



Case series

Malignant Brenner tumor of the ovary: Case series and review of treatment strategies

Yingao Zhang^a, S. Allison Staley^b, Katherine Tucker^b, Leslie H. Clark^{a,b,*}^a UNC School of Medicine, 321 S Columbia St, Chapel Hill, NC 27516, United States^b Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, NC, United States

ARTICLE INFO

Keywords:

Malignant Brenner tumor
MBT
Ovarian carcinoma
Treatment
Review
Case series

ABSTRACT

Malignant Brenner tumor (MBTs) is a rare histological subtype of epithelial ovarian cancer, accounting for < 0.05% of all ovarian neoplasms. As such, current evidence on the treatment of MBTs is predominantly limited to case studies and small case series. To add to existing literature, we performed a retrospective review of 10 cases of MBT diagnosed and treated at a single institution between 1999 and 2018.

For the 10 cases included in our cohort, the median age was 64 and the median tumor stage was IIa/IIb. All patients underwent either a primary or interval debulking surgery and achieved an R0 resection per classifications set by the Union for International Cancer Control (UICC). Lymph node dissections were performed on 6 patients and found no evidence of positive nodal disease. 7 patients received platinum-based adjuvant chemotherapy and experienced a median progression-free survival (PFS) of 37 months. Recurrent disease was varied in terms of locoregional versus distant spread, and these patients had largely suboptimal responses to salvage chemotherapy with doxorubicin, gemcitabine, and eribulin. Sites of metastatic disease included the liver, lungs, bone, and brain.

While there is no consensus for the optimal treatment of this rare disease, MBTs seem to respond well to adjuvant platinum-taxane treatment after complete surgical resection, consistent with the current management approach of other epithelial ovarian cancers. Recurrent disease is considerably more difficult to manage, and clinicians may consider a wider avenue of treatment options to include hormonal, biologic, and radiation therapies.

1. Introduction

Brenner tumor of the ovary is a rare subtype of epithelial neoplasms that accounts for up to 1% of all ovarian tumors. Brenner tumors can be further classified as benign, proliferative (borderline), or malignant by histopathological review. The majority of these tumors are benign or proliferative, with malignant Brenner tumors (MBT) making up < 5% of all diagnosed Brenner tumors. Consequently, studies on MBTs is limited to case reports and case series, with only 3 single-center cohorts of 10 or more patients described in the literature (Austin and Norris, 1987; Gezginç et al., 2012; Han et al., 2015).

Optimal surgical resection of MBTs remains widely accepted as a mainstay of therapy, consistent with ovarian tumors of other histologies (Verleye et al., 2009). However, there is no consensus as to the optimal regimen for adjuvant treatment in these patients. The role of adjuvant chemotherapy and/or radiation therapy are poorly tested. We sought to add to the limited data available on this rare histologic subtype by

describing the demographic, clinical, and survival data for 10 cases of MBT at a single tertiary care center. Furthermore, we provide a current review of treatment strategies available.

2. Methods

Following institutional review board approval (IRB #18-0914), we conducted a retrospective review of patients diagnosed with MBT at a single tertiary care institution from 1999 to 2018. Patients were identified through the EPIC-linked search tool EMERSE (Electronic Medical Record Search Engine) by search keywords “malignant Brenner tumor” and “MBT”. Patients with non-Brenner-type tumors, benign Brenner tumors, and borderline/proliferative Brenner tumors were then excluded through a review of surgical pathology records. For the remaining patients, demographics, tumor characteristics, surgical data, adjuvant treatment information, and survival indices were abstracted from medical records. Extent of surgical resection was measured per

* Corresponding author at: 101 Manning Drive, CB 7572, Chapel Hill, NC 27599, United States.

E-mail addresses: zhangya@med.unc.edu (Y. Zhang), leslie_clark@med.unc.edu (L.H. Clark).

<https://doi.org/10.1016/j.gore.2019.02.003>

Received 16 January 2019; Received in revised form 7 February 2019; Accepted 9 February 2019

Available online 12 February 2019

2352-5789/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1
Demographic and oncologic summary of MBT case series patients.

