available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Randomized evidence on chemotherapy and hormonal therapy regimens for advanced endometrial cancer: An overview of survival data

Nikolaos P. Polyzos[a,b], *Nicholas Pavlidis*[c,*], *Evangelos Paraskevaidis*[b], *John P.A. Ioannidis*[a,d]

[a]*Department of Hygiene and Epidemiology, University of Ioannina, School of Medicine, Ioannina 45110, Greece*
[b]*Department Obstetrics and Gynaecology, University of Ioannina, School of Medicine, Ioannina 45110, Greece*
[c]*Division of Medical Oncology, University of Ioannina, School of Medicine, Ioannina 45110, Greece*
[d]*Institute for Clinical Research and Health Policy Studies, Department of Medicine, Tufts University School of Medicine, Boston, MA, United States*

ARTICLE INFO

Article history:
Received 21 September 2005
Accepted 27 September 2005
Available online 11 January 2006

Keywords:
Endometrial cancer
Advanced
Chemotherapy
Hormonal therapy
Bias
Systematic review
Survival

ABSTRACT

Several chemotherapy and hormonal therapy regimens have been used in advanced endometrial cancer. In this review we have systematically evaluated the available data from randomized trials on survival. We searched MEDLINE, EMBASE and the Cochrane Library (last search April 2005) for randomized controlled trials evaluating various chemotherapy or hormonal therapy regimens in locally advanced or metastatic endometrial cancer. We focused on survival outcomes and examined trial characteristics pertaining to quality and potential biases. Across 17 eligible trials (2964 patients randomized), only 4 regimens were involved in more than one trial, and only two trials had used the same comparison of regimens. A statistically significant effect in survival was seen only in one recent trial, but it was borderline ($P = 0.032$) and amounted to only 3 months difference in median survival. Three more trials reported some survival benefits, but these were seen only after specific adjustments, and the difference was against the experimental arm in one of these three trials. Only four trials (24%) apparently analyzed all randomized patients and none of the trials were blinded. Median survival was seemingly longer in more recent compared with older trials, but this effect was driven by the inclusion of significantly fewer patients with poor performance status in more recent trials ($P < 0.001$). Overall, randomized evidence on systemic treatment in advanced endometrial cancer is fragmented and survival benefits for specific regimens are questionable.

© 2005 Elsevier Ltd. All rights reserved.

1. Introduction

Treatment of advanced stage endometrial cancer is challenging. Radiation, the standard modality along with surgery, for treatment of early disease [1–4] and local or regional recurrences [5,6], has no clear benefit in advanced stage patients or patients with non-localized recurrent disease [7–9]. Chemotherapy and/or hormonal therapy are often considered to be the only active treatments in advanced disease [10].

* *Corresponding author:* Tel.: +30 26510 99394; fax: +30 26510 97505/99394.
E-mail address: npavlid@cc.uoi.gr (N. Pavlidis).
0959-8049/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2005.09.026

Many different chemotherapy and hormonal therapy agents have been tested in this setting. The most common regimens in clinical practice include doxorubicin, cisplatin and paclitaxel (either as single agents or in combination), and medroxyprogesterone acetate [10]. The activity of hormonal regimens, mainly progestins, is thought to be influenced by certain prognostic factors, such as receptor content [11]. However, response rates are unlikely to be high and the exact impact on survival is uncertain [11–13]. It is also unclear if chemotherapy offers any survival benefit. Several phase I or II uncontrolled trials have been conducted to evaluate the efficacy of the most commonly used regimens either as single agents [14] or as combinations [15–19] in an effort to identify better treatments. However, what is the current evidence on the efficacy of available systemic therapies? Do they prolong survival? There is concern that for some advanced stage cancers, progress has been limited, and randomized clinical trials literature may be subject to biases [20]. Is there evidence that biases may also be operating in the literature on advanced endometrial cancer treatment?

In order to address these questions, we performed an overview of all randomized trials of systemic therapies in patients with advanced endometrial cancer. We analyzed the available data and examined whether there is evidence for superior survival outcomes with specific chemotherapeutic or hormonal regimens against others. This overview aims to provide insights for helping guide future clinical research in this field.

