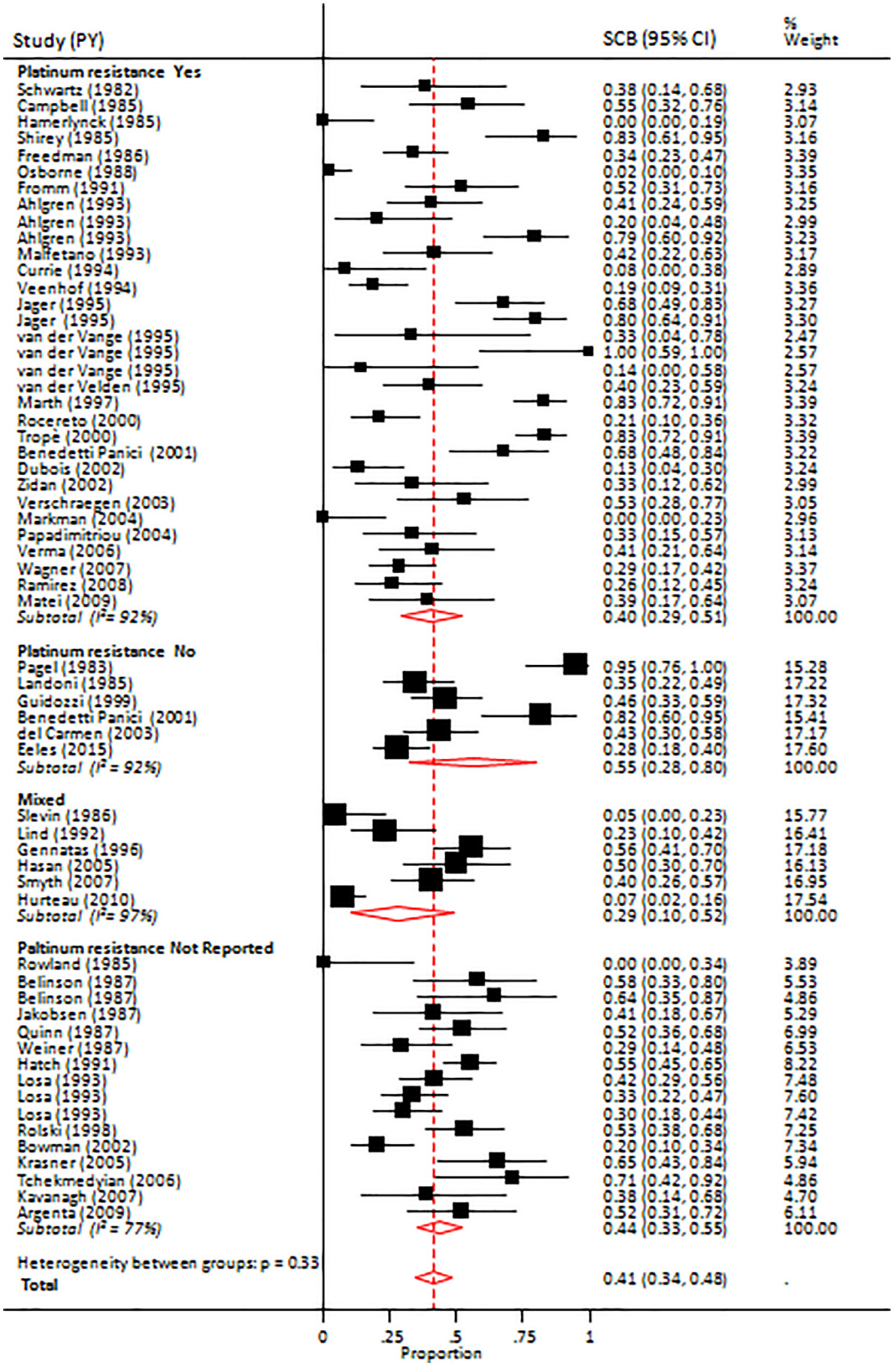

Fig. 4. Forest plot of the association between endocrine therapy by responsiveness to platinum-based chemotherapy and summary clinical benefit rate (SCBR) in ovarian cancer.

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with $I^2 = 58\%$ for the five studies including exclusively ER+ tumors, and 37% (95% CI, 0.27–0.48) with $I^2 = 92\%$ for studies with unknown receptor status, without significant difference ($p = 0.54$).

