

# Are Too Many Imaging Tests Being Performed in Women With an Adnexal Mass?

Rachel Kupets, MD, MSc,<sup>1</sup> Kimberly Fernandes, MSc,<sup>2</sup> Gennady Miroshnichenko, MD, MSc,<sup>3</sup> Lawrence Paszat, MD, MSc, FRCPC<sup>2</sup>

<sup>1</sup>Department of Gynecologic Oncology, Sunnybrook Regional Cancer Centre, Toronto ON

<sup>2</sup>Institute for Clinical Evaluative Sciences, Toronto ON

<sup>3</sup>Department of Gynaecologic Oncology, University of Toronto, Toronto ON

## Abstract

**Objective:** To evaluate the patterns of radiologic imaging requested by family physicians and gynaecologists in the work-up of women found to have an adnexal mass on pelvic ultrasound, and to evaluate whether advanced imaging tests are associated with more appropriate referral of women with a high-risk adnexal mass to gynaecologic oncologists.

**Methods:** Centralized provincial databases of health care usage were used to identify women aged 45 and older who had a pelvic ultrasound examination between 2006 and 2008. Subsequent imaging tests ordered were identified according to physician specialty. For women who proceeded to laparotomy, logistic regression was performed to determine which imaging tests enabled primary physicians to make appropriate referrals of women with high risk adnexal tumours to a gynaecologic oncologist.

**Results:** We identified 193 261 women aged 45 and older who had a pelvic ultrasound. Of these, 19 949 (10.3%) had a subsequent laparotomy; 2223 women were categorized as having a benign adnexal mass, 627 were categorized as having a malignant adnexal mass, and the remainder had another diagnosis such as uterine fibroid. Up to 12% of women had a pelvic MRI, and 58% of women had a CT scan after a pelvic ultrasound. Family physicians referred 95% of women with a high-risk ovarian mass to a gynaecologic surgeon rather than to a gynaecologic oncologist, and gynaecologists referred 47% of such women to a gynaecologic oncologist after imaging. Gynaecologic oncologists operated on 55% of women with a malignant adnexal mass. On multivariate analysis, a preoperative CT scan (OR 3.58;  $P < 0.001$ ) and a CT scan and MRI (OR 7.78;  $P < 0.001$ ) were associated with surgery performed by a gynaecologic oncologist, but a preoperative MRI alone was not significantly associated (OR 1.86;  $P = 0.09$ ). After ultrasound alone the mean time to surgery was 100 days; this increased significantly when further imaging tests were performed (with additional CT to 131 days, with MRI to 170 days, and with CT and MRI to 179 days;  $P = 0.002$ ).

**Conclusion:** Performing a pelvic MRI after a pelvic ultrasound does not increase the rate of referral of women with a high-risk adnexal mass to a gynaecologic oncologist. A consensus on appropriate imaging and triage is needed when an adnexal mass is identified on ultrasound.

## Résumé

**Objectif :** Évaluer les tendances en ce qui concerne les tests radiologiques d'imagerie demandés par les médecins de famille et les gynécologues dans le cadre du bilan des femmes chez qui la présence d'une masse annexielle a été constatée par échographie pelvienne, ainsi qu'évaluer si la tenue de tests d'imagerie avancée est associée à une orientation plus adéquate des femmes qui présentent une masse annexielle les exposant à des risques élevés vers des gynécologues-oncologues.

**Méthodes :** Des bases de données centralisées provinciales sur l'utilisation des soins de santé ont été utilisées pour identifier les femmes de 45 ans ou plus qui avaient subi un examen échographique pelvien entre 2006 et 2008. Les tests d'imagerie demandés subséquemment ont été identifiés en fonction de la spécialité du médecin. Pour ce qui est des femmes qui en sont venues à subir une laparotomie, une régression logistique a été menée pour déterminer quels ont été les tests d'imagerie qui ont permis aux médecins primaires d'orienter adéquatement les femmes qui présentaient une masse annexielle les exposant à des risques élevés vers un gynécologue-oncologue.

