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# A Meta-Analysis Study of Polychemotherapy versus Monochemotherapy in Patients of Metastatic Breast Cancer

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**ABSTRACT**

Polychemotherapy and intermittent monochemotherapy regimens in metastatic breast cancer were examined in a meta analysis that included both tumor response rate and toxicities. Randomized controlled studies (conducted during 1990-2008) comparing monochemotherapy and poly-chemotherapy in advanced breast cancer patients were selected from electronic databases. Meta-analysis for response rate and toxicities [nausea and vomiting, toxic death, alopecia and reduced white cell count (WCC)] was performed using the Mantel-Haenszel method. The heterogeneity among the trials was assessed through a $\chi 2$ statistic, I2 and visual inspection of the forest plots. Analysis of eligible studies reveals statistical significant difference in response rate (OR 0.72, 95% CI 0.65-0.79), nausea and vomiting (OR 0.80, 95% CI 0.67-0.59), Alopecia (OR 0.75, 95% CI 0.64-0.88) and reduced WCC (OR 0.55, 95% CI 0.48-0.62) which favours polychemotherapy except toxic death (OR 0.87, 95% CI 0.58-1.29). There was marked evidence of heterogeneity in all end points except toxic death. This meta analysis shows the superiority of efficacy but not of safety of polychemotherapy over that of a single agent. However, the choice of treatment should be based on the response to the therapy, toxicity, patient preference, presence of metastases or imminent complications requiring aggressive and rapid tumor control.

**Keywords:** Meta Analysis, Monochemotherapy, Polychemotherapy, Nausea, Reduced WCC, Response rate, Toxic death, Vomiting.

## INTRODUCTION

Breast cancer is the most common type of cancer in women and the prevalent common cause of cancer associated death in this gender. Metastatic breast cancer is a cancer that has advanced and spread beyond the breast and regional lymph nodes. The patients with metastatic breast cancer constitute a heterogeneous population; hence the goals of therapy range from symptom palliation and minimization of toxicity to prolongation of overall survival in elderly women and good performance status, respectively. Metastatic breast cancer can be grouped as "low risk" and "moderate/high risk" based on the extent of disease. Patients with positive hormone status with limited metastatic burden (in soft tissues and bones) and more than two years of disease free interval but without visceral involvement are considered as relatively low risk patients. On the other hand, negative hormone status with extensive metastatic burden involving viscera with disease free interval of less than two years is regarded as moderate to high risk. [1] Treatment of metastatic breast cancer with chemotherapy has

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undergone several distinct historical phases. Treatment with single chemotherapeutic agents was first introduced as early as 1960s but it often showed low tumor response. Combination regimens or polychemotherapy (Cyclophosphamide, Methotrexate and 5-Fluorouracil) developed in 1970s indicated substantial improvement in tumor response. Then in 1980s, Anthracyclines were incorporated into newer generation regimen (Doxorubicin and Cyclophoshamide) and Taxanes emerged in 1990s. Administration of intermittent cycles of these early and new chemotherapy combinations resulted in high (complete) response rates [2] and thus, remained the mainstay of treatment for the metastatic disease. Overall, polychemotherapy is considered to be useful in women whose cancer is hormone refractory, expected to be hormone resistant, estrogen receptor negative, or with life threatening or visceral disease. [3-5] Usually, because of its superior tumor response rates, polychemotherapy is favoured by many clinicians over single agents for the treatment of metastatic breast cancer. It is not known, however, whether giving more intensive chemo-therapy regimens results in better health outcomes, when both response rate and toxicity are considered. When this therapeutic concept was explored in uncontrolled studies in advanced breast cancer; the studies resulted in an overall higher response rate and complete remissions, compared to single drug treatment. [6] Most women with advanced disease, however, receive single chemotherapy either as their first treatment, because their disease has become resistant to some treatments, multiple sites of recurrence or where visceral disease is not easily treated by local modalities [7] or in combination with other types of treatments. Although there is no overwhelming clinical evidence in favour of using it, it is widely accepted that women with metastatic disease should receive some form of combinational chemotherapy during the course of their disease.

The aim of this review was to compare whether the treatment with a more intensive polychemotherapy regimen was in-deed better than using a single agent in terms of tumor response rates and containment of toxicities for women with advanced disease. We did not consider survival comparison in this paper as higher response rates predict longer survival according to a meta-analysis conducted by Bruzzi *et. al.* [8] This was further supported by a meta analysis conducted by Fossati *et. al.* [9] comparing polychemotherapy with single agents found that the response rate and overall survival were higher in the polychemotherapy pooled data.

## MATERIALS AND METHODS

A literature search was performed for prospective randomized clinical trials in metastatic breast cancer comparing polychemotherapy and monochemotherapy. Formal computer-aided searches of electronic databases (PubMed, Medline, TRIPS, CEBM, and Science Direct) were performed by scrutiny of the reference lists of trials, review articles, abstracts and meeting proceedings. Electronic as well as manual search of specific journals (International Journal of Cancer, British Journal of Cancer, Cancer, American Journal of Clinical Oncology, Oncology, Annals of Oncology, Breast Cancer Research Treatment and Journal of Clinical Oncology), review of bibliography from eligible trials and use of the See Related Articles links in the search engines. The key words used in these electronic literature searches were: cancer, malign, metastatic, advanced breast cancer, breast carcinoma, RCT, single agent, multiple agents, monochemotherapy, and polychemotherapy.

We considered all randomized controlled trials comparing monochemotherapy and polychemotherapy in patients with advanced breast cancer only. We excluded trials on earlier stages of the disease. We also excluded non-randomized, pseudo-randomized trial and if trials included other concomitant interventions like hormonal therapy, surgery, and radiotherapy or radio isotopic treatment. Details are shown in Fig. 1. As mentioned in the introduction, outcome measures considered for this meta analysis are response rate and toxicity only.