The CBRs of endocrine therapy by platinum resistance is illustrated in Fig. 4. There was a trend to a lower therapeutic activity in platinum resistant disease (SCBR = 40%, 95% CI, 0.29–0.51) compared with platinum sensitive disease (SCBR = 55%, 95% CI, 0.28–0.80), even though the difference was not significant ($P = 0.29$) possibly because only four studies were reported in platinum sensitive disease. The stratification by tamoxifen dose, illustrated in Supplementary Fig. 1, showed no difference in response rate between the standard dose of 20 mg per day (SCBR = 49%, 95% CI, 0.10–0.92) derived from 5 studies and higher doses, SCBR = 41% (95% CI, 0.26–0.57) from 21 studies.

A sensitivity analysis was performed by omitting one study at a time and calculating the pooled estimates and 95% CIs for the remaining studies. The leave-one-out procedure showed minimal and no significant change on the summary estimate (range: min 0.4100, max 0.4288) when any one of the studies was excluded (data not shown). For the main analysis we chose the RECIST criteria when possible, but 13 studies evaluated the SCBR based on CA125 response. When two estimates of clinical response based on two different criteria were available, we calculated also the SCBR based on CA125 response but the summary results did not change: SCBR = 41% (95% CI, 0.33–0.48). No indication for publication bias was found ($P = 0.98$).

3.4. Mortality from randomized trials

From six out of 9 two-arm randomized trials including 700 patients it was possible to compare OS with hormonal treatment vs other [30,42,59,60,62,63]. From these 6 trials we were able to extract data to calculate a summary estimate for the risk of death comparing endocrine agents with other treatments or placebo. We found a significant reduced risk of death (SOR = 0.69, 0.95%CI: 0.50–0.97) obtained from a fixed effect model since between-study heterogeneity was not significant ($I^2 = 43\%$). Figs. 5 and 6 illustrate the results of mortality stratified by first line regimen and tumor grade. Although the low number of studies prevents definitive conclusions, a possible greater effect in low grade tumors was apparent.

3.5. Quality assessment of randomized trials

The methodological quality of randomized clinical trials was generally quite low: two of them did not reach the planned sample size [62,63], three did not report the power sample size calculation [30,42,59], only one was double blind [42]. Important information were missing in the majority of the trials: drop-out rate, adherence, intention to treat analysis, pre-specified outcomes and subgroup analyses, balance of groups' baseline characteristics that could affect outcomes. Conversely, the two most recent trials [59,62] had the best quality and showed a significant reduced risk of mortality and the biggest weight in the meta-analysis.

4. Discussion

In this comprehensive review and meta-analysis including 44 single arm trials and nine randomized trials, we showed that hormonal therapy in advanced EOC leads to an acceptable 41% CBR (95% CI, 0.34–0.49). Furthermore, summary estimates suggest that hormonal therapy may reduce mortality, even if the results should be taken with caution since there are indications for a publication bias due to heterogeneity in study design. To our knowledge, this is the first and most comprehensive meta-analysis up to date to evaluate the activity of endocrine treatment in advanced EOC. A total of 2490 EOC patients were summarized and this sample allows a robust statistical power is an important strength of this study. Sensitivity analysis suggested that no single study influenced the pooled estimates qualitatively.

The main limitation of the present study is the significant between-study heterogeneity for the estimates on clinical benefit ($I^2 = 89\%$), possibly reflecting a different quality among studies conducted over several decades. Other important weaknesses are the poorly defined patient and tumor characteristics, including number of prior therapeutic lines and platinum sensitivity, lack of measurements and heterogeneity in steroid receptor assay methods, insufficient indication of tumor histology subtype and different response criteria among studies due to the known difficulty in measuring advanced EOC.

In line with phase II trials, most of the individual studies had a limited number of patients. Only two studies had a sample size of >100 subjects [31,43].