Case	Age	BMI	Presenting symptom	Pre-Op CA-125 (U/mL)	Surgery ^a	Stage	Grade	Nodal disease	Adjuvant treatment (# cycles)	Recurrence treatment (# cycles)	Clinical outcomes
1	77	23	AUB	43	TAH, BSO, Omentectomy, LND	IIB	3	No	CT (5); R1 none		PFS 116 mo, OS 117 mo; DOD
2	58	38	Pelvic pressure	12.6	TAH, BSO, Omentectomy, LND	IA	3	No	CT (6)		PFS 42 mo; NED
3	60	26	Abdominal pain	91.7	BSO, Omentectomy, LND	IIB	3	No	CT (6); R1 DC (3) + spine PRT; R2 Tam, Gem (4), eribulin (5)		PFS 12 mo; AWD
4	67	29	Abdominal pain	25.4	BSO, Omentectomy, LND	IIA	2	No	CT (6)		PFS 5 mo; NED
5	39	22	Abdominal pain	494.8	TAH, BSO, Omentectomy	IVB	3	n/a	CD (6); R1 NSGY resection + WBRT; R2, R3 Cyberknife		PFS 17 mo; OS 45 mo; DOD
6	70	42	Incidental ovarian mass on ultrasound	10.5	TAH, BSO, Omentectomy	IC1	3	n/a	CT (6)		PFS 37 mo; NED
7	69	20	Abdominal pain, AUB	264	TAH, BSO, Omentectomy, LND	IB	3	No	CT (6)		PFS 78 mo; NED
8	82	19	Abdominal pain	n/a	TAH, BSO, Omentectomy	IIIB	1	n/a	CT-NACT (6); R1 n/a		PFS 28 mo; AWD (LTF)
9	58	27	Pelvic pressure	9.1	TAH, BSO	IA ^b	2	n/a	None		PFS 126 mo; NED
10	49	23	Abdominal pain	10.8	TAH, BSO, Omentectomy, LND	IA	1	No	n/a		LTF

Abbreviations – AWD: alive with disease; AUB: abnormal uterine bleeding; BSO: bilateral salpingo-oophorectomy; CD: carboplatin/docetaxel; CT: carboplatin/paclitaxel; DC: doxorubicin/carboplatin; DOD: died of disease; Gem: gemcitabine; LTF: lost to follow-up; LND: lymph node dissection; n/a: data not available for review; NACT: neoadjuvant chemotherapy; NED: no evidence of disease; NSGY: neurosurgery; OS: overall survival; PFS: progression-free survival; PRT: palliative radiation therapy; TAH: total abdominal hysterectomy; Tam: tamoxifen; WBRT: whole brain radiation therapy.

^a Patients 3 and 4 underwent prior hysterectomies for benign indication and thus are not designated here.

^b This patient was clinically staged and did not receive staging surgery.

classifications set by the Union for International Cancer Control (UICC) (Hermanek and Wittekind, 1994). MBT diagnoses were confirmed by final pathologic review of surgical specimens. Progression-free survival (PFS) was measured as time from initial surgery to time of first biopsy- or radiologic-proven disease recurrence, or last follow-up visit in the absence of recurrent disease. For patients who underwent neoadjuvant chemotherapy (NACT), the starting timepoint for measuring PFS was set at the date of NACT initiation. When applicable, overall survival (OS) was measured as time from initial surgery to date of death. Descriptive statistics were performed.

3. Results

A total of 10 patients were identified with MBT during the study period (Table 1). The mean age of these patients at time of diagnosis was 63 years (range 39–82). The mean BMI was 26.9 kg/m² (range 19–42 kg/m²). Overall, 6/10 (60%) patients initially presented with abdominal pain, with one of these patients presenting also with abnormal uterine bleeding (AUB). Two of ten (20%) patients presented with pelvic pressure. One patient presented with AUB only. One patient was found to have an incidental complex adnexal mass on pelvic ultrasound performed for a benign indication. Nine of ten patients had a pre-operative CA-125 drawn with 44% (4/9) patients having an elevated measurement (range 9.1–494.8 U/mL).