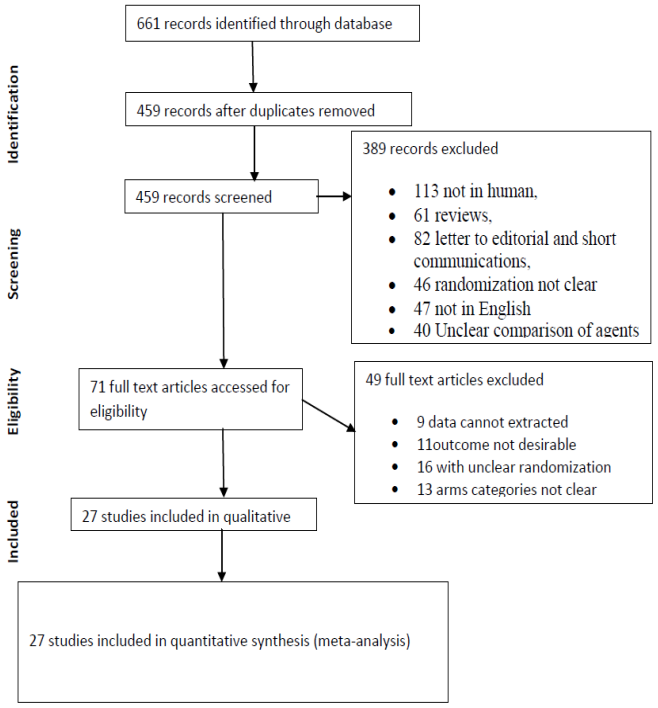


**Fig. 1: Flowchart of included studies for meta-analysis**

**Response Rate:** The proportion of patients with a complete or partial response is included in the analysis. Complete response is defined as complete disappearance of all measurable disease for some minimum time period. Partial response is defined as shrinkage of tumour such that shrinkage post-treatment is <50% of shrinkage pre-treatment for some minimum time period in the absence of growth of any lesion or the appearance of new lesions.

| Study or Subgroup | Monochemotherapy Events | Total | Polychemotherapy Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Albain KS 2004 | 57 | 262 | 107 | 267 | 9.3% | 0.42 [0.28, 0.61] |
| ANZBCTG 2001 | 47 | 197 | 70 | 194 | 6.0% | 0.56 [0.36, 0.86] |
| Berruti D 2002 | 47 | 93 | 53 | 92 | 3.0% | 0.75 [0.42, 1.34] |
| Bishop J 1999 | 31 | 107 | 36 | 102 | 2.9% | 0.75 [0.42, 1.34] |
| Bonneterre J 2002 | 37 | 88 | 35 | 90 | 2.2% | 1.14 [0.63, 2.08] |
| Ejelertsen B 2004 | 81 | 194 | 96 | 194 | 6.3% | 0.73 [0.49, 1.09] |
| Erkisi M 1997 | 16 | 30 | 12 | 30 | 0.6% | 1.71 [0.62, 4.77] |
| Falkson G 1990 | 17 | 54 | 19 | 57 | 1.4% | 0.92 [0.41, 2.04] |
| Fraser S 1993 | 6 | 21 | 11 | 19 | 0.9% | 0.29 [0.08, 1.08] |
| French Epi 1991 | 37 | 140 | 54 | 135 | 4.5% | 0.54 [0.32, 0.90] |
| GEICAM 2007 | 33 | 127 | 45 | 125 | 3.8% | 0.62 [0.36, 1.07] |
| Heidemann E 2002 | 30 | 127 | 43 | 133 | 3.6% | 0.65 [0.37, 1.12] |
| Icli F 2005 | 21 | 101 | 33 | 100 | 2.9% | 0.53 [0.28, 1.01] |
| Joensuu H 1998 | 67 | 153 | 79 | 150 | 5.0% | 0.70 [0.45, 1.10] |
| Nabboltz JM 1999 | 59 | 203 | 21 | 189 | 1.7% | 3.28 [1.90, 5.66] |
| Nielsen D 1990 | 38 | 76 | 28 | 67 | 1.7% | 1.39 [0.72, 2.70] |
| Nielsen D 2000 | 45 | 81 | 43 | 74 | 2.2% | 0.90 [0.48, 1.70] |
| Norris B 2000 | 44 | 152 | 55 | 151 | 4.4% | 0.71 [0.44, 1.15] |
| O'Shaughnessy J 2001 | 18 | 62 | 5 | 33 | 0.5% | 2.29 [0.76, 6.87] |
| O'Shaughnessy J 2002 | 77 | 256 | 107 | 255 | 8.4% | 0.59 [0.41, 0.86] |
| Sjostrom J 1999 | 61 | 143 | 29 | 140 | 1.9% | 2.85 [1.68, 4.82] |
| Sledge G 2003 | 81 | 244 | 108 | 244 | 8.1% | 0.63 [0.43, 0.90] |
| Stockler M 2006 | 42 | 214 | 18 | 109 | 2.1% | 1.23 [0.67, 2.27] |
| Takayama T 2000 | 8 | 57 | 20 | 54 | 2.0% | 0.28 [0.11, 0.70] |
| Tashiro H 1994 | 6 | 30 | 11 | 30 | 1.0% | 0.43 [0.14, 1.38] |
| Thomas E 2008 | 54 | 377 | 130 | 375 | 12.5% | 0.32 [0.22, 0.45] |
| Venturino A 2000 | 8 | 33 | 10 | 33 | 0.8% | 0.74 [0.25, 2.19] |
| **Total (95% CI)** | | **3622** | | **3442** | **100.0%** | **0.72 [0.65, 0.79]** |
| Total events | 1068 | | 1278 | | | |

Heterogeneity: Chi² = 113.33, df = 26 (P < 0.00001); I² = 77%

Test for overall effect: Z = 6.49 (P < 0.00001)

