RESEARCH COMMUNICATION

Efficacy of Exemestane After Nonsteroidal Aromatase Inhibitor Use In Metastatic Breast Cancer Patients

Sun Hye Kim[1], In Hae Park[1,2], Hyewon Lee[1], Keun Seok Lee[2], Byung-Ho Nam[1], Jungsil Ro[1,2]

Abstract

Background : Previous studies have suggested a lack of complete cross-resistance between steroidal (exemestane) and non-steroidal aromatase inhibitors (nSAI). Methods : Eighty-eight metastatic breast cancer (MBC) patients who received 25 mg of exemestane orally once a day at the National Cancer Center, Korea, between 2003 and 2009, were reviewed retrospectively. All patients had received nSAI for metastatic disease prior to exemestane therapy. Results : The median age was 52 years (range, 33–79), and 13 (14.8%) patients were premenopausal who concomitantly received GnRH agonist. Exemestane was given as a second- (80.7%) or third-line (19.3%) hormone therapy. The clinical benefit (CB) rate (complete response + partial response + stable disease ≥ 24 weeks) was 30.7%, with a median CB duration of 10.0 months (range, 6.3–78.7). The median progression-free survival (PFS) was 3.0 months (95% confidence interval [CI], 1.99–4.01) and the overall survival (OS) 21.5 months (95% CI, 17.96–25.04), with a median follow-up of 50.3 months. Patients who achieved CB had longer OS than those patients who did not (29.6 vs 17.9 months; P =0.002). On univariate analysis of predictive factors, patients who had achieved CB from previous nSAI tended to show lower CB rate (24.6% vs 44.4%, respectively; P=0.063) and shorter PFS (2.8 vs 4.8 months, respectively; p=0.233) than patients who had not. Achieving CB from previous nSAI became independent predictive factor for CBR to exemestane on multivariable analysis (Odds ratio = 2.852, P = 0.040). Conclusions : Exemestane after nSAI failure was effective in prolonging CB duration. The drug's efficacy seemed to be inferior in patients who had benefit from previous nSAI use.

Key words: Exemestane - aromatase inhibitor - cross resistance - metastatic breast cancer

Asian Pacific J Cancer Prev, **13**, 979-983

Introduction

Over 60%–75% of postmenopausal patients with metastatic breast cancer (MBC) have hormone-receptor-positive tumors (Nam et al., 2008). Endocrine therapy, with its more favorable toxicity profile than chemotherapy, is the preferred treatment modality for these patients. Aromatase inhibitors (AIs), widely used as endocrine therapies, block estrogen synthesis by inhibiting the action of the enzyme aromatase, which converts androgen into estrogen (Smith and Dowsett, 2003). AIs are categorized as two types: an irreversible steroidal aromatase inhibitor (SAI) including exemestane, and nonsteroidal aromatase inhibitors (nSAIs), such as anastrozole and letrozole (Smith and Dowsett, 2003). As more patients are treated with AIs, the identification of the optimal population and the best sequence of administration for nSAI and SAIs have become important issues. Previous studies have suggested a lack of complete cross-resistance between nSAI and exemestane (Lonning et al., 2000; Gennatas et al., 2006; Steele et al., 2006; Chin et al., 2007; Chia et al., 2008). However, there is insufficient evidence of this and the responsible mechanisms are not yet fully understood.

We report the clinical outcome results of exemestane treatment as a second- or third-line hormonal therapy in MBC patients after nSAI failure.

Materials and Methods

Patients with MBC who took 25 mg of exemestane orally daily after third-generation nSAI failure, between January 2003 and December 2009, were included in the study. The patients were pre- or postmenopausal women who had received up to third-line chemotherapy for metastatic disease. The patients were identified in the Breast Cancer Database at the National Cancer Center,

*[1]Center for Clinical Trials, [2]Center for Breast Cancer, National Cancer Center, Goyang, Korea *For correspondence: jungsro@ncc.re.kr*

Korea, and their medical records and radiological images were reviewed. All patients were followed-up until death or December 2010. The immunohistochemistry (IHC) of 3 different biological factors (estrogen receptor (ER), SP1, Ventana; progesterone receptor (PgR), 1E2, Ventana; Human Epidermal Growth Factor 2 (HER2), polyclonal, DAKO) using paraffin-embedded tissues according to reporting recommendations for tumor marker prognostic studies (McShane et al., 2005). A cut-off value of 10% or more of positively stained nuclei was used to define ER and PgR positivity. HER2 was scored as 0–3+ according to the method recommended with the DAKO HercepTest, and cases with IHC scores of 3+ or 2+ with gene amplification by fluorescence in situ hybridization, (FISH) was considered positive for HER2. The tumor response was reassessed based on the RECIST criteria 1.0 (Therasse et al., 2000). Complete responses (CR) and partial responses (PR) were collectively defined as objective responses. CR, PR and stable disease (SD) for ≥ 24 weeks were classified as a clinical benefit (CB). Disease free interval (DFI) was defined as the time elapsing from the diagnosis of primary breast cancer to the diagnosis of metastasis. Progression-free survival (PFS) was defined as the time from the start of exemestane treatment until progression or death from any cause. Overall survival (OS) was defined as the time from the start of exemestane treatment until death from any cause. Categorical variables were compared using chi-square test and continuous variables were compared using Wilcoxon rank sum test. A two-tailed p value less than 0.05 was considered significant. Survival curves were estimated using the Kaplan–Meier method and compared by a log rank test. We defined clinical efficacies as clinical benefit rates (CBR) and PFS, and analyzed predictive factors for them. The odds ratio (OR) was used as the basic measure of the relative risk for CBR and is expressed with a 95% confidence interval (95% CI). A logistic regression model was used to estimate and test for the association of variables with CBR while simultaneously adjusting for variables included in the model. Variables associated with CBR and PFS on univariate analysis ($p < 0.10$) were included in the multivariate analysis. Statistical analyses were performed with SPSS for Window version 18.0.