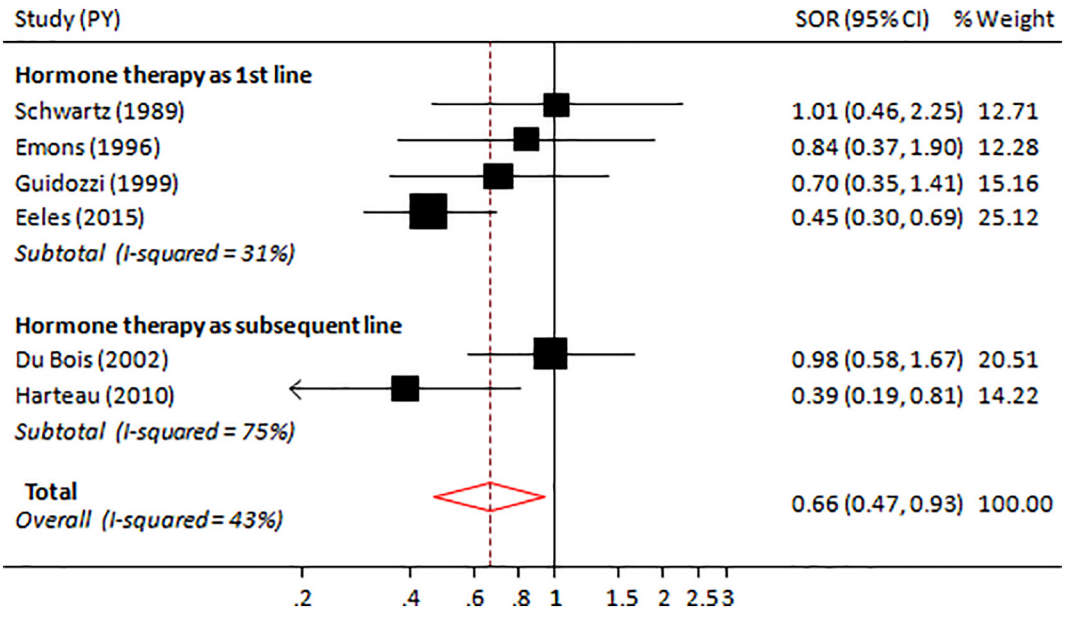

Fig. 5. Forest plot of the association between endocrine therapy and summary estimate for death risk stratified by first line regimen.

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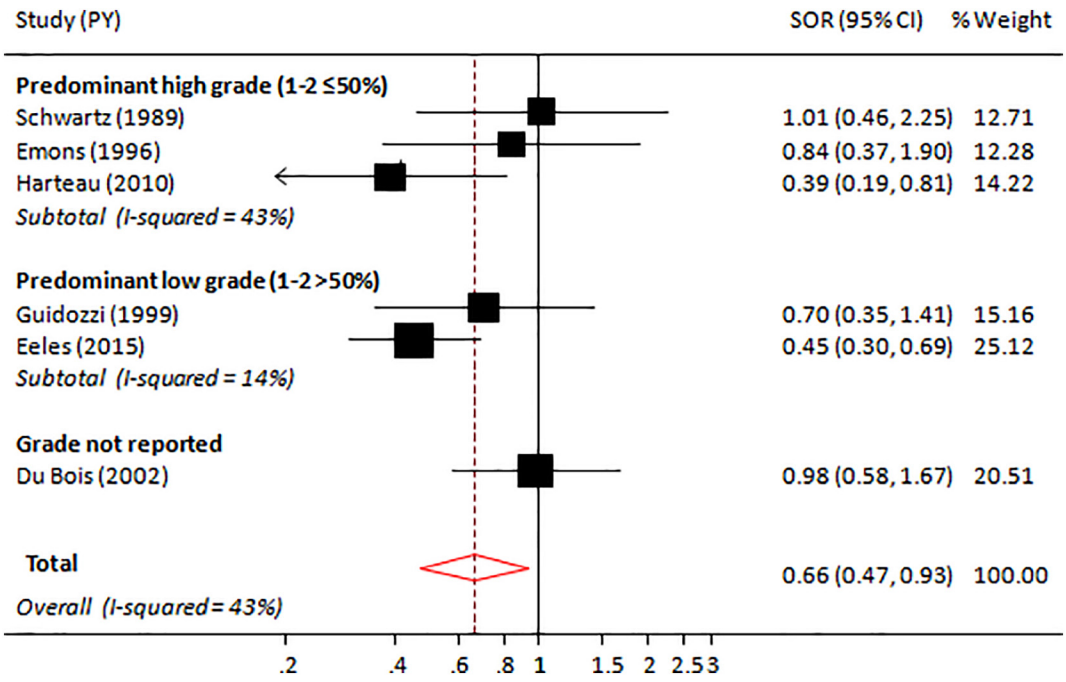

Fig. 6. Forest plot of the association between endocrine therapy and summary estimate for death risk stratified by tumor grade.