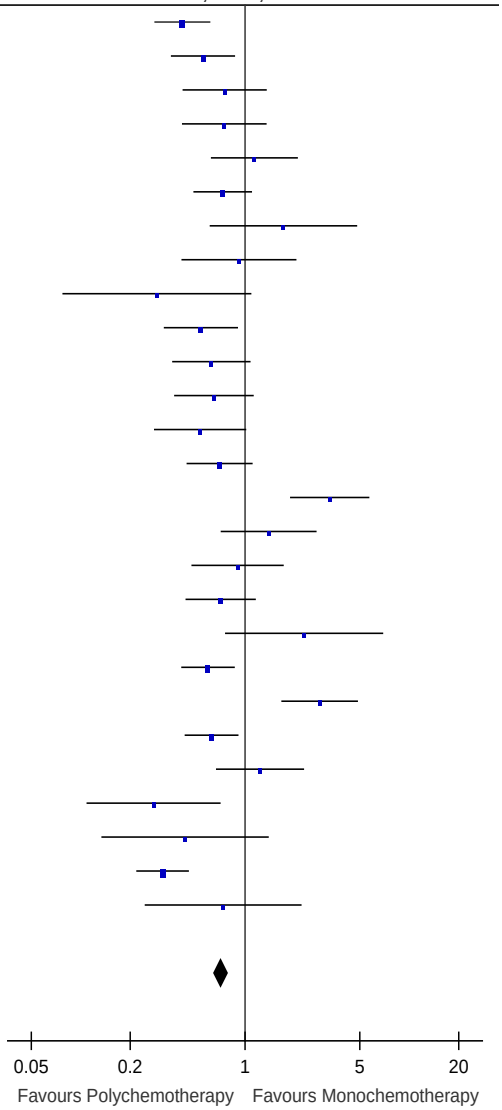


**Fig. 2: Forest Plot Comparison of Response rate in Monochemotherapy and Polychemotherapy**

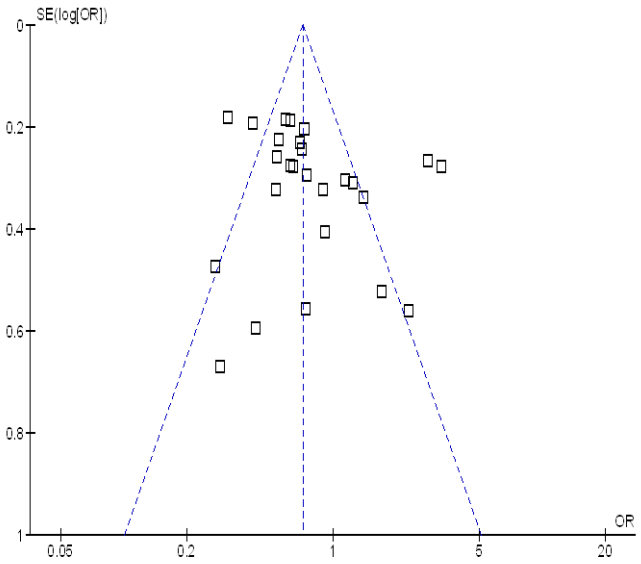


**Fig. 3: Funnel plot of Response rate Comparison**

Evaluation of tumor response in daily clinical practice of oncology may not be performed according to predefined criteria. It may, rather, be based on a subjective medical judgment that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. It might be appropriate to make a distinction between "clinical improvement" and "objective tumor response" in routine patient management outside the context of a clinical trial.

**Toxicity:** While considering toxicities, only severities of grade 3 or above by WHO criteria 10 were considered. Toxicities of interest were nausea and vomiting, alopecia, and reduction in the level of white cell count (WCC<2000 – leukopenia, neutropenia). Reviewed literature search to identify studies (between 1990 to 2008) [10-11] that are randomized controlled trials evaluating the response rate and toxicities (nausea and vomiting, toxic death, alopecia and reduced WCC) of monochemotherapy and polychemotherapy of advanced breast cancer. Any disagreement in the rejection process was first handled, when this could not be done, independent reviewer's opinion was sought.

