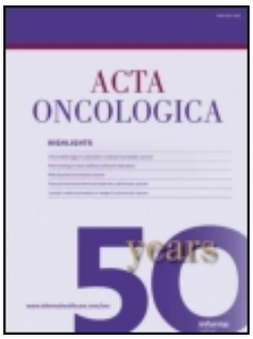

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Analyzing Toposimerase II-α and HER-2/neu co-amplification seems to be of limited value in epithelial ovarian cancer

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that receive a dose of D_{min} or D_{max}. If this is the case, the differential DVH and cumulative DVH should be similar to the DVHs shown in Figure 3, not the left-top DVH plot of Figure 1 shown in Mavroidis and Lind's letter (a similar plot can be found in the Figure 6 in [3]). Here we present Figure 3 to help the reader understand the dose-volume relations used in those examples.

In summary, $\overline{\overline{D}}$ and EUD are the same concept, which is useful to summarize the biological effect of various complex treatment plans. While outcome modeling with Binomial statistics may better estimate the TCP values at low dose regions for cases with a rather flat dose response ($\gamma \leq 1$), Poisson statistics still provide reliable outcome estimates for radiation therapy in the clinical practice.

References

[1] Wang JZ, Mayr NA, Yuh WT. Behind EUD. Acta Oncol 2008;47:971–2.

[2] Lind BK, Mavroidis P, Hyodynmaa S, Kappas C. Optimization of the dose level for a given treatment plan to maximize the complication-free tumor cure. Acta Oncol 1999;38: 787–98.

[3] Mavroidis P, Lind BK, Brahme A. Biologically effective uniform dose (D) for specification, report and comparison of dose response relations and treatment plans. Phys Med Biol 2001;46:2607–30.

[4] Wigg DR. Plausible parameter values of normal tissues and tumors that may be used for predictive models and bioeffect planning. In: Applied Radiobiology and Bioeffect Planning. Madison, Wisconsin, USA: Medical Physics Publishing; 2001. p. 234–76.

[5] Levegrun S, Jackson A, Zelefsky MJ, Skwarchuk MW, Venkatraman ES, Schlegel W, et al. Fitting tumor control probability models to biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer: Pitfalls in deducing radiobiologic parameters for tumors from clinical data. Int J Radiat Oncol Biol Phys 2001;51:1064–80.

[6] Wang JZ, Guerrero M, Li XA. How low is the α/β ratio for prostate cancer? Int J Radiat Oncol Biol Phys 2003;55: 194–203.

[7] Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. Med Phys 1997;24: 103–10.

[8] Wyatt RM, Beddoe AH, Dale RG. The effects of delays in radiotherapy treatment on tumour control. Phys Med Biol 2003;48:139–55.

[9] Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 1999;43:1095–101.

[10] Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys 2002;52:6–13.

[11] Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50: 1021–31.

[12] King CR, Mayo CS. Is the prostrate alpha/beta ratio of 1.5 from Brenner & Hall a modeling artifact. Int J Radiat Oncol Biol Phys 2000;47:536–9.

[13] Wang JZ, Li XA, Yu CX, DiBiase SJ. The low α/β ratio for prostate cancer: What does the clinical outcome of HDR brachytherapy tell us? Int J Radiat Oncol Biol Phys 2003;57: 1101–8.

[14] Wang JZ, Stewart RD, Carlson DJ, Jennings K, Li XA, Guerrero M. Reply to 'Comments on 'Comparison of in vitro and in vivo α/β ratios for prostate cancer'' [letter]. Phys Med Biol 2005;50:L5–8.

Analyzing Toposimerase II-α and HER-2/neu co-amplification seems to be of limited value in epithelial ovarian cancer

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To the Editor

Recurrent chemoresistant ovarian cancer remains a therapeutic challenge; in randomized Phase III trials the best response rates to chemotherapy have been at best 12–13% and even so, short-lived [1,2]. Among available agents, pegylated liposomal doxorubicin is a noteworthy alternative [3]. Pegylated liposomal doxorubicin is, however, quite expensive and has

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inconvenient side effects as hand-foot syndrome and stomatitis [2]. Consequently, a situation where at least ten patients need to be treated to get one or two responses is definitely less than optimal.