**Résultats :** Nous avons identifié 193 261 femmes de 45 ans ou plus qui avaient subi une échographie pelvienne. Parmi ces femmes, 19 949 (10,3 %) en sont venues à subir une laparotomie; 2 223 femmes ont été catégorisées comme présentant une masse annexielle bénigne, 627 ont été catégorisées comme présentant une masse annexielle maligne et le reste de ces femmes ont obtenu un autre diagnostic (comme celui de fibrome utérin). Jusqu'à 12 % des femmes ont subi une IRM pelvienne et 58 % des femmes ont subi une tomodensitographie à la suite de l'échographie pelvienne. Les médecins de famille ont orienté 95 % des femmes qui présentaient une masse ovarienne les exposant à un risque élevé vers un gynécologue-chirurgien plutôt que vers un gynécologue-oncologue; les gynécologues ont orienté 47 % de ces femmes vers un gynécologue-oncologue à la suite de l'imagerie. Les gynécologues-oncologues ont opéré 55 % des femmes qui présentaient une masse annexielle maligne. Dans

**Key Words:** Pelvic mass, imaging patterns, referral patterns

Competing interests: None declared.

Received on August 2, 2012

Accepted on October 29, 2012

le cadre d'une analyse multivariée, une tomographie préopératoire (RC, 3,58;  $P < 0,001$ ) et une combinaison tomographie-IRM (RC 7,78;  $P < 0,001$ ) ont été associées à l'exécution d'une chirurgie par un gynécologue-oncologue, mais la seule tenue d'une IRM préopératoire n'a pas présenté une association significative (RC, 1,86;  $P = 0,09$ ). À la suite de la seule tenue d'une échographie, le délai moyen avant la chirurgie était de 100 jours; ce délai a connu une hausse considérable lorsque d'autres tests d'imagerie ont été menés (131 jours dans le cas d'une tomographie additionnelle, 170 jours dans le cas de l'IRM et 179 jours dans le cas de la combinaison tomographie-IRM;  $P = 0,002$ ).

**Conclusion :** La tenue d'une IRM pelvienne à la suite d'une échographie pelvienne ne donne pas lieu à une hausse du taux d'orientation des femmes qui présentent une masse annexielle les exposant à un risque élevé vers un gynécologue-oncologue. Un consensus quant à ce qui est adéquat en matière d'imagerie et de triage, lorsqu'une masse annexielle est identifiée au moment de l'échographie, s'avère requis.

J Obstet Gynaecol Can 2013;35(3):246–251

## INTRODUCTION

The purpose of an imaging test in the evaluation of a pelvic mass in women is to identify the location of the mass, to describe the characteristics of the mass, and to enable the ordering physician to determine the next steps in referring the patient to the appropriate surgical specialist. Imaging tests cannot provide a histologic diagnosis, nor can they provide the stage of early ovarian cancers accurately.

The Society of Obstetricians and Gynaecologists of Canada's initial evaluation and referral guidelines for management of pelvic/ovarian masses state that if findings on ultrasound and the clinical scenario are suspicious for malignancy, then further radiologic evaluations such as CT and MRI scans before subspecialty referral are unlikely to be beneficial.<sup>1</sup>

The American Congress of Obstetricians and Gynecologists' guidelines on the management of adnexal masses state that for the evaluation of adnexal masses adding other imaging modalities to transvaginal ultrasound is of limited value. In fact, the sensitivity, specificity, and positive likelihood ratio for malignancy for ultrasound and for MRI are the same and are superior to those of CT scans.<sup>2</sup>

## ABBREVIATIONS

CIHI	Canadian Institute for Health Information
CT	computed tomography
LHIN	Local Health Integration Networks
MRI	magnetic resonance imaging
OHIP	Ontario Health Insurance Plan

There is evidence to demonstrate that there are significant gains in length of survival for women with early and advanced ovarian cancer when they are operated on and have clinical management provided by gynaecologic oncologists instead of general gynaecologists and surgeons.<sup>3</sup>

The purpose of this population-based study was to determine the patterns of imaging of pelvic masses in women over the age of 45 in the province of Ontario by the specialty of the ordering physician, and to determine whether imaging tests influenced the referral of women with a high-risk ovarian mass to a gynaecologic oncologist in the years 2006 to 2008.