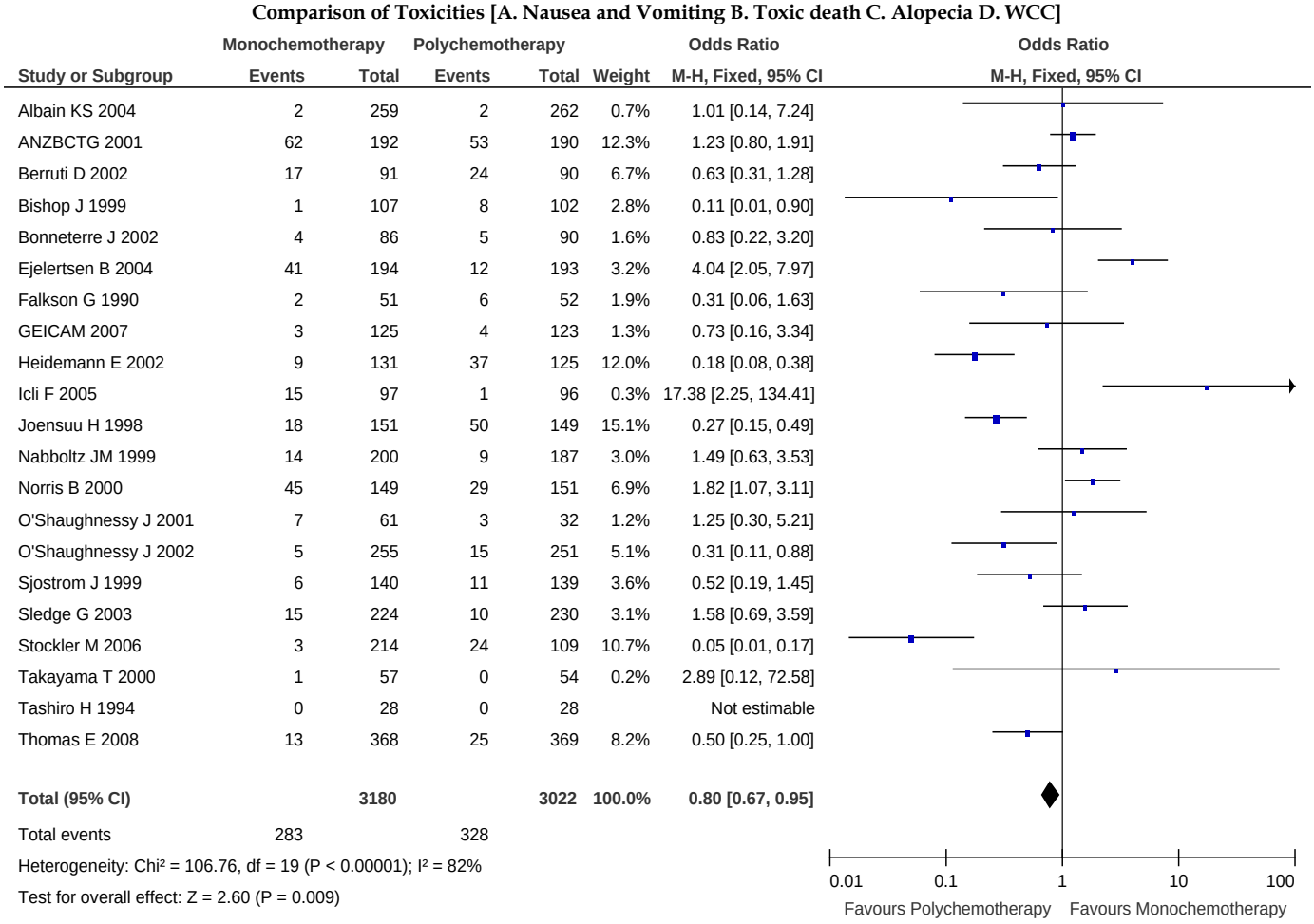


**Fig. 4: Forest plot comparison of Toxicity: A. Nausea and Vomiting**

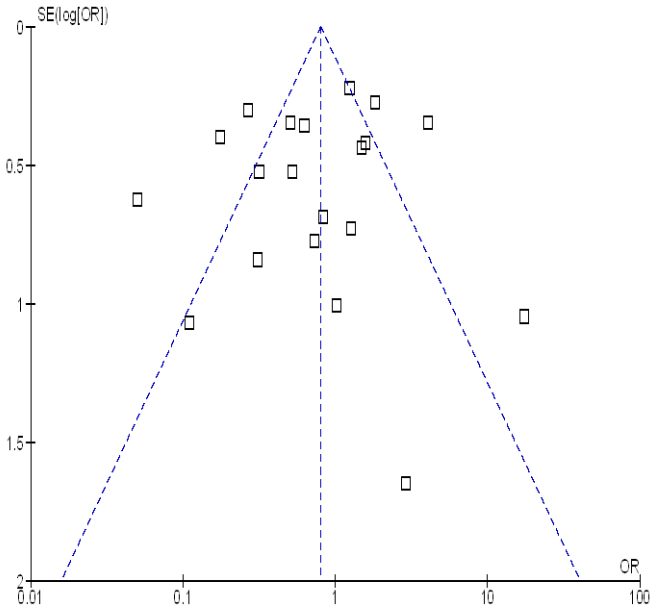


**Fig. 5: Funnel plot of Nausea and Vomiting Comparison**

Each study was reviewed according to its design and how the study was con-ducted to assess the potential for bias. Items assessed were sequence generation, randomization, incomplete outcome data and selective outcome reporting. Blinding was not assessed as the nature of interventions prevents it. It was not possible to assess method of allocation concealment used in most of the studies due to lack of information. Studies published in languages other than English were excluded. The period examined was 1990-2008 only because before 1990 there was large variations in chemotherapy regimens pattern. We have attempted to identify unpublished studies but fail to gather relevant information.

**Statistical Methods**

Meta-analyses of response rate and toxicities were performed using the Mantel-Haenszel method. Response rate and toxicities (nausea and vomiting, toxic death, alopecia and reduced WCC) were analyzed as dichotomous variables using fixed-effect model as there was significant heterogeneity to calculate a weighted estimate (Odds Ratio) and 95% confidence interval (CI) across the studies. The heterogeneity between the trials was assessed through a $\chi 2$ statistic, with given degrees of freedom. A level of significance of 0.10 was used to determine statistical significance instead of traditional 0.05. The reason for using this level was that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is why an alpha value of 0.10 rather than conventional 0.05 was used to determine the cut-off statistical significance.