2. Patients and methods

2.1. Search strategy and eligibility criteria

The protocol was designed as part of an overarching effort to appraise the evidence on the treatment of advanced stage malignancies on survival. It follows the same principles, as that used for an overview of trials in advanced lung cancer [20]. We searched MEDLINE, EMBASE and the Central Library of Controlled Trials of the Cochrane Library until April of 2005. The search strategy used "cancer or neoplasia" and "endometrial or uterine" with an array of terms suggestive of randomized controlled trials, as recommended by the Cochrane Collaboration Reviewer Handbook. The full strategy is available upon request. In addition, we identified all previous reviews of randomized trials in this field and perused their references. Finally, cross-searches were performed in MEDLINE using the names of investigators who were lead authors in at least one eligible trial.

We considered all randomized controlled trials that compared at least two arms of different chemotherapy or hormonal therapy regimens in patients with advanced endometrial cancer (stage IIIB or IV, unresectable, or recurrent) with at least 5 patients per arm. We excluded non-randomized trials or pseudo-randomized trials with alternate allocation of subjects, trials limited to non-advanced disease and those limited to cancer of the uterine cervix. For trials that had included also some patients with non-advanced disease or other malignancies, we focused on the eligible patient subgroups. We accepted randomized trials comparing different dosing schemes and schedules of the same agent or combination of agents. For completeness, we also recorded trials comparing chemotherapy or hormone therapy against best supportive care without any systemic treatment.

Trial reports were scrutinized to identify potential duplication and overlap, in which case only the latest report with the most complete information was retained. Meeting abstracts were excluded as they provide insufficient information for appraisal of a study and its results. We set no language restriction.

2.2. Data extraction

From each eligible trial report we recorded authors, publication year, journal, sample size (total randomized, considered eligible, per arm), regimens compared, type of chemotherapy or hormone therapy, country(ies) of the investigators, study population eligibility criteria, the percentage of patients with performance status 2 or worse and stage IV disease per arm, and information on prior treatment.

Furthermore, we recorded the median survival per arm, and whether there was any statistically significant difference in median survival between compared arms ($P < 0.05$ on two-tailed inference). When several different analyses were reported, we preferred the log-rank test results over other statistics and unadjusted analyses over adjusted analyses, since the main principle of randomization is that it should generate similar compared groups and remove the need for adjustments for measured or unmeasured confounders [21]. All claimed survival differences were scrutinized to evaluate on what analyses they had been based.

We also recorded qualitative parameters including blinding, adequate reporting of the mode of randomization (generation of randomization sequence), allocation concealment, and whether all patients randomized were included in the survival analysis according to a strict intention-to-treat principle. We also recorded any mention of planned interim analyses. All data were extracted by two investigators (N.P.P. and J.P.A.I.) and consensus was reached through discussion.

2.3. Analysis

We classified regimens and comparisons according to the exact chemotherapy or hormone therapy being used; according to broad categories defined by the use of taxanes (paclitaxel), doxorubicin and/or cisplatin, and/or hormonal agents; and according to whether monotherapy or at least two agents were involved. Using Spearman correlation analyses, we evaluated whether the publication year was related with sample size, proportion of patients with performance status 2 or worse, and proportion of patients with stage IV; data on proportion of patients with previous chemotherapy, hormonal therapy, or radiotherapy were too sparse or disparate to allow similar meaningful analysis.

We also probed whether the reported median survival improved over time, and if so, whether this was potentially related to selection biases. The median survival in each arm was regressed against the year of publication, sample size of the study arm, and proportion of patients with poor performance status. Multivariate regression models were also evaluated considering all variables. Results should be interpreted

cautiously for this analysis since the randomization contrasts are not maintained and there are relatively few observations (study arms).

Analyses were conducted in statistical package for social sciences (SPSS) 12.0 (SPSS Inc., Chicago, IL). *P*-values are two-tailed, unless specified otherwise.

3. Results

3.1. Eligible trials

The electronic searches yielded 3830 items from MEDLINE, 1115 from EMBASE and 1129 from Cochrane Central. Of those, 33 potentially eligible articles were scrutinized in full text. Eighteen of the 33 were excluded (9 not randomized or pseudo-randomized, 2 with fewer than 5 subjects per arm, 1 comparing hormonal therapy against no therapy, and 4 trials with preliminary/incomplete data from abstracts/proceedings). Fifteen trials qualified and another two were identified through cross-referencing for a total of 17 eligible trials [22–38]. In the search for additional trials comparing systemic therapy against best supportive care or no therapy at all, we found only one randomized trial [11]. This trial compared progestins against no therapy and included patients with various disease stages (total $n = 429$, of which 47 had advanced disease, but only 26 were analyzed after various exclusions). The study found no overall difference in mortality rates ($P = 0.71$) and 5-year survival was 73.4% in the progestin group vs. 79.9% in the control group; no separate data were provided for advanced stage patients.