## METHODS

We performed a retrospective population-based study using data at the Institute of Clinical Evaluative Sciences, which contains the health records for 12.5 million residents in the province of Ontario. Using OHIP billing codes, we identified all women on whom a pelvic ultrasound had been performed between January 1, 2006, and December 31, 2008, with identification of an adnexal mass. The OHIP contains physician billing claims per individual patient for medical and surgical services dating from July 1, 1991. Exclusion criteria were age under 45 years; having had a pelvic ultrasound or pelvic-abdominal CT or MRI in the previous five years; any previous gynaecologic, colorectal, genitourinary, or breast cancer; any previous gynaecologic surgery; any previous small or large bowel resection; or any prior history of inflammatory bowel disease or diverticulitis up to the day before the index pelvic ultrasound. The study cohort comprised women who satisfied the inclusion and exclusion criteria and who went on to have a laparotomy for management of the mass within two years of the initial pelvic ultrasound.

Variables obtained from the Registered Persons Database and Canadian Census were age, income quintiles, urban versus rural dwelling, and residential location within each of the province's 14 Local Health Integration Networks.

Linkage of the cohort to the OHIP database and CIHI-Discharge Abstract Database, (which records procedure codes from all inpatient and outpatient hospital admissions) was performed to obtain data regarding investigations and procedures completed within two years after the initial pelvic ultrasound, such as repeat pelvic or transvaginal ultrasound, preoperative pelvic or abdominal CT and/or MRI, and the date and type of surgical procedure. Links to the OHIP and the Corporate Physicians' Database (which contains data on physician specialty in the province of Ontario) produced data on consultations carried out by

**Table 1. Age distribution of cohort of patients**

Age of patient, years	Imaging ordered by non-gynaecologist, n (%)	Imaging ordered by gynaecologist, n (%)
45 to 49	42 870 (24)	4365 (30)
50 to 54	32 698 (18)	3324 (23)
55 to 59	25 197 (14)	2292 (16)
60 to 64	20 421 (11)	1624 (11)
65 to 69	16 444 (9)	1152 (8)
70 to 74	13 930 (8)	726 (5)
≥ 75	27 264 (15)	954 (6.6)

general gynaecologists and gynaecologic oncologists, and on the specialty of the physicians who ordered preoperative investigations and performed surgery.

The characteristics of the cohort of women referred for initial pelvic ultrasound by a physician other than a gynaecologist were compared with those of women referred by a gynaecologist to determine whether age, comorbidities, or location of dwelling (rural vs. urban and LHIN) affected referral patterns.

The study cohort was divided according to the most responsible final diagnosis of benign adnexal mass and malignant adnexal mass. Imaging usage patterns and the time from investigation to pelvic surgery were retrospectively determined for these two groups.

Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC). The Student *t* test was used for comparison of continuous data, and the chi-square test for categorical data, with 95% confidence intervals. Two sets of multivariate logistic regression analysis were performed. The first set of analyses was modelled to determine the odds of having one or more CT and/or MRI examinations before the first pelvic surgical procedure. The second set of analyses was constructed to determine the odds of patients with a malignant adnexal mass having a surgical intervention performed by a gynaecologic oncologist in. Clinically important variables thought to potentially influence preoperative imaging and referral were chosen a priori and entered into the models. A two-tailed  $P < 0.05$  was considered statistically significant.

Approval for the study was granted by the Sunnybrook Hospital Research Ethics Board.

## RESULTS

Between January 2006 and December 2008, 1 847 254 pelvic ultrasound examinations were ordered by non-gynaecologists, and 204 896 pelvic ultrasounds were

ordered by gynaecologist. Of the women examined, 193 261 women over the age of 45 had a pelvic ultrasound and met the study criteria. Of these women, 178 824 had an ultrasound ordered by a non-gynaecologist, 14 383 by a gynaecologist, and 54 by a gynaecologic oncologist. The ultrasound images were read by 1073 radiologists.

Of this cohort, 19 949 women (10%) went on to have pelvic surgery. Overall, 3326 women in our study cohort had a diagnosis of malignancy, including 627 adnexal/ovarian cancers, 2107 cancers of the uterus and cervix, and 592 non-gynaecologic cancers; 2223 women had benign adnexal pathology.

The age distribution of the cohort is shown in Table 1. The majority of women were between the ages of 45 and 54. The final diagnoses of pelvic masses characterized as a benign or malignant adnexal mass are shown in Table 2.