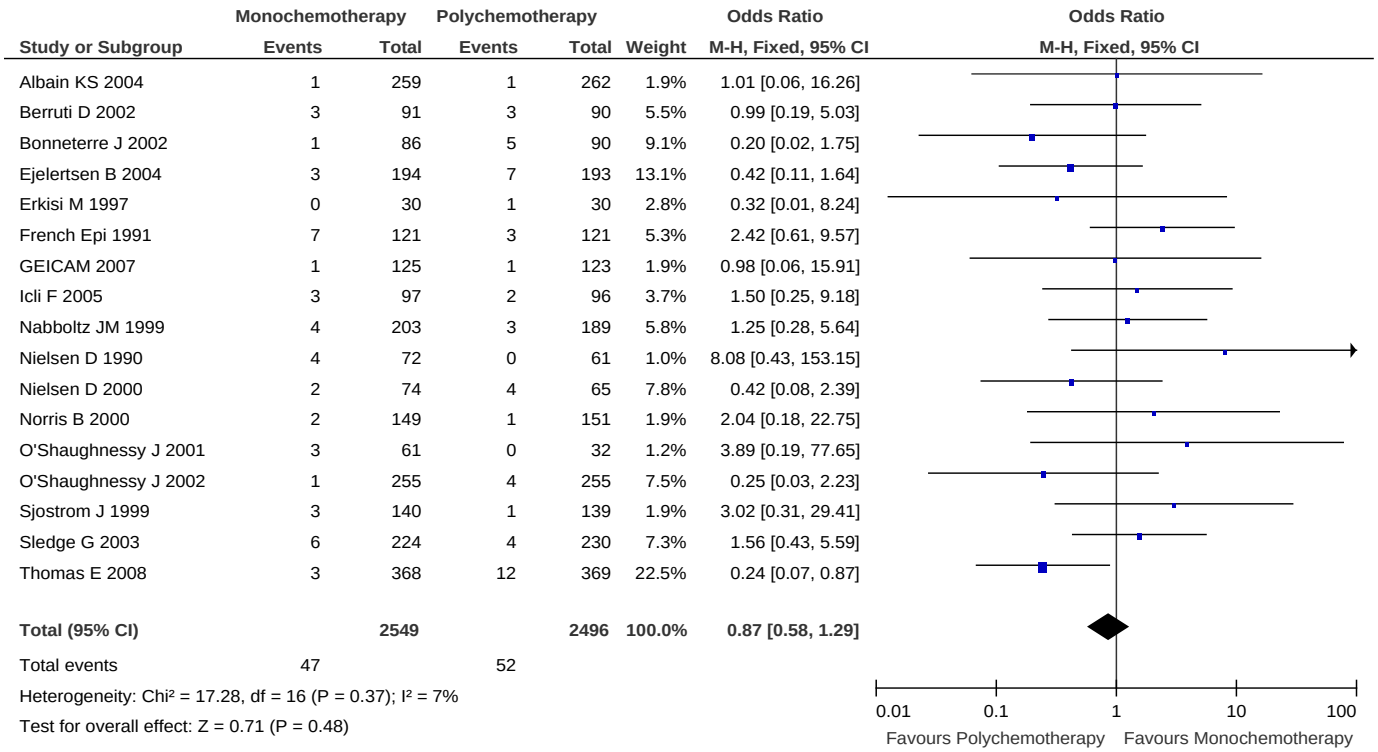


**Fig. 6: Forest plot of comparison: B. Toxic Death.**

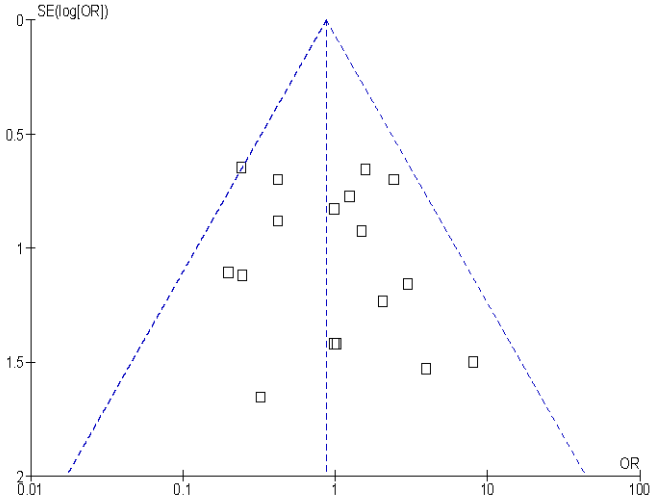


**Fig. 7: Funnel plot of Toxic Death Comparison**

I² statistic and visual inspection of the forest plots and funnel plots were also used to examine heterogeneity of data. I² value represents the percentage of the total variation across trials due to heterogeneity rather than chance (I² value <25% is low and >75% is high). All analyses were done using RevMan 5 (Cochrane Collaboration).

## RESULTS

This search resulted in the identification of 27 eligible studies enrolling a total of 7064 women. Response rate was reported in all the studies included in this analysis. Studies reporting nausea and vomiting (21 studies), toxic death (17 studies), alopecia (14 studies) and reduced WCC (22 studies) are listed along with all studies reporting the tumor response rates in Table 1. Heterogeneity was statistically significant ($P$<0.00001) in all instances except toxic death. This is likely to reflect clinical diversity of the participants (menopausal status, hormone receptor status, disease stage) and interventions (the varying efficacy of the comparator regimens, the different agents, dosages and schedules) leading to an intervention effect which was different in different trials. Women receiving combination regimens experienced a statistically significant improvement ($P$<0.00001) in response rate. The incidences of nausea and vomiting, alopecia and detrimental effect on WCC were significantly higher in polychemotherapy but no significant difference was observed for toxic death. Response rate was compared in all the 27 identified studies (Total 7064 randomized women) as shown in Fig. 2-3. Statistically significant difference was observed between monochemotherapy and polychemotherapy which favours polychemotherapy with an OR of 0.72 (95% CI 0.65 to 0.79) for randomized patients. There was significant heterogeneity across trials of response rate ($\chi^2$=113.33, 26 df, $p$<0.00001, I2 =77%).

Results of the analysis of toxicities are shown in Fig. 4-11. There was a statistical significant difference for nausea and vomiting (OR of 0.80, 95% CI 0.67 to 0.95), alopecia (OR of 0.75, 95% CI 0.64 to 0.88) and reduced WCC (OR of 0.55, 95% CI 0.48 to 0.62) but not for toxic death (OR of 0.87, 95% CI 0.58 to 1.29). There was evidence of heterogeneity for analysis of toxicity data ad-dressing nausea and vomiting ($\chi^2$ =106.76, 19 df, $p$<0.00001, I2 =82%), alopecia ($\chi^2$=304.35, 11 df, $p$<0.00001, I2 =96%) and reduced WCC ($\chi^2$ =371.45, 19 df, $p$<0.00001, I2 =95%) but not in case of toxic death (chi squared =17.28, 16 df, $p$=0.37, I2 =07%).