Like other hormone-responsive tumors, it is likely that EOC expressing high levels of ER or PgR have the best responses to endocrine treatment. However, the subgroup analysis by hormone receptor status showed no significant difference in response between ER+ and/or PgR+ patients and those with unknown receptors. In clinical studies where ER and PgR levels were measured in responders and non-responders to hormonal therapy, correlation has been variable. In the GOG trial of tamoxifen, there was a trend to a direct correlation, with 8 of 9 CR (89%) having elevated ER levels [31]. The high variability in terms of CBR among the studies with ER/PgR assessment might be due to differences in methods of measurements and the heterogeneity of receptor expression within the same tumor or between primary tumor and metastases [57,58]. Importantly, it seems that the average level of receptors concentrations in ovarian cancer cells is lower than in breast or endometrial cancer cells [29] so that these quantitative differences may lead to a different magnitude of clinical response.

We investigated the possible differential effect of endocrine therapy in resistant or sensitive to platinum-based chemotherapy patients demonstrating a non-significant trend to a greater activity in platinum sensitive (SCBR = 65%, 95% CI, 0.22–0.98) compared with platinum resistant tumors (SCBR = 41%, 95% CI, 0.30–0.52, P = 0.16). While this observation is biologically plausible, caution is necessary given the low number of studies including platinum resistant disease.

We also explored the possible dose depending activity of tamoxifen clustering high (>20 mg) versus standard dose (=20 mg). We did not observe any trend between doses but the high heterogeneity among groups prevents any firm conclusion. It has been shown that in vitro the chemosensitizing activity of tamoxifen starts at a concentration of 0.1 mM and the potential mechanism of the antiproliferative effect of tamoxifen plus platinum compound is still unclear [67].

The recent study by Sieh et al. [8] on nearly 3000 women with invasive EOC undergoing central hormone receptor assay provides evidence for the prognostic role of ER and PgR and the potential hormonal sensitivity of EOC. Expression of ER and PgR was associated with subtype-specific survival, with highest positivity for endometrioid carcinoma and low-grade serous carcinoma, intermediate for high-grade serous carcinoma, the most frequent and lethal subtype, and lowest for mucinous carcinoma and clear-cell carcinoma. In a recent retrospective study by Gershenson et al., [68] 203 women with stage II–IV low-grade serous carcinoma who received hormonal maintenance therapy following primary treatment had a better outcome. Median progression-free survival was 26.4 months with surveillance and 64.9 months with hormonal therapy (P < 0.001) although no significant difference in OS was observed between groups (102.7 v 115.7 months; P = 0.042). Whereas ER and PgR were assessed in a proportion of the patients, low grade serous carcinoma is known to express the highest level of steroid receptors and to be platinum resistant [8].

Remarkably, a significant mortality effect was found summarizing data from 6 randomized trials: the Summary Odd Ratio indicates a significant reduction in risk of mortality when patients are treated with endocrine therapy (SOR: 0.66, 95% CI, 0.47–0.93). Explorative analyses by first line of treatment and tumor grade was hampered by the low numbers, but a possible tendency for a greater effect in first line and low grade tumors was noted. Grade 3 or higher toxicity was extremely low. The relationship with hormonal treatment is also difficult to assess since many adverse events may also be related to chemotherapy or the surgical menopause.

Taken together, these findings provide the rationale for determining ER and PgR in the majority of EOC at diagnosis and to launch phase III trials in the first line treatment of ER+ or PgR+ disease concomitant to standard chemotherapy. If proven to be beneficial, such an inexpensive and well tolerated treatment would be extremely cost effective in the management of this dismal disease.

In conclusion, our findings indicate that endocrine therapy has a reasonable activity in advanced EOC. While our data are hampered by the heterogeneity of trials encompassing nearly 40 years, clinical trials in the first line treatment of advanced hormone receptor positive EOC are warranted.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2017.06.036.

Disclaimers

No potential conflict of interest was reported by the authors.

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