The preoperative imaging according to the specialty of the ordering physician in the cohort of women with an adnexal mass is shown in Table 3. Of women found to have benign adnexal disease, 61% had a repeat pelvic ultrasound and 25% had a CT scan of the abdomen and pelvis; up to 70% of these tests were ordered by a non-gynaecologist. Non-gynaecologists ordered 61% of MRIs in the women who had these tests.

Of women categorized as having a malignant adnexal mass, 38% had a repeat ultrasound and 58% had a CT scan of the abdomen and pelvis; 71% of these tests were ordered by a non-gynaecologist. A non-gynaecologist ordered 60% of MRIs in these women. Furthermore, of women who underwent surgery for a malignant mass, 35% had only a pelvic ultrasound before surgery, 54% had a CT scan and pelvic ultrasound, 6% had an MRI and pelvic ultrasound, and 5% had a CT scan, MRI, and pelvic ultrasound before surgery.

**Table 2. Final diagnosis of benign and malignant adnexal masses**

Benign adnexal mass (n = 2223)		Malignant adnexal mass (n = 627)	
Diagnosis	Frequency %	Diagnosis	Frequency %
Benign ovarian neoplasm	50	Malignant ovarian neoplasm	82
Unspecified ovarian cyst	42	Neoplasm of uncertain behaviour of ovary	13
Endometriosis of the ovary	5	Secondary malignant neoplasm of ovary	3
Non inflammatory disorder of ovary/fallopian tube	3	Malignant neoplasm of fallopian tube	2

**Table 3. Patterns of imaging by ordering physician's specialty for benign or malignant adnexal mass**

	Proportion of patients undergoing test, %	Tests ordered by non-gynaecologist, %	Number of tests, mean ± SD
Benign adnexal mass			
Repeat pelvic ultrasound	61	60	1.74 ± 1.05
Abdominal ultrasound	14.4	70	1.16 ± 0.43
CT abdomen	25	71.4	1.05 ± 0.26
MRI pelvis	11.9	61	1.03 ± 0.18
Malignant adnexal mass			
Repeat pelvic ultrasound	38.4	56.4	1.43 ± 0.84
Abdominal ultrasound	23	62.3	1.38 ± 0.75
CT abdomen	58.4	71	1.23 ± 0.54
MRI pelvis	10.8	58.8	1.03 ± 0.17

**Table 4. Time to surgery for women with a malignant adnexal mass and type of imaging**

Value	No CT/No MRI	CT/No MRI	MRI/No CT	MRI/CT	P
Days, mean ± SD	100 ± 118	132 ± 154	170 ± 160	178 ± 165	0.002
Days, median (interquartile range)	60 (34 to 115)	76 (46 to 146)	104 (56 to 236)	120 (83 to 193)	< 0.001

Of patients with masses that were categorized as benign, 96% were referred to a gynaecologist when the physician ordering the initial ultrasound was a non-gynaecologist, and 12% of these women were subsequently referred to a gynaecologic oncologist. When the physician ordering the ultrasound was a gynaecologist, 13% of these patients were then referred to a gynaecologic oncologist.

Of patients with masses that were categorized as malignant, 95% were referred to a gynaecologist when the physician ordering the initial ultrasound was a non-gynaecologist, and 58% of those patients were subsequently referred to a gynaecologic oncologist. When the physician ordering the ultrasound was a gynaecologist, 47% of these patients were referred to a gynaecologic oncologist.

The time from first pelvic ultrasound to surgery for women who had an operation for a malignant adnexal mass based on the imaging patterns is shown in Table 4. The mean time to surgery for women who had only a preoperative pelvic ultrasound was 100 days; for women who subsequently had a pelvic MRI, the mean time to surgery was 170 days, and for those who had both a CT scan and MRI, the mean time to surgery was almost 180 days.

The results of the logistic regression were adjusted by LHIN or region and are shown in Table 5; having a CT scan or a CT scan and MRI were strongly associated with a referral to a gynaecologic oncologist, but having an MRI alone did not improve the rate of referral to a gynaecologic oncologist of patients with a high-risk adnexal mass.