**Table 1: Characteristics of included studies**

| Author & Year | Total | Mono/Poly Chemotherapy (Randomized Number) | Mono/Polychemotherapy (Assessable Number) |
|---|---|---|---|
| **Albain KS 2004** [12] | 529 | 262/267 | 259/262 *‡£ |
| **ANZBCTG 2001** [13] | 391 | 197/194 | 192/190 *†£ |
| **Berruti D 2002** [14] | 185 | 93/92 | 91/90 *‡£ |
| **Bishop J 1999** [15] | 209 | 107/102 | 107/102 *†£ |
| **Bonneterre J 2002** [16] | 178 | 88/90 | 86/90 *‡†£ |
| **Ejelertsen B 2004** [17] | 387 | 194/193 | 194/193 *‡£ |
| **Erkisi M 1997** [18] | 60 | 30/30 | 30/30 ‡ |
| **Falkson G 1990** [19] | 111 | 54/57 | 51/52 *£ |
| **Fraser S 1993** [20] | 40 | 21/19 | |
| **French Epi 1991** [21] | 275 | 140/135 | 121/121 ‡ |
| **GEICAM 2007** [22] | 252 | 127/125 | 125/123 *‡†£ |
| **Heidemann E 2002** [23] | 260 | 127/133 | 131/125 *† |
| **Icli F 2005** [24] | 201 | 101/100 | 97/96 *‡£ |
| **Joensuu H 1998** [25] | 303 | 153/150 | 151/149 *†£ |
| **Nabholtz JM 1999** [26] | 392 | 203/189 | 200/187 *‡£ |
| **Nielsen D 1990** [27] | 143 | 76/67 | 72/61 ‡ |
| **Nielsen D 2000** [28] | 155 | 81/74 | 74/65 ‡£ |
| **Norris B 2000** [29] | 303 | 152/151 | 149/151 *‡†£ |
| **O'Shaughnessy J 2001** [30] | 95 | 62/33 | 61/32 *‡†£ |
| **O'Shaughnessy J 2002** [31] | 511 | 256/255 | 255/251 *‡†£ |
| **Sjostrom J 1999** [32] | 283 | 143/140 | 140/139 *‡†£ |
| **Sledge G 2003** [33] | 489 | 244/245 | 224/230 *‡£ |
| **Stockler M 2006** [34] | 323 | 214/109 | 214/109 *†£ |
| **Takayama T 2000** [35] | 111 | 57/54 | 57/54 *£ |
| **Tashiro H 1994** [36] | 60 | 30/30 | 30/30 *†£ |
| **Thomas E 2008** [37] | 752 | 377/375 | 368/369 *‡†£ |
| **Venturino A 2000** [38] | 66 | 33/33 | 33/33 †£ |
| **Total** | 7064 | 3622/3442 | - |

*Nausea and vomiting ‡Toxic death †Alopecia £WCC

Analysis of the response rate (27 studies) involves randomized participants and toxicities [Nausea and vomiting (21 studies), Toxic death (17 studies), Alopecia (14 studies) and WCC (22 studies)] analysis is based on assessable participants as mentioned in table.

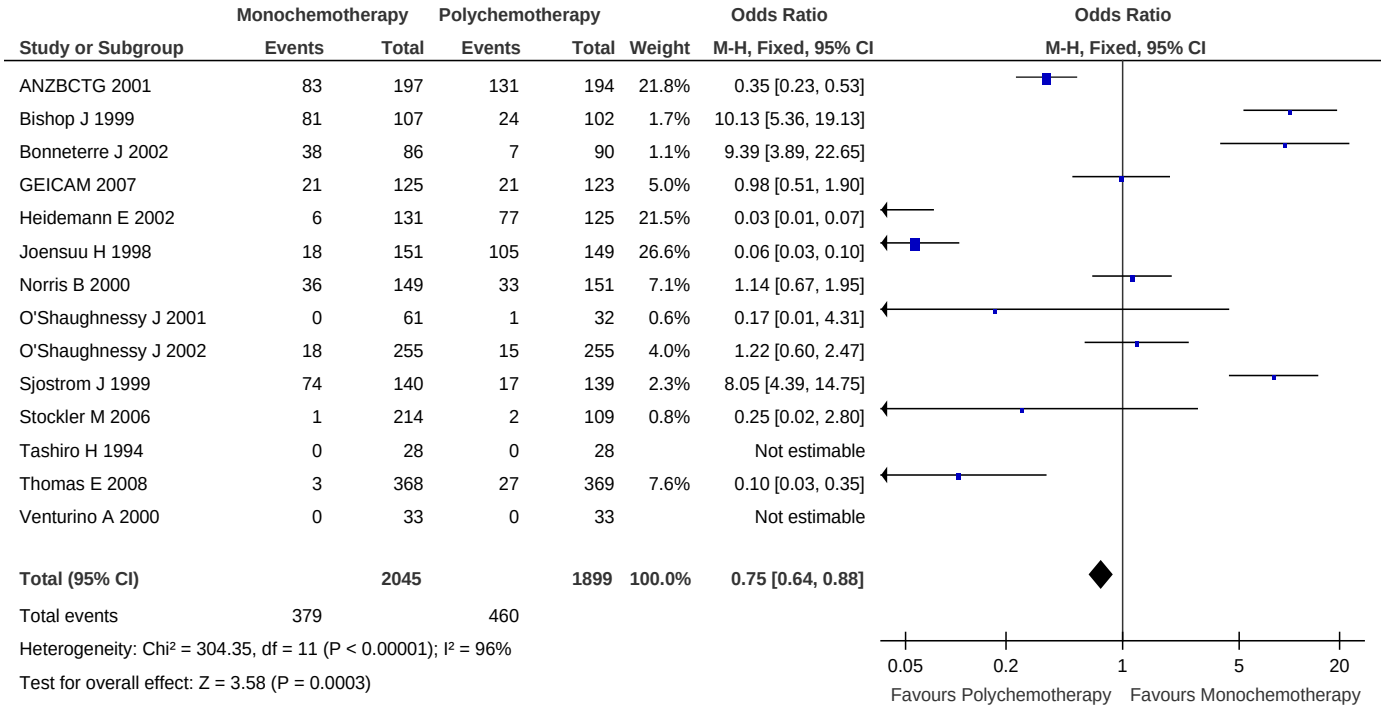


**Fig. 8: Forest plot of comparison: C. Alopecia**.

## DISCUSSION

Research on the treatment of advanced breast cancer over the last two decades has produced an impressively large number of randomized trials.[38] Such a long-lasting scientific endeavor involving thousands of patients scattered over hundreds of articles, should be summarized to allow a comprehensive assessment of the quality and clinical relevance of available information.