The 17 eligible trials (Table 1) had been published over a period of 27 years. The median sample size was 131 (interquartile range, 47–312). One early trial included patients with non-advanced disease [31]. The median eligible sample size was 114 (interquartile range, 42–290). A total of 2964 subjects were randomized and 2771 were considered eligible for survival analyses. Thirteen trials involved USA investigators, 1 was performed in Canada and 3 were conducted in Europe. Highly experienced trial groups were typically involved in the conduct of these trials, including the Gynecologic Oncology Group (GOG, $n = 8$ trials), the Eastern Collaborative Oncology Group (ECOG, $n = 3$ trials), the European Organization for Research and Treatment of Cancer (EORCT) Gynaecological Cancer Group ($n = 2$ trials), and 4 other teams (one trial each). There was considerable variability in the percentage of patients with poor performance status and stage IV disease (Table 1). Inclusion of patients with previous chemotherapy use was uncommon, while inclusion of patients with previous hormonal therapy was common (9/14 trials had included variable percentages of such patients), while typically half or more of the randomized patients had received radiotherapy previously, in all trials that provided this information (Table 1).

3.2. Compared chemotherapy and hormonal therapy regimens

Overall, 7 monotherapies and 14 combinations of different agents had been tested (Table 1). The most commonly assessed hormonal regimen, medroxyprogesterone acetate, was tested in 3 trials (5 arms), two of which compared different schedules and doses thereof. The most commonly assessed chemotherapeutic regimen, cisplatin + doxorubicin, was utilized in 5 trials (6 arms), one of which compared different schedules of the regimen. Four arms used doxorubicin monotherapy and 2 arms used cyclophosphamide monotherapy, otherwise all other 17 regimens had been involved only once in a single arm of a single published randomized trial. The only comparison that was evaluated in more than 1 published randomized trial was doxorubicin versus the combination of doxorubicin + cisplatin: two trials were published for this comparison, but still the total sample size amounted to only 458 patients.

Five trials involved comparison of monotherapy against combinations, 5 compared monotherapies only and 7 compared at least two different combinations of agents. Twenty-one arms used only chemotherapeutic regimens (containing paclitaxel $n = 2$; doxorubicin $n = 6$; doxorubicin + cisplatin $n = 7$; other $n = 6$), 8 arms used only hormonal regimens, and 5 arms used both hormonal and chemotherapeutic regimens. Paclitaxel-containing regimens had been used only in the most recent trials published in 2004, and the doxorubicin + cisplatin combination regimen had also been used mainly after 2000 (only one arm in a trial prior to 2000).

3.3. Quality measures

Of the 17 trials, 3 (17%) described in sufficient detail an appropriate mode of randomization and 8 (47%) described in sufficient detail an appropriate mode of allocation concealment. Only 4 trials (23%) were reported where a strict "intention-to-treat" analysis seemed to have been performed, including all patients randomized in the analysis of survival (Table 2). Planned interim analyses were mentioned in 3 (17%) trials [22,23,26]. None of the 17 trials could be blinded.

3.4. Survival

Median survival data could be retrieved for 13 trials. The other 4 trials had small sample sizes and apparently there had been no statistically significant difference between the compared arms regarding survival, but no exact data were provided.

The only trial with statistically significant difference in survival in adjusted analyses compared doxorubicin + cisplatin versus doxorubicin + cisplatin + paclitaxel + G-CSF [22]. The compared arms did not differ only in regards to the chemotherapy regimen, but also regarding the receipt or not of a haemopoetic growth factor which was deemed necessary to control the risk of neutropenia in the triple chemotherapy arm. The difference in median survival amounted to 3 months, and it was of borderline statistical significance (12.3 months vs. 15.3 months, $P = 0.032$). The trial had performed a planned interim analysis and the investigators mentioned that they did consider alpha-spending correction in interpreting the significance level.