Table 1. Baseline Demographics of Patients

Characteristic		No. patients	%
Age	Median	52	
	Range	33-79	
Menopause status	Premenopausal	13	14.8
	Postmenopausal	75	85.2
Hormone receptor status	ER and PR positive	59	67.4
	ER or PR positive	29	32.6
HER2 status	Positive	5	5.7
	Negative	79	89.8
	Unknown	4	4.5
Stage at initial diagnosis	I	9	10.2
	II	24	27.3
	III	25	28.4
	IV	21	23.9
	Unknown	9	10.2
Sites of metastatic disease	Bone	59	67.0
	Lymph node	42	47.7
	Skin/soft tissue	19	21.6
	Hematogenous lung or pleura	44	50.0
	Lymphangitic lung or liver	12	13.6
	Brain	3	3.4
Number of involved organs	1	25	28.4
	2	30	34.1
	3	27	30.7
	≥ 4	6	6.8
Prior treatment	Adjuvant hormone therapy	52	59.0
	Adjuvant chemotherapy	53	60.2
	Palliative hormone therapy		
	-Tamoxifen	15	17.0
	-AIs	88	100
	Palliative chemotherapy	52	59.1
Response to previous nSAI	CR+PR	12	13.6
	SD ≥24 weeks	47	53.4
	SD <24 weeks	12	13.7
	PD	15	17.0
	Unknown	2*	2.3

* These two patients stayed on exemestane for more than 24 weeks.

Table 2. Overall Tumor Response to Exemestane

Response	No. patients	%
CR or PR	0	0
SD ≥ 6 months	27	30.7
SD < 6 months	9	10.2
PD	52	59.1
Clinical benefit rate	27	30.7

Results

Patient characteristics

The baseline demographics are shown in Table 1. The median age of the total population (88 patients) was 52 years (range, 33–79), and 13 premenopausal patients (14.8%) received a concomitant gonadotropin-releasing hormone (GnRH) agonist. The median DFI was 3.7 years (range, 0.4–18.1), excluding 23.9% with de novo stage IV disease. More than two thirds of patients had multiple metastases and 12 (13.6%) had lymphangitic lung or liver metastasis. Other diseases included skin/soft-tissue, lymph-node, bone, pleura, brain, and hematogenous lung metastases. All patients had ER- and/or PgR-positive tumors and the majority (89.8%) was HER2 negative. Fifty-two (59.0%) patients received adjuvant hormone therapy and 53 (60.2%) received adjuvant chemotherapy. Of the 52 patients (59.0%) who received palliative chemotherapy, 21.3% received one, 27.0% two, and 11.2% up to three lines of chemotherapy. Fifteen patients (17.0%) received tamoxifen for MBC. All patients received nSAI in the metastatic setting: letrozole in 67.0% and anastrozole in 33.0% of patients. Seventy (79.5%) patients received exemestane as the second-line hormone therapy and 18 (20.5%) as the third-line therapy. Forty-five patients (51.1%) received exemestane consecutively following nSAI.

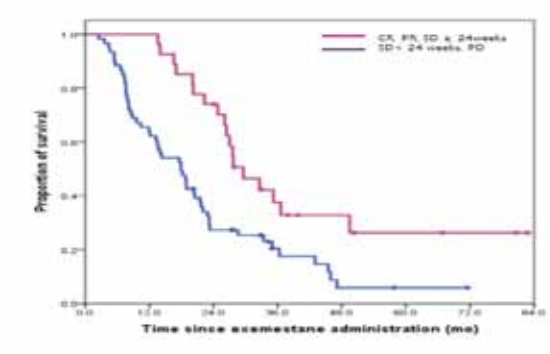

Figure 1. Overall Survival by Response to Exemestane

Efficacy of exemestane

The efficacy data for exemestane are summarized in Table 2. Although no patient achieved CR or PR, 27 had stable disease for ≥ 24 weeks, with a CBR of 30.7% and a median CB duration of 10.0 months (range, 6.3–78.7). CBR was not affected by menopausal status, DFI, previous treatment, or burden of metastatic disease (Table 3). None of the five patients with HER2-positive tumors achieved CB. Patients with lymphangitic lung or liver metastases showed non-inferior CBR (25.0%) to that of patients with soft-tissue (31.0%) or bone metastases (31.9%); P = 0.89) in this series of patients. The CBR obtained by the subsequent exemestane treatment did not differ significantly between the two groups of patients who did and did not achieve CBR with the initial nSAI (25.0% vs 38.5%