All patients underwent total hysterectomy and bilateral salpingo-oophorectomy (BSO). Omentectomy was performed in 7/10 (70%) patients, and lymph node dissections were performed in 6/10 (60%) patients. All patients achieved an R0 resection, and none of the patients with lymph node dissections were found to have positive nodal disease. Tumor size described on preoperative imaging ranged from 6.5 to 25 cm in largest dimension, with a mean of 13.9 cm (stdev ± 6.5 cm). After surgical staging, 4/10 (40%) patients had stage 1 disease, 3/10 (30%) patients had stage 2 disease, one (10%) patient had stage 3 disease, and one (10%) patient had stage 4 disease. One patient underwent initial surgery at an outside institution for benign indications with an incidental finding of MBT on final surgical pathology. 6/10 (60%) of the tumors were high grade, 2/10 (20%) were moderate grade, and 2/10 (20%) were low grade.

Of the 10 patients, 1/10 (10%) received neoadjuvant chemotherapy (NACT) prior to surgery with carboplatin/paclitaxel (CT) and 7/10 (70%) received adjuvant chemotherapy after primary surgery (Table 1). One patient was lost to follow-up immediately following surgery, and another patient did not receive adjuvant therapy due to delayed oncologic consultation and incomplete surgical staging. Of the 7 patients who received adjuvant chemotherapy, 6/7 (86%) received 6 cycles of CT and 1/7 (14%) received 6 cycles of carboplatin/docetaxel (CD), with a median PFS of 37 months (range: 5–116 months). No patients received adjuvant radiation therapy.

To date, five patients (50%) are alive with no evidence of disease. The median follow-up duration is 42 months (mean: 57.6 months; range: 5–126 months). Of the remaining 5 patients, one was lost to follow-up after surgery. The other 4 patients suffered disease recurrence, with a median progression-free survival (PFS) of 22.5 months (range: 12–116 months). Of the patients who recurred, 3 (75%) had distant metastases and 1 (25%) had locoregional recurrence. Of the 3 patients who recurred with distant disease, one died before receiving salvage treatment, one underwent radiation for a brain lesion and died subsequently, and the third was lost to follow-up after her recurrence (current disease status unknown). The patient who presented with locoregional recurrence (Patient 3 in Table 1) presented 12 months after initial treatment with CT. Her disease continued to progress despite multiple treatment regimens, including doxorubicin/carboplatin (DC), tamoxifen, gemcitabine, and palliative radiation therapy (RT) for bony invasion into the lumbar spine. Most recently, she was trialed on eribulin, but was discontinued after 5 cycles (4 months) of treatment given disease progression found on interval imaging.

Table 2
Overview of selected MBT case reports and case series to date, including current study. Patient age, tumor stage, and PFS are reported as median values.

Authors	Year	Country	Cases reviewed	Age	Stage	Surgery (# pts)	Adjuvant treatment (# pts)	Clinical outcomes (# pts) ^b
Austin & Norris	1987	United States	16	60	IA	TAH, BSO (11); TAH, USO (2); USO (1)	RT (2), RT + chemotherapy ^a (1), none (14)	NED (9), DOD (5), DWED (2); PFS n/a
Gezginç, et al.	2011	Turkey	13	50	IIIC	TAH, BSO, omentectomy, LND (13)	CT (10), none (3)	AWD (7), NED (5), DWED; PFS 21 mo
Han, et al.	2014	South Korea	10	55.5	IA/IC	TAH, BSO, omentectomy, LND, appendectomy (8), USO (2)	CT (5), PT (1), none (4)	NED (6), AWD (1), DOD (2), DWED (1); PFS 16 mo
Lang, et al.	2017	United States	1	77	IIC	BSO, omentectomy, LND (1) ^c	CT (1)	NED (1); PFS 12 mo
Current study	2019	United States	10	64	IIA/IIIB	TAH, BSO, Omentectomy, LND (4); TAH, BSO, Omentectomy (3); BSO, Omentectomy, LND (2); TAH, BSO (1)	CT (6), CT-NACT (1), CD (1), none (2)	NED (5), AWD (2), DOD (2), LTF (1); PFS 23 mo ^d

Abbreviations – AWD: alive with disease; BSO: bilateral salpingo-oophorectomy; CD: carboplatin/docetaxel; CT: carboplatin/docetaxel; DOD: died without evidence of disease; LTF: lost to follow-up; LND: lymph node dissection; n/a: data not available for review; NACT: neoadjuvant chemotherapy; NED: no evidence of disease; PFS: progression-free survival; PT: cisplatin/paclitaxel; RT: radiation therapy; TAH: total abdominal hysterectomy; USO: unilateral salpingo-oophorectomy.