**Table 5. Factors associated with gynaecologic oncologist performing surgery in women with a malignant ovarian mass**

Variable	Value	Univariate analysis			Multivariate analysis		
		OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Age at date of index pelvic ultrasound	For every 5 yr increase	1.02	(0.947 to 1.097)	0.607	0.99	(0.913 to 1.071)	0.780
Modified income quintile	Reference group: Rural/Q1						
	Q2/Q3	0.93	(0.621 to 1.390)	0.721	0.84	(0.535 to 1.305)	0.430
	Q4/Q5	0.99	(0.660 to 1.473)	0.946	1.06	(0.679 to 1.659)	0.795
Was referring physician for index pelvic ultrasound a gynaecologist?	Yes vs. no	0.84	(0.416 to 1.694)	0.625	1.11	(0.509 to 2.410)	0.797
CT/MRI prior to first pelvic surgery?	No CT or MRI	1.00	Reference		1.00	Reference	
	1+ CT but no MRI	2.88	(2.020 to 4.117)	< 0.001	3.58	(2.432 to 5.268)	< 0.001
	1+ MRI but no CT	1.86	(0.937 to 3.706)	0.076	1.86	(0.899 to 3.862)	0.094
	1+ MRI and 1+ CT	7.99	(2.941 to 21.689)	< 0.001	7.78	(2.763 to 21.883)	< 0.001

## DISCUSSION

It is estimated that one in five physician–patient encounters results in imaging tests being requested.<sup>4</sup> In patients with gynaecologic complaints, pelvic and transvaginal ultrasound examinations are typically the first tests used to evaluate the uterus and adnexa and are the most sensitive and specific tests available for this purpose.<sup>2</sup> Ultrasound examinations are not able to provide a definitive histologic diagnosis and are not a replacement for a pathology report; however, when ultrasound scans are interpreted correctly by radiologists and the findings appropriately applied to a clinical context, appropriate decisions regarding triage of patients to surgical specialists for surgical intervention can be made. If however, the results of the imaging are equivocal or vague, or if the attending physician is unable to make an appropriate clinical judgement, additional interventions may be performed and may result in unnecessary additional imaging or inappropriate or incomplete surgical interventions.

Women with ovarian pathology have well-recognized clinical symptoms, and pelvic ultrasound examinations can typically determine whether findings in an ovarian mass suggest a significant risk of malignancy or if there is in fact disseminated disease.<sup>2</sup>

In this study, we identified 193 261 women aged 45 and over who had not had any pelvic or abdominal imaging in the previous five years or previous laparotomy. Seventeen percent of the women in this cohort were found to have a gynaecologic malignancy. Of those with a malignancy, 83% had a gynaecologic cancer, and of those with

a gynaecologic cancer, 23% had ovarian cancer. The remaining women had a uterine or cervical malignancy. In the study cohort, 93% of ultrasound imaging tests were initiated by non-gynaecologists. For those women who had surgery demonstrating benign adnexal disease, up to 60% had additional imaging, and non-gynaecologists were responsible for initiating up to 70% of those tests. Of women who had surgery demonstrating ovarian or fallopian tube malignancies, up to 58% had additional imaging, and non-gynaecologists were responsible for initiating up to 71% of all additional imaging tests. The large discrepancy between specialists in gynaecology and non-specialists in ordering imaging suggests that non-specialists may prefer making referral decisions on the basis of multiple imaging reports. This results in increased MRI examinations of ovarian masses that assess the same characteristics of adnexal masses as ultrasound examinations. CT scans were also ordered in 25% to 58% of cases, presumably to screen for metastatic disease; this is unnecessary in patients with benign masses, and is inappropriate in women with malignant masses because cancer staging is a surgically based process. Women thought to have early ovarian cancer on the basis of imaging will have upstaging 30% of the time with comprehensive surgical staging.<sup>1</sup> Non-specialists often feel that the specialist will require additional imaging for treatment planning, and request the imaging accordingly, while specialists frequently deny that they make these requests.<sup>5</sup>

In this study we also found that despite the multiple imaging ordered by non-gynaecologists, 95% of women who had imaging for a final diagnosis of ovarian

cancer were referred by non-gynaecologists to general gynaecologists rather than to gynaecologic oncologists, and gynaecologists retained 50% or more of these patients in their practices. This finding implies that imaging test results are not used appropriately to triage high-risk patients to the appropriate specialists, thereby delaying appropriate surgical management of ovarian malignancy. This finding is consistent with the finding of Elit et al. that almost 40% of women with ovarian cancer in Ontario were operated on by community physicians.<sup>6</sup> Our findings are also similar to those of Goff et al., who found that family physicians refer 39% of patients with a high-risk adnexal mass to gynaecologic oncologists, internists refer 51% of such patients to gynaecologic oncologists, and gynaecologists refer 66% of such patients appropriately.<sup>7</sup>

We found significant increases in wait time to surgery because additional imaging tests were ordered. Arguably, because there is a questionable need for these according to guidelines from both the SOGC<sup>1</sup> and ACOG,<sup>2</sup> the additional imaging causes unnecessary treatment delays which can result in diminished survival rates in patients with ovarian cancer.