Three more trials claimed survival differences in various secondary analyses. Aapro [25] found no difference between doxorubicin + cisplatin vs. doxorubicin alone in the main analysis ($P = 0.11$ for log-rank test), but claimed significance after adjusting for performance status ($P = 0.024$). Thigpen [28] found that median survival was worse by 4.1 months in

Table 1 – Eligible randomized trials for comparisons of chemotherapy and hormonal therapy in advanced endometrial cancer

Author, year	N (eligible)	Location	Regimens compared	N per arm	Median survival	Performance status 2 or worse (%)	Stage IV disease (%)	Previous systemic therapy (%)	Previous radiotherapy (%)
Fleming, 2004	273 (263)	USA	Doxo + CisPl	129	12.3	15 (12)	28 (22)	H allowed (NA), no Ch	66 (51)
			Doxo + CisPl + Paclitaxel + GCSF	134	15.3	11 (8)	36 (27)	H allowed (NA), no Ch	62 (46)
Fleming, 2004	328 (317)	USA	Doxo + CisPl	157	12.6	15 (10)	41 (26)	29 (18) H, no Ch	83 (53)
			Doxo + Paclitaxel + GCSF	160	13.6	13 (8)	36 (23)	31 (20) H, no Ch	81 (51)
Thigpen, 2004	299 (281)	USA	Doxo	150	9.2	25 (17)	NA	44 (29) H, no Ch	93 (62)
			Doxo + CisPl	131	9.0	29 (22)	NA	46 (35) H, no Ch	89 (68)
Gallion, 2003	352 (342)	USA	Doxo + Cis Pl (schedule 1)	169	11.2	29 (17)	NA	H allowed (NA), no Ch	96 (57)
			Doxo + CisPl (schedule 2)	173	13.2	24 (14)	NA	H allowed (NA), no Ch	95 (55)
Aapro, 2003	177 (177)	Europe	Doxo	87	7.0	17 (20)	NA	15 (17) H, 1 (1) Ch	48 (55)
			Doxo + CisPl	90	9.0	15 (17)	NA	25 (28) H, no Ch	40 (44)
Pandya, 2001	66 (62)[a]	USA	Megestrol	20	12.0	4 (20)	NA	No H, 2 (10) Ch	16 (80)
			Megestrol + TMX	42[a]	8.6	7 (17)	NA	No H, 2 (5) Ch	35 (83)
Thigpen, 1999	324 (299)	USA	MPA (schedule 1)	145	11.1	30 (21)	32 (22)	No H, no Ch	98 (68)
			MPA (schedule 2)	154	7.0	38 (25)	36 (23)	No H, no Ch	99 (64)
Pawinski, 1999	74 (61)	Europe	Cyc	29	NA	7 (24)	NA	10 (34) H, 15 (52) Ch	20 (69)
			Ifosfamide	32	NA	6 (19)	NA	7 (22) H, 16 (50) Ch	21 (66)
Thigpen, 1994	387 (356)	USA	Doxo	132	6.9	50 (29)	NA	No Ch	116 (68)
			Doxo + Cyc	144	7.3	60 (33)	NA	No Ch	132 (71)
Ayoub, 1988	46 (43)	Canada	Cyc + Doxo + 5FU	20	11.0	NA	7 (35)	No H, no Ch	10 (50)
			Cyc + Doxo + 5FU + MPA + TMX	23	14.0	NA	9 (39)	No H, no Ch	11 (48)
Edmonson, 1987	30 (30)	USA	CisPl	14	4.2	7 (50)	12 (86)	No H, no Ch	8 (57)
			CisPl + Doxo + Cyc	16	6.7	7 (44)	12 (75)	No H, no Ch	11 (68)
Piver, 1986	18 (18)	USA	Mel + 5FU + MPA	9	7.7[b]	NA	NA	No H, no Ch	NA
			Mel + 5FU + MPA + TMX	9	7.7[b]	NA	NA	No H, no Ch	NA
Cohen, 1984	295 (253)	USA	Mel + 5FU	122	10.6	31 (20)[c]	NA	H allowed (NA), no Ch	NA
			Mel + 5FU + Cyc	131	10.1		NA	H allowed (NA), no Ch	NA
Rendina, 1984	93 (93)	Italy	TMX	45	NA	NA	4 (9)	NA	NA
			MPA	48	NA	NA	5 (10)	NA	NA
Horton, 1982	131 (114)	USA	Megestrol + Cyc + Doxo	56	6.2	17 (30)	NA	21 (37) H, no Ch	NA
			Megestrol + Cyc + Doxo + 5FU	58	6.2	18 (31)	NA	22 (38) H, no Ch	NA
Sall, 1979	24 (22)	USA	MPA (schedule 1)	11	NA	NA	NA	NA	NA
			MPA (schedule 2)	11	NA	NA	NA	NA	NA
Horton, 1978	47 (40)	USA	Doxo	21	NA	NA	NA	21 (100) H, No Ch	NA
			Cyc	19	NA	NA	NA	19 (100) H, No Ch	NA