^a Specific chemotherapy regimen was not reported.

^b Overall survival (OS) statistics were not uniformly reported through studies listed and thus not represented here.

^c Patient underwent prior hysterectomy for benign indication.

^d PFS calculation excludes one patient lost to follow-up immediately after initial surgery.

4. Discussion

Initial treatment for MBTs, similar to other epithelial ovarian carcinomas, is surgical debulking, consistent with previously published case reports and case series (Table 2). The role of lymph node dissection (LND) in this rare cancer subtype is unclear. Gezginç et al. (2012) reported 13 cases of MBT, all of whom received LND in addition to TAH, BSO, and omentectomy. Out of 10 patients reported by Han et al. (2015), 8 received LND. However, neither authors reported presence of nodal disease in their cohorts. In a recent population analysis, Nasioudis et al. (2016) demonstrated that only 49% (99/202) of all MBT patients undergoing surgery received LND. Of these patients, only 5 (5.1%) were diagnosed with positive nodal disease (Nasioudis et al., 2016). 6/10 (60%) patients in this cohort displayed radiologic evidence of possible nodal involvement and underwent LND during initial surgery. Of these 6, none had positive nodal disease on final surgical pathology. Our data is consistent with existing literature, and suggests that while LND should be considered in patients with MBT, its routine use is likely low yield. Rather, the decision to pursue LND during initial operative management should take into account imaging studies and physical exam findings, as well as consideration of the morbidity risk of added surgical time and procedures in the context of the individual patient. Furthermore, it is important to consider that intraoperative frozen section may be limited in effectively identifying this rare tumor type, and the role for nodal sampling should take into account the entire clinical picture.

The role of adjuvant chemotherapy in early stage MBT is less clear. Gezginç et al. (2012) initially proposed that patients with at least stage IC should receive adjuvant treatment. In their reported series of 13 patients with MBT, 3 patients had either stage IA or IB disease and did not receive chemotherapy. Two of these patients (67%) were without evidence of disease at an average follow-up of 47 months. The third patient experienced recurrence 12 months after initial surgery. Alternatively, a more conservative approach has been described, which recommends observation for patients with stage IA disease only (Han et al., 2015). Han et al. reported on 10 MBT cases, with 4 patients who did not receive chemotherapy for stage IA disease. All 4 patients were released from oncologic surveillance after an average of 75 months of follow-up with no evidence of disease. In our cohort, 4 patients were either staged as IA or IB (3 surgically staged and one clinically staged). One of these patients was lost to follow-up immediately following surgery. Excluding this patient, two fully staged patients (stage IA/grade 3 and stage IB/grade 3) received 6 cycles of adjuvant chemotherapy and currently have no evidence of disease with an average follow-up of 60 months. One patient (stage IA/grade 2) did not receive adjuvant treatment following incomplete surgical staging with negative imaging. She is currently alive without evidence of disease at 126 months after initial diagnosis. Based on the lack of patients observed in our cohort, we cannot speak to the role of observation in MBT, but this represents an area that warrants future research. General treatment recommendations for high-grade early stage epithelial ovarian cancer are reasonable to extrapolate to this population with consideration of 3–6 cycles of adjuvant chemotherapy. Patients should be counseled that the absolute benefit of therapy is unknown.