Even though we restricted this meta-analysis to reports published since 1990 to 2008, the data set eventually gathered in this analysis is large and embraces 7064 patients from 27 trials. Studies involve more heterogeneous populations, since patients differ not

only in terms of the tumor burden, menopausal status, hormone receptor status and disease stage but also interventions (the varying efficacy of the comparator regimens, the different agents, dosages and schedules). Considerable heterogeneity was evident across the various response rate and toxicity analysis. This is likely to reflect clinical diversity of the participants leading to an intervention effect which was different in different trials.

Outcome measures considered for this meta-analysis were response rate, and toxicity. Response rate is so deeply rooted in oncologic practice this is the only outcome measure universally re-ported. This most commonly used end point, the response rate, has convention-ally been examined in trials and allows the early determination of the anti-tumor activity of the new therapy. Response rate determinations reflect tumors that exhibit a complete regression or show a defined reduction for a specified time period. Bruzzi *et. al* [8] also examined the relationship between response rates and survival and results of this study support the hypothesis that the achievement of an objective response to chemotherapy in metastatic breast cancer is associated with a true survival benefit. This was one of the reasons for not considering survival analysis in this paper. Further, since survival data can be confounded by non-drug related factors, we focused on drug induced tumor response associated toxicities only in our present analysis.

Polychemotherapy was associated with significantly improved response rate. Addition of one or more agents to the first single drug generally created a more intense regimen resulting in a greater response rate. This approach, however, was also associated with a higher toxicity related to nausea, vomiting, alopecia and reduced white cell count. Rates of toxic or treatment related death was statistically not different between the two groups.

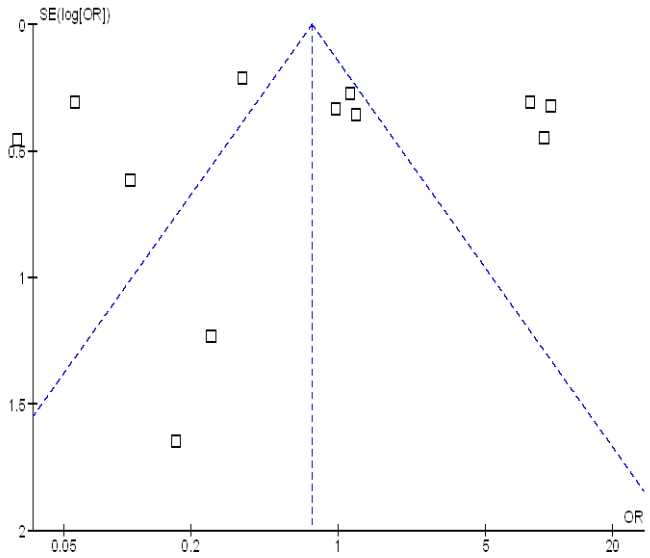


**Fig. 9: Funnel plot of Alopecia Comparison**

| Study or Subgroup | Monochemotherapy Events | Total | Polychemotherapy Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Albain KS 2004 | 11 | 259 | 48 | 262 | 6.4% | 0.20 [0.10, 0.39] |
| ANZBCTG 2001 | 56 | 197 | 60 | 194 | 6.0% | 0.89 [0.57, 1.37] |
| Berruti D 2002 | 2 | 91 | 4 | 90 | 0.5% | 0.48 [0.09, 2.71] |
| Bishop J 1999 | 29 | 107 | 66 | 107 | 6.7% | 0.23 [0.13, 0.41] |
| Bonneterre J 2002 | 65 | 86 | 60 | 90 | 2.0% | 1.55 [0.80, 2.99] |
| Ejelertsen B 2004 | 23 | 194 | 97 | 193 | 11.9% | 0.13 [0.08, 0.22] |
| Falkson G 1990 | 48 | 51 | 22 | 52 | 0.2% | 21.82 [6.01, 79.23] |
| GEICAM 2007 | 55 | 125 | 75 | 123 | 5.9% | 0.50 [0.30, 0.83] |
| Icli F 2005 | 18 | 97 | 11 | 96 | 1.3% | 1.76 [0.78, 3.96] |
| Joensuu H 1998 | 16 | 151 | 41 | 149 | 5.1% | 0.31 [0.17, 0.59] |
| Nabboltz JM 1999 | 188 | 200 | 176 | 187 | 1.5% | 0.98 [0.42, 2.28] |
| Nielsen D 2000 | 59 | 74 | 60 | 65 | 1.8% | 0.33 [0.11, 0.96] |
| Norris B 2000 | 129 | 149 | 132 | 151 | 2.4% | 0.93 [0.47, 1.82] |
| O'Shaughnessy J 2001 | 5 | 61 | 13 | 32 | 2.2% | 0.13 [0.04, 0.41] |
| O'Shaughnessy J 2002 | 38 | 255 | 40 | 255 | 4.7% | 0.94 [0.58, 1.52] |
| Sjostrom J 1999 | 108 | 140 | 22 | 139 | 0.7% | 17.95 [9.83, 32.79] |
| Sledge G 2003 | 111 | 224 | 126 | 230 | 8.7% | 0.81 [0.56, 1.17] |
| Stockler M 2006 | 3 | 214 | 24 | 109 | 4.4% | 0.05 [0.01, 0.17] |
| Takayama T 2000 | 0 | 57 | 0 | 54 | | Not estimable |
| Tashiro H 1994 | 0 | 28 | 0 | 28 | | Not estimable |
| Thomas E 2008 | 21 | 368 | 210 | 369 | 27.5% | 0.05 [0.03, 0.07] |
| Venturino A 2000 | 6 | 33 | 1 | 33 | 0.1% | 7.11 [0.81, 62.79] |
| **Total (95% CI)** | | **3161** | | **3008** | **100.0%** | **0.55 [0.48, 0.62]** |
| Total events | 991 | | 1288 | | | |