Abbreviations: NA, not available; Doxo, doxorubicin; CisPl, cisplatin; Cyc, cyclophosphamide; MPA, medroxyprogesterone acetate; TMX, tamoxifen; Mel, melphalan; 5FU, fluorouracil; GCSF, granulocyte colony stimulating factor; H, hormonal therapy; Ch, chemotherapy.
a Includes data also on 25 patients directly assigned to the combination arm after the megestrol arm was closed early due to poor accrual; separate data on the 17 randomized patients are not provided for any characteristic or outcome.
b Based on data from 50 patients (18 randomized and another 32 allocated to the triple therapy arm, after the quadruple therapy arm was discontinued).
c Based on 155 patients from both arms with data on performance status (no separate data per arm).

Table 2 – Quality of the reporting of eligible trials

First author, year	Allocation concealment	Generation of allocation sequence	Inclusion of all randomized participants
Fleming, 2004	A	?	B
Fleming, 2004	A	?	B
Thigpen, 2004	A	A	B
Gallion, 2003	A	A	B
Aapro, 2003	A	A	A
Pandya, 2001	A	?	B
Thigpen, 1999	?	?	B
Pawinski, 1999	?	?	B
Thigpen, 1994	?	?	B
Ayoub, 1988	?	?	B
Edmonson, 1987	?	?	A
Piver , 1986	?	?	A
Cohen, 1984	?	?	B
Rendina, 1984	?	?	A
Horton, 1982	?	?	B
Sall, 1979	A	?	B
Horton, 1978	A	?	B

Abbreviations/coding: A, yes; B, no; ?, not specified.

the experimental arm of a trial comparing high-dose oral medroxyprogesterone against the traditional lower dose. No comment was made on the statistical significance of this difference, but it was stated that the risk of death was significantly greater (relative risk increase 31%, $P = 0.026$) after adjusting for performance status, progesterone-receptor level, tumour grade, and age. Finally, Thigpen [30] found no difference in the main unadjusted analysis comparing doxorubicin + cyclophosphamide against doxorubicin (difference in median survival 0.4 months, $P = 0.24$ one-tailed), but a significant benefit was observed after adjusting for performance status, grade, liver metastasis, and other intra-abdominal metastasis. The adjusted 17% relative risk reduction was of borderline significance and it was based on a one-tailed P-value ($P = 0.048$ one-tailed).

In terms of the absolute impact on median survival, differences between arms were very small and typically did not exceed 3.5 months, with the exception of the one trial mentioned above [28], where a difference of 4.1 months was observed, but this was in fact deleterious (against the experimental arm).

3.5. *Evolution over time and correlates of median survival*

There was strong evidence that more recent trials were including a smaller percentage of patients with poor performance status (correlation coefficient between year of publication and proportion of subjects with performance status 2 or worse −0.83, $P = 0.001$) and there was also evidence that more recent trials were getting larger than earlier published trials (correlation coefficient between year of publication and sample size 0.56, $P = 0.019$ for all randomized patients and 0.61, $P = 0.009$ for patients considered eligible). There was no clear selection difference over time for the proportion of patients with stage IV disease (correlation coefficient 0.06, $P = 0.91$), but many data were missing.

In univariate analyses, the observed median survival was borderline related to the sample size (regression coefficient 1.8 months per 100 patients' increase in the eligible sample size, $P = 0.060$), it was clearly affected by the proportion of patients with poor performance status (−2.3 months per 10% increase, $P < 0.001$), and median survival also significantly improved over time (1.6 months increase per decade, $P = 0.016$). However, this was entirely explained by the greater proportion of patients with worse disease in earlier trials. In a multivariate model, there was absolutely no effect of improved survival in more recent trials (0.0 months per decade, $P = 0.99$), and no effect of sample size on survival (0.2 months per 100 patients' increase, $P = 0.89$), while the effect of performance status remained unaltered (−2.3 months per 10% increase in the proportion of patients with performance status 2 or worse, $P < 0.001$). Performance status accounted for over two-thirds of the observed variability in median survival in these data (coefficient of determination $R^2 = 0.72$).