The vast majority of MBT patients who underwent adjuvant chemotherapy received 6 cycles of CT as first-line treatment, consistent with the current recommendations for epithelial ovarian cancers (Ozols et al., 2003). Regimens after recurrence were more variable in our reported cohort. Favorable responses have been reported with the addition of docetaxel, topotecan, doxorubicin, gemcitabine, and bevacizumab, as well as radiation in patients with recurrent disease (Gezginç et al., 2012; Han et al., 2015; Lang et al., 2017). This is the first report to our knowledge that describes the usage of eribulin in the management of an MBT. For patient 3 in our cohort, this drug was selected due to the patient's increasing renal impairment and history of severe taxane-induced neuropathy. Eribulin is a hepatically-cleared

non-taxane microtubule inhibitor that has been recently shown in phase 3 trials to improve survival outcomes in patients with advanced solid tumors, specifically breast cancer, liposarcoma, and leiomyosarcoma (Smith et al., 2010; Cortes et al., 2011; Schöffski et al., 2016). When compared to taxanes, eribulin was shown to cause a significantly decreased rate of high-grade neuropathy, and did not appear to worsen symptoms in patients with existing low-grade neuropathy (Cortes et al., 2011; Jain and Cigler, 2012). Additionally, eribulin has been shown to have favorable responses in both preclinical and small-scale clinical settings for both epithelial ovarian and urothelial neoplasms (Quinn et al., 2010; Hensley et al., 2012). Even though our patient progressed after 5 cycles of treatment, eribulin should not be excluded in the discussion of secondary and tertiary regimens for recurrent metastatic disease, and warrants further research in this population.

Given the limited role of radiation therapy for adjuvant treatment in epithelial ovarian cancer, this is not a widely-used treatment modality in MBT. A recent SEER-based population analysis reported that 2.4% of MBT patients received radiation of any kind during the course of their treatment (Nasioudis et al., 2016). Primary radiation was not given to any patients in our cohort, and only two patients (20%) received radiation for palliative purposes. However, new studies have shown that targeted radiation treatment with concurrent chemotherapy may confer a survival benefit for the patient with recurrent disease refractory to > 2 different chemotherapeutics (Chundury et al., 2016). Targeted radiation may also be beneficial for patients with locoregional recurrence who undergo complete surgical resection. A recent case report by Lang et al. demonstrated a PFS of 24 months following the addition of bevacizumab and tumor bed radiation to CT for locoregionally-recurrent MBT after interval debulking.

5. Conclusion

In this contemporary review of 10 patients with MBT, the majority of patients were treated with platinum-taxane adjuvant chemotherapy after primary surgery with a median PFS of 37 months. Recurrence rates were lower than expected for high-grade serous ovarian cancer, but still overall high given the stage distribution of our cohort. Treatment for recurrent disease in these patients included gemcitabine, tamoxifen, doxorubicin, and eribulin, though disease recurred after all of these regimens. The role of radiation in these patients is largely limited to palliation and local control following tumor recurrence.

COI statement

The authors declare that they have no conflict of interest.

Author contributions

Y.Z. performed the chart review and data collection with support from A.S. All authors discussed the results and provided critical

feedback. Y.Z. wrote the manuscript and table in consultation with A.S., K.T., and L.C. L.C. designed and supervised the project.