Published data support a survival benefit for women with both early and advanced ovarian cancer when managed by gynaecologic oncologists.<sup>3</sup> Patterns of care studies have found that 40% of advanced ovarian cancer surgeries performed by community surgeons resulted in an open biopsy alone, and 46% of clinically early cancers resulted in a unilateral salpingo-oophorectomy.<sup>6</sup> Additionally, the risk of re-operation is significantly decreased when a gynaecologic oncologist is present at the first operation.<sup>8</sup> The role of imaging tests should be to improve the rate of referral of women with probable ovarian cancer to gynaecologic oncologists, but our multivariate analysis found that additional MRI imaging did not increase these referral rates. This indicates that the addition of MRI to pelvic ultrasound is of no benefit when evaluating an isolated adnexal mass; having a CT scan does increase rates of referral to gynaecologic oncologists, presumably because of the presence of widely metastatic disease.

A strength of our study is that it was population-based, resulting in our ability to evaluate a large patient database. A weakness of our study is that we did not perform chart audits to determine the documented indication for ordering imaging tests or the reason for further imaging

tests. However, we can assume that in each case the patient had pelvic symptoms that led to imaging and that the initial pelvic ultrasound detected an abnormality. Additionally, we did not evaluate the role the radiologist had in ordering multiple imaging tests. Not uncommonly the radiologist will recommend additional imaging, influencing the clinician to order additional tests. Lastly, we did not evaluate the quality of the imaging reports. Some of these may have been insufficiently detailed to allow interpretation of the findings as consistent with either benign or malignant disease.

## **CONCLUSION**

We have found that a significant proportion of women with a high-risk adnexal mass undergo multiple imaging tests that do not improve the rate of referral of these women to the care of gynaecologic oncologists. Not only are many of these tests unnecessary according to clinical practice guidelines but they also increase wait times to surgery significantly. Although major financial investments in imaging resources have been made, the issue of evidence-based care and communication between non-specialists, specialists, and radiologists has yet to be addressed.

## **REFERENCES**

1. Le T, Giede C, Salem S, Lefebvre G, Rosen B, Bentley J, et al. Initial evaluation and referral guidelines for management of pelvic/ovarian masses. *J Obstet Gynaecol Can* 2009;31:668–80.
2. Graham L. ACOG releases guidelines on management of adnexal masses. *Am Fam Physician* 2008;77:1320–3.
3. Mayer AR, Chambers SK, Graves E, Holm C, Tseng PC, Nelson BE, et al. Ovarian cancer staging: does it require a gynecologic oncologist? *Gynecol Oncol* 1992;47:223–7.
4. You JJ, Laupacis A, Newman A, Bell CM. Non-adherence to recommendations for further testing after outpatient CT and MRI. *Am J Med* 2010;123:557 e1–e8.
5. You JJ, Levinson W, Laupacis A. Attitudes of family physicians, specialists and radiologists about the use of computed tomography and magnetic resonance imaging in Ontario. *Healthc Policy* 2009;5:54–65.
6. Elit L, Schultz S, Prysbyz R, Barbera L, Saskin R, Gunraj N, et al. Patterns of care in the initial management of women with ovarian cancer in Ontario. *Eur J Gynaecol Oncol* 2009;30:361–4.
7. Goff BA, Miller JW, Matthews B, Trivers KF, Andrilla CH, Lishner DM, et al. Involvement of gynecologic oncologists in the treatment of patients with a suspicious ovarian mass. *Obstet Gynecol* 2011;118:854–62.
8. Elit L, Bondy SJ, Paszat L, Przybyz R, Levine M. Outcomes in surgery for ovarian cancer. *Gynecol Oncol* 2002;87:260–7.