Heterogeneity: Chi² = 371.45, df = 19 (P < 0.00001); I² = 95%

Test for overall effect: Z = 9.72 (P < 0.00001)

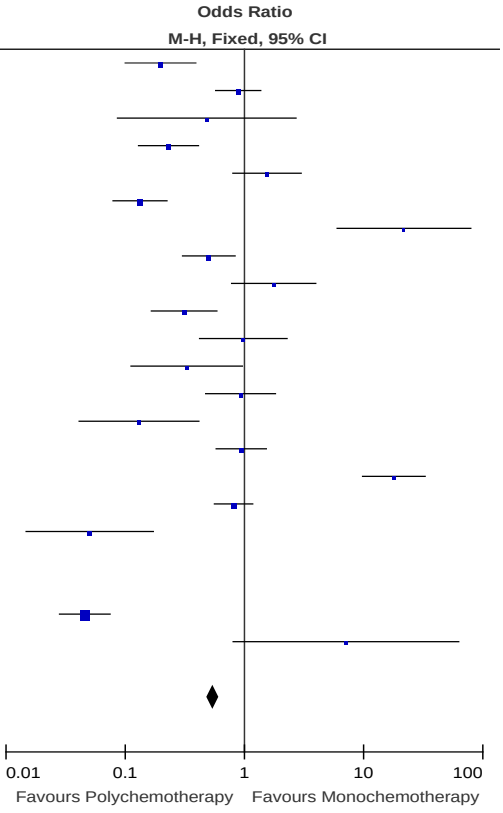


**Fig. 10: Forest plot of comparison: D. WCC**

Chemotherapy is currently the only therapeutic option for women with endocrine resistant metastatic breast cancer, extensive visceral localizations or life threatening disease. The most used chemotherapeutic

agents are anthracyclines, taxanes, alkylating agents, antimetabolites, and vinca alkaloids. As single agents, they produce an ORR (Objective response rate) of 20%-80% [39-41] where as the combinations seem to increase the ORR but not the percentage of complete responses (CRs). In the pretaxane era, several combination regimens were developed, and these yielded higher ORRs, in comparison with monochemotherapies. [26, 42-50] Two phase II trials [51-52] and three phase II randomized trials [53-55] have compared combination chemotherapy with planned sequential therapy. There was no significant difference in efficacy but a better safety profile with sequential therapy in the majority of trials. Further indirect support to the sequential use of cytotoxic drugs can be derived from the results of other trials showing that single agents were superior to combinations because of better tolerance and similar efficacy [22, 28] or better clinical out-come. [14, 25] However, polychemotherapy remained the major clinical dogma and standard care for hormone resistant metastatic breast cancer for many years. Use of polychemotherapy was based on the assumption that the use of non-cross resistant agents with non overlapping toxicities would results in therapeutic synergy. Furthermore meta analysis with 15 studies performed by Fossati *et. al*. [9] reported similar results of higher response rate in the polychemotherapy pooled data as obtained in this study.

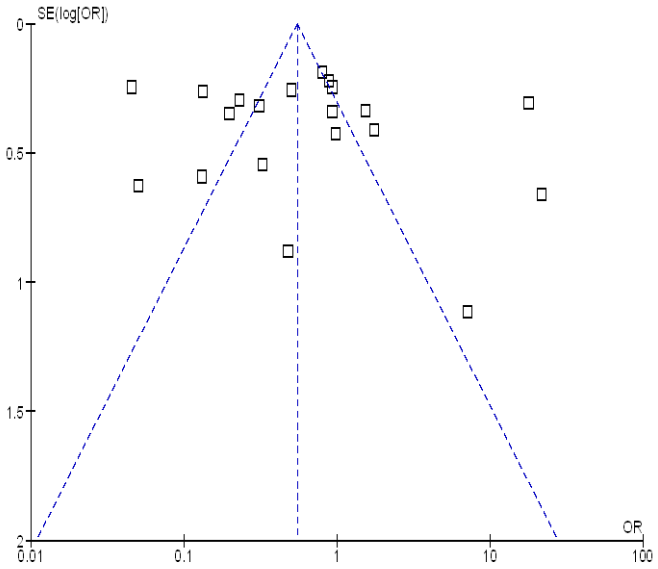


**Fig. 11: Funnel plot of WCC Comparison**

Despite the general observation of the superior response of polychemotherapy, individualized treatment is preferable and should be based on several factors, such as tumor-associated symptoms, extent of visceral disease, comorbidities, age, and performance status. In any case, life expectancy in this setting is relatively short, and a gain of a few months must be balanced with treatment related toxicity, patient QoL, and patient preference. At present, in the absence of specific predictive factors to prospectively select a subgroup of responsive patients, polychemotherapy should be reserved for patients with rapidly progressing visceral metastatic disease, or in emergency situations in which a rapid response is warranted. There are still many unanswered questions and new drugs are under evaluation. The scarcity of agreement on standards of care renders the treatment of metastatic breast cancer complex. Furthermore, this disease requires a multidisciplinary team approach, with the early involvement of psychosocial support and palliative interventions as part of routine patient care. Patients must be encouraged to be actively involved in the treatment decision making process and their enrolment in well designed trials is highly recommended. With the development of new technologies, namely genomics and proteomics, it is now known that metastatic breast cancer is not just a single entity but a complex disease with considerable molecular diversity that often translates into different clinical phenotypes. A better definition of these subtypes will probably change our treatment approach, moving from the era of empirically based treatment to the era of tailored therapies for each individual patient.
Polychemotherapy seems to offer a better response rate in advanced breast cancer. However, it results in more toxicity like nausea vomiting, alopecia and reduced WCC. Availability of wide spectrum of chemotherapeutic agents for metastatic breast cancer, the choice of treatment should be based on the response to the therapy, the toxicity, individual patient's preference and the presence of life threatening metastases or imminent complications that require aggressive management and rapid tumor control.

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