4. Discussion

This overview suggests that the evidence for the use of hormonal and chemotherapeutic regimens in women with advanced endometrial cancer remains fragmented and relatively weak. A considerable randomized literature on systemic therapy for these patients has emerged in the last 3 decades and these trials have been conducted by experienced investigators. Nevertheless, strictly speaking, neither hormonal treatment nor chemotherapy have ever been explicitly proven to offer any clear survival benefit against best supportive care in these patients. Leaving this important proof of concept aside, new regimens seem to have been tested following the current mode of treatment for other cancers and the potentially promising results of small phase I/II uncontrolled studies on tumour response. Regimens are then tested against even newer regimens, typically with an expanding number of drugs. This has led to combination treatments that may be quite toxic (causing significant neutropenia, cardiac toxicity, and neurotoxicity) with unclear survival benefits.

The only trial [22] that has found a modest survival benefit in unadjusted analyses had borderline statistical significance, and the observed benefit is small in terms of the absolute survival improvement. The accompanying high levels of incremental neurotoxicity in that trial [22] make such a benefit even more debatable. Moreover, one borderline statistically significant finding may be expected simply by chance among 17 trials. It is interesting that several other trials have claimed potential survival differences, not all of them in favour of the experimental regimens. However, these are based on adjusted analyses that may not be the most appropriate approach for properly randomized trials [21]. Selective adjustments and flexibility in outcome analyses may yield formally significant results of questionable validity [39].

The considerable variability in the regimens being used (21 different regimens in 17 trials) further testifies to the difficulty in identifying effective treatments. Despite approximately 3000 randomized patients, only two regimens have been directly compared for their impact on survival in more than one trial and even for this comparison fewer than 500 patients have been assessed. Trials conducted to date are probably underpowered to detect plausible survival differences given the anticipated effectiveness of the currently available regimens. Running very large trials may pose considerable challenges to the field.

Lack of double-blinding, reporting on the mode of randomization, and allocation concealment have been associated with spuriously inflated treatment effects in other medical domains [40,41]. Several trials analyzed here did not score high on reporting of these quality aspects. Nevertheless, blinding is not convenient for chemotherapy trials and perhaps comparative survival may not be as easily affected by methodological shortcomings, unless accompanied by additional biases such as lack of intention-to-treat analysis, and lack of prespecified stopping rules. Moreover, reporting does not always reflect the actual study design [42]. For example, some trials not reporting adequately on the generation and concealment of the randomized sequence may still have generated and concealed the randomization sequence appropriately. This is very likely for several trials analyzed here that were conducted by experienced multicenter teams. Finally, methodological shortcomings such as those noted here have not been associated with inflated outcomes in all medical domains [43].

Regardless of these caveats, meticulous study design and reporting would be useful in this field, as in any medical field [41]. The large majority of trials on advanced endometrial cancer excluded some randomized patients from the survival analyses due to various ineligibility criteria. The extent to which this may introduce bias is unknown, but ideally these patients should have been analyzed, for survival at least, according to a strict intention-to-treat respecting their original randomization [21]. Of greater concern is the use of several adjusted secondary analyses that were employed to make sporadic survival benefit claims. Selective reporting of outcomes is an increasingly recognized problem in clinical trials across medicine [39,44], and endometrial cancer trials are unlikely to be spared.

We also documented a strong selection trend over time in the composition of the study populations. There was a clear decrease in the proportion of enrolled patients with poor performance status in randomized trials over time. Performance status is a very strong predictor of survival and may account to a large extent for the observed improvement in survival over time. However, no true improvement in survival remains once the estimates are adjusted for the performance status. We should acknowledge that this is only an ecological adjustment, and thus should be interpreted cautiously. However, a similar selection bias has been previously described for randomized trials of advanced non-small cell lung cancer [20]. While sophisticated methodologists and investigators are aware of the danger of comparing such data across trials, many clinicians often naively compare survival estimates across trials performed on different populations at different periods of time. Thus one may get a false sense that progress is made in this field or other similar fields of systemic treatment. The available evidence suggests that no major advances in survival have been achieved in this field [45].