References

- Austin, R.M., Norris, H.J., 1987. Malignant Brenner tumor and transitional cell carcinoma of the ovary: a comparison. *Int. J. Gynecol. Pathol.* 6 (1), 29–39 (3570630).
- Chundury, A., Apicelli, A., DeWees, T., Powell, M., Mutch, D., Thaker, P., Robinson, C., Grigsby, P.W., Schwarz, J.K., Apr 1, 2016. Intensity modulated radiation therapy for recurrent ovarian cancer refractory to chemotherapy. *Gynecol. Oncol.* 141 (1), 134–139. <https://doi.org/10.1016/j.ygyno.2016.02.005>.
- Cortes, J., O'Shaughnessy, J., Loesch, D., Blum, J.L., Vahdat, L.T., Petrakova, K., Chollet, P., Manikas, A., Diéras, V., Delozier, T., Vladimirov, V., Mar 12, 2011. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 377 (9769), 914–923. [https://doi.org/10.1016/S0140-6736\(11\)60070-6](https://doi.org/10.1016/S0140-6736(11)60070-6).
- Gezginç, K., Karatayli, R., Yazici, F., Acar, A., Çelik, Ç., Çapar, M., Tavli, L., Aug 1, 2012. Malignant Brenner tumor of the ovary: analysis of 13 cases. *Int. J. Clin. Oncol.* 17 (4), 324–329. <https://doi.org/10.1007/s10147-011-0290-7>.
- Han, J.H., Kim, D.Y., Lee, S.W., Park, J.Y., Kim, J.H., Kim, Y.M., Kim, Y.T., Nam, J.H., Apr 1, 2015. Intensive systemic chemotherapy is effective against recurrent malignant Brenner tumor of the ovary: an analysis of 10 cases within a single center. *Taiwan. J. Obstet. Gynecol.* 54 (2), 178–182. <https://doi.org/10.1016/j.tjog.2014.03.008>.
- Hensley, M.L., Kravetz, S., Jia, X., Iasonos, A., Tew, W., Pereira, L., Sabbatini, P., Whalen, C., Aghajanian, C.A., Zarwan, C., Berlin, S., May 1, 2012. Eribulin mesylate (halichondrin B analog E7389) in platinum-resistant and platinum-sensitive ovarian cancer: a 2-cohort, phase 2 study. *Cancer* 118 (9), 2403–2410. <https://doi.org/10.1002/cncr.26569>.
- Hermanek, P., Wittekind, C., Feb 1, 1994. The pathologist and the residual tumor (R) classification. *Pathol. Res. Pract.* 190 (2), 115–123. [https://doi.org/10.1016/S0344-0338\(11\)80700-4](https://doi.org/10.1016/S0344-0338(11)80700-4).
- Jain, S., Cigler, T., 2012. Eribulin mesylate in the treatment of metastatic breast cancer. *Biologics Targets Ther.* 6, 21. <https://doi.org/10.2147/BTT.S19811>.
- Lang, S.M., Mills, A.M., Cantrell, L.A., Nov 1, 2017. Malignant Brenner tumor of the ovary: review and case report. *Gynecol. Oncol. Rep.* 22, 26–31. <https://doi.org/10.1016/j.gore.2017.07.001>.
- Nasioudis, D., Sisti, G., Holcomb, K., Kanninen, T., Witkin, S.S., 2016 Jul 1. Malignant Brenner tumors of the ovary; a population-based analysis. *Gynecol. Oncol.* 142 (1), 44–49. <https://doi.org/10.1016/j.ygyno.2016.04.538>.
- Ozols, R.F., Bundy, B.N., Greer, B.E., Fowler, J.M., Clarke-Pearson, D., Burger, R.A., Mannel, R.S., DeGeest, K., Hartenbach, E.M., Baergen, R., Sep 1, 2003. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J. Clin. Oncol.* 21 (17), 3194–3200. <https://doi.org/10.1200/JCO.2003.02.153>.
- Quinn, D.I., Aparicio, A., Tsao-Wei, D.D., Groshen, S.G., Dorff, T.B., Synold, T.W., Stadler, W.M., Gandara, D.R., Lara Jr., P., Newman, E.M., May 20, 2010. California Cancer Consortium. Phase II study of eribulin (E7389) in patients (pts) with advanced urothelial cancer (UC)—Final report: a California Cancer Consortium-led NCI/CTEP-sponsored trial. *J. Clin. Oncol.* 28 (15 suppl), 4539. https://doi.org/10.1200/jco.2010.28.15_suppl.4539.
- Schöffski, P., Chawla, S., Maki, R.G., Italiano, A., Gelderblom, H., Choy, E., Grignani, G., Camargo, V., Bauer, S., Rha, S.Y., Blay, J.Y., Apr 16, 2016. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet* 387 (10028), 1629–1637. [https://doi.org/10.1016/S0140-6736\(15\)01283-0](https://doi.org/10.1016/S0140-6736(15)01283-0).
- Smith, J.A., Wilson, L., Azarenko, O., Zhu, X., Lewis, B.M., Littlefield, B.A., Jordan, M.A., Jan 20, 2010. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. *Biochemistry* 49 (6), 1331–1337. <https://doi.org/10.1021/bi901810u>.
- Verleye, L., Ottevanger, P.B., Van der Graaf, W., Reed, N.S., Vergote, I., Mar 1, 2009. EORTC-GCG process quality indicators for ovarian cancer surgery. *Eur. J. Cancer* 45 (4), 517–526. <https://doi.org/10.1016/j.ejca.2008.09.031>.