Topoisomerase IIα (*TOP2A*) is purported to be the main intracellular target of anthracyclines [4]. In breast cancer, *TOP2A* gene amplification seems to be associated with *HER-2/neu* gene amplification [5]. Indeed, there is evidence that coamplification of these genes in breast cancer renders the cancer cells especially sensitive to anthracyclines [4], although also conflicting results have been published [5]. After Mano et al. showed that evaluating amplification of *TOP2A* and *HER-2/neu* by fluorescent in situ hybridization (FISH) is feasible even in epithelial ovarian carcinoma [6], we decided 1) to perform a preliminary analysis of the rate of *TOP2A* and *HER-2/neu* amplification by chromogenic in situ hybridization (CISH) [7] in epithelial ovarian cancer, and 2) to retrospectively correlate the amplification to the clinical efficacy of pegylated liposomal doxorubicin in patients with recurrent chemoresistant ovarian cancer.

Ten patients with recurrent chemoresistant ovarian cancer gave their informed consent to the study. The median age of the patients was 58.5 years (range 43–79). Of the tumors, seven were serous, two were endometrioid, and one was mucinous. We chose both patients who had responded to pegylated liposomal doxorubicin and patients who had not responded. The study was approved by the local Ethics Committee.

The original paraffin blocks from the primary operation we retrieved from the archives. The digoxigenin-labeled probes for *HER-2/neu* and *TOP2A* needed for CISH were obtained from Zymec Inc. (South San Francisco, CA). The hybridization method used has been described in detail previously [7]. Hybridization was evaluated with an Olympus BX50 microscope (Olympus, Tokyo, Japan) using an X40 objective. Amplification of *HER-2/neu* and TOP2A was defined as the presence of six or more copies in more than 30% of nuclei or as presence of an easily identifiable gene copy cluster, the gene copies of which could not be enumerated. The laboratory was blinded as regards to the clinical outcome of the patients.

Four of the carcinomas had responded to pegylated liposomal doxorubicin, as evaluated by the tumor marker Ca-12-5. Three tumors showed stabilization, while the remaining three progressed in spite of the treatment. *HER-2/neu* gene was found to be amplified only in one endometrioid carcinoma that was unresponsive to doxorubicin. In no instance could we find any amplification of *TOP2A* gene.

Immunohistochemical (IHC) methods were originally used to study the over-expression of *TOP2A* and *HER-2/neu* in cancer cells. Because of difficulties in standardization of IHC, in situ hybridization techniques developed to detect the actual amplification rate have now replaced the IHC methods [8]. Of the in situ hybridization techniques, the newer CISH provides an accurate and practical alternative to the older FISH [4,7].

To our knowledge, Mano et al. were the first to compare *TOP2A* and *HER-2/neu* amplification and expression in epithelial ovarian carcinoma [6]. They found on one hand that the correlation between the expression and the amplification of the respective genes was poor, and on the other hand that there was an excellent correlation between *HER-2/neu* and *TOP2A* amplification. Using more stringent criteria, the amplification rates were 12.5 and 7.8%, respectively. The researches did not compare the amplification rates to in vitro or clinical efficacy of pegylated liposomal doxorubicin.

The article by Mano et al. encouraged us to study the amplification rate of *TOP2A* and *HER-2/neu* in epithelial ovarian cancer and, moreover, to attempt to correlate the rates to the therapeutic effect of pegylated liposomal doxorubicin. Unfortunately, no tumor was found to harbor amplification of *TOP2A*, and even *HER-2/neu* was amplified only once, in a tumor not responsive to doxorubicin. There are obvious shortcomings in our preliminary retrospective study: The samples studied originated from the primary operation, i.e. were chemotherapy-naïve, and pegylated liposomal doxorubicin was started not until the tumors had developed a taxane-platinum resistance. It is possible that the amplification of *TOP2A* and/or *HER-2/neu* is a late phenomenon associated e.g. with the development of a resistance to taxanes and platinum compounds in ovarian cancer. It is, however, difficult to obtain histological samples from recurrent ovarian cancer that is as a rule treated with second-line chemotherapy, rather than re-operated.

In conclusion, the rarity of amplification of *HER-2/neu*, combined with the non-existence of amplification of *TOP2A* and with a poor correlation to the clinical outcome as found in the present study, discourages us from continuing our efforts.

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References

[1] ten Bokkel Huinink W, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997;15:2183–93.

[2] Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: A randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312–22.

[3] Gordon AN, Tonda M, Sun S, Rackoff W, on behalf of the Doxil Study 30–49 investigators. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 2004;95:1–8.

[4] Tanner M, Isola J, Wiklund T, Erikstein B, Kellokumpu-Lehtinen P, Malmström P, et al. Topoisomerase IIα gene amplification predicts favorable treatment response to tailored and dose-escalated anthracycline-based adjuvant chemotherapy in HER-2/neu-amplified breast cancer: Scandinavian Breast Group Trial 9401. J Clin Oncol 2006;24:2428–36.

[5] Villman K, Sjöström J, Heikkilä R, Hultborn R, Malmström P, Bengtsson NO, et al. TOP2A and HER2 gene amplification as predictors of response to antthracycline treatment in breast cancer. Acta Oncol 2006;45:590–6.

[6] Mano MS, Awada A, Di Leo A, Durbecq V, Paesmans M, Cardoso F, et al. Rates of topoisomerase II-alpha and HER-2 gene amplification and expression in epithelial ovarian carcinoma. Gynecol Oncol 2004;92:887–95.

[7] Isola J, Tanner M, Forsyth A, Cooke TG, Watters AD, Bartlett JMS. Interlaboratory comparison of *HER-2* oncogene amplification as detected by chromogenic and fluorescence *in situ* hybridization. Clin Cancer Res 2004;10:4793–8.

[8] Di Leo A, Gancberg D, Larsimont D, Tanner M, Jarvinen T, Rouas G, et al. HER-2 amplification and topoisomerase IIα gene aberrations as predictive markers in node-positive breast cancer patients randomly treated either with an anthracycline-based therapy or with cyclophosphamide, methotrexate, and 5-fluorouracil. Clin Cancer Res 2002;8:1107–16.

Motesanib diphosphate (AMG 706), an oral angiogenesis inhibitor, demonstrates clinical efficacy in advanced thymoma

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To the Editor

In May 2000, a 23-year-old male underwent thymectomy and adjuvant radiotherapy for Masaoka stage II thymoma with positive resection margins. In December 2003, CT and positron emission tomography (PET) showed biopsy-proven bilateral pleural recurrence. Left-sided surgical pleurodesis was followed by four cycles of CAP chemotherapy (cisplatin, doxorubicin, cyclophosphamide) with complete remission on CT and PET. However, bilateral pleural disease recurred in March 2005, and he received four cycles of ChlVPP chemotherapy (chlorambucil, vinblastine, procarbazine and prednisolone) and radiotherapy to the left chest wall and diaphragm. Residual disease was seen on CT and PET and he pursued non-conventional therapies over the next 12 months.

Upon return in September 2006, he had multiple new pulmonary nodules and progressive pleural disease. In June 2007 there was significant pulmonary and pleural progression, and he was enrolled onto a phase IB study of motesanib diphosphate (AMG 706) in advanced solid tumours. Motesanib diphosphate is a novel oral, highly specific inhibitor of vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, Kit and platelet-derived growth factor receptor (PDGFR).

The patient received 75 mg of motesanib diphosphate twice daily in three week cycles (two weeks on treatment, one week off). He had stable disease by RECIST (Response Evaluation Criteria in Solid Tumours), although there was a modest increase in tumour measurements that reached a maximum after 11 cycles (January 2008). Subsequently there

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