We could not probe into the extent of potential publication bias and time lag bias in this field. There is considerable evidence from many clinical domains that trials with "negative" results, especially small ones, may have difficulty being

published [46] or may be published with considerable delays compared with trials who find significant benefits for the tested interventions [47]. It would not be surprising if several trials on advanced endometrial cancer have not been published at all. Any publication bias would mean that the evidence is even more "negative" and definitively against the routine use of any of these regimens.

We did not examine other outcomes, such as response rates or progression-free survival. For such intermediate outcomes, several regimens may indeed show far more promise than they do for survival, and this has been clearly documented both in single-arm phase II studies as well as in randomized trials [22,24]. However, given the potential toxicity of these regimens, any claimed effects on response rates and disease progression would offer soft ground for the adoption of these treatments in routine clinical practice.

Conflict of interest statement

None declared.

REFERENCES

1. Piver MS, Hempling RE. A prospective trial of postoperative vaginal radium/cesium for grade 1–2 less than 50% myometrial invasion and pelvic radiation therapy for grade 3 or deep myometrial invasion in surgical stage I endometrial adenocarcinoma. *Cancer* 1990;**66**:1133–8.
2. Stryker JA, Podczaski E, Kaminski P, et al. Adjuvant external beam therapy for pathologic stage I and occult stage II endometrial carcinoma. *Cancer* 1991;**67**:2872–9.
3. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004;**92**:744–51.
4. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000;**355**:1404–11.
5. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. *Gynecol Oncol* 2000;**77**:66–72.
6. Nag S, Martinez-Monge R, Copeland LJ, et al. Perineal template interstitial brachytherapy salvage for recurrent endometrial adenocarcinoma metastatic to the vagina. *Gynecol Oncol* 1997;**66**:16–9.
7. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. *Gynecol Oncol* 1984;**17**:85–103.
8. Goff BA, Goodman A, Muntz HG, et al. Surgical stage IV endometrial carcinoma: a study of 47 cases. *Gynecol Oncol* 1994;**52**:237–40.
9. Randall ME, Spirtos NM, Dvoretsky P. Whole abdominal radiotherapy versus combination chemotherapy with doxorubicin and cisplatin in advanced endometrial carcinoma (phase III): Gynecologic Oncology Group Study No. 122. *J Natl Cancer Inst Monogr* 1995;**19**:13–5.
10. Benedet JL, Bender H, Jones 3rd H, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int J Gynaecol Obstet* 2000;**70**:209–62.
11. Macdonald RR, Thorogood J, Mason MK. A randomized trial of progestogens in the primary treatment of endometrial carcinoma. *Brit J Obstet Gynaecol* 1988;**95**:166–74.
12. Podratz KC, O'Brien PC, Malkasian Jr GD, et al. Effects of progestational agents in treatment of endometrial carcinoma. *Obstet Gynecol* 1985;**66**:106–10.
13. Piver MS, Barlow JJ, Lurain JR, et al. Medroxyprogesterone acetate (Depo-Provera) vs. hydroxyprogesterone caproate (Delalutin) in women with metastatic endometrial adenocarcinoma. *Cancer* 1980;**45**:268–72.
14. Hirai Y, Hasumi K, Onose R, et al. Phase II trial of 3-h infusion of paclitaxel in patients with adenocarcinoma of endometrium: Japanese Multicenter Study Group. *Gynecol Oncol* 2004;**94**:471–6.
15. Scudder SA, Liu PY, Wilczynski SP, et al. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. *Gynecol Oncol* 2005;**96**:610–5.
16. Fleming GF, Fowler JM, Waggoner SE, et al. Phase I trial of escalating doses of paclitaxel combined with fixed doses of cisplatin and doxorubicin in advanced endometrial cancer and other gynecologic malignancies: a Gynecologic Oncology Group study. *J Clin Oncol* 2001;**19**:1021–9.
17. Dimopoulos MA, Papadimitriou CA, Georgoulias V, et al. Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. *Gynecol Oncol* 2000;**78**:52–7.
18. Deppe G, Malviya VK, Malone JM, et al. Treatment of recurrent and metastatic endometrial carcinoma with cisplatin and doxorubicin. *Eur J Gynaecol Oncol* 1994;**15**:263–6.
19. Barrett RJ, Blessing JA, Homesley HD, et al. Circadian-timed combination doxorubicin-cisplatin chemotherapy for advanced endometrial carcinoma. A phase II study of the Gynecologic Oncology Group. *Am J Clin Oncol* 1993;**16**:494–6.
20. Ioannidis JP, Polycarpou A, Ntais C, et al. Randomised trials comparing chemotherapy regimens for advanced non-small cell lung cancer: biases and evolution over time. *Eur J Cancer* 2003;**39**:2278–87.
21. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;**134**:663–94.
22. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2004;**22**:2159–66.
23. Fleming GF, Filiaci VL, Bentley RC, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. *Ann Oncol* 2004;**15**:1173–8.
24. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. *J Clin Oncol* 2004;**22**:3902–8.
25. Aapro MS, van Wijk FH, Bolis G, et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. *Ann Oncol* 2003;**14**:441–8.
26. Gallion HH, Brunetto VL, Cibull M, et al. Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2003;**21**:3808–13.
27. Pandya KJ, Yeap BY, Weiner LM, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). *Am J Clin Oncol* 2001;**24**:43–6.

28. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose–response study by the Gynecologic Oncology Group. *J Clin Oncol* 1999;**17**:1736–44.
29. Pawinski A, Tumolo S, Hoesel G, et al. Cyclophosphamide or ifosfamide in patients with advanced and/or recurrent endometrial carcinoma: a randomized phase II study of the EORTC Gynecological Cancer Cooperative Group. *Eur J Obstet Gynecol Reprod Biol* 1999;**86**:179–83.
30. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 1994;**12**:1408–14.
31. Ayoub J, Audet-Lapointe P, Methot Y, et al. Efficacy of sequential cyclical hormonal therapy in endometrial cancer and its correlation with steroid hormone receptor status. *Gynecol Oncol* 1988;**31**:327–37.
32. Edmonson JH, Krook JE, Hilton JF, et al. Randomized phase II studies of cisplatin and a combination of cyclophosphamide-doxorubicin-cisplatin (CAP) in patients with progestin-refractory advanced endometrial carcinoma. *Gynecol Oncol* 1987;**28**:20–4.
33. Piver MS, Lele SB, Patsner B, et al. 5-Fluorouracil and medroxyprogesterone acetate in metastatic endometrial carcinoma. *Obstet Gynecol* 1986;**67**:261–4.
34. Cohen CJ, Bruckner HW, Deppe G, et al. Multidrug treatment of advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Obstet Gynecol* 1984;**63**:719–26.
35. Rendina GM, Donadio C, Fabri M, et al. Tamoxifen and medroxyprogesterone therapy for advanced endometrial carcinoma. *Eur J Obstet Gynecol Reprod Biol* 1984;**17**:285–91.
36. Horton J, Elson P, Gordon P, et al. Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. *Cancer* 1982;**49**:2441–5.
37. Sall S, DiSaia P, Morrow CP, et al. A comparison of medroxyprogesterone serum concentrations by the oral or intramuscular route in patients with persistent or recurrent endometrial carcinoma. *Am J Obstet Gynecol* 1979;**135**:647–50.
38. Horton J, Begg CB, Arseneault J, et al. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. *Cancer Treat Rep* 1978;**62**:159–61.
39. Chan AW, Hrobjartsson A, Haahr MT, et al. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;**291**:2457–65.
40. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.
41. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42–6.
42. Ioannidis JP, Lau J. Can quality of clinical trials and meta-analyses be quantified?. *Lancet* 1998;**352**:590–1.
43. Balk EM, Bonis PA, Moskowitz H, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002;**287**:2973–82.
44. Chan AW, Krleza-Jeric K, Schmid I, et al. Outcome reporting bias in randomized trials funded y the Canadian Institutes of Health Research. *CMAJ* 2004;**171**:735–40.
45. Ioannidis JP, Pavlidis N. Levels of absolute survival benefit for systemic therapies of advanced cancer. A call for standards. *Eur J Cancer* 2003;**39**:1194–8.
46. Easterbrook PJ, Berlin JA, Gopalan R, et al. Publication bias in clinical research. *Lancet* 1991;**337**:867–72.
47. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA* 1998;**279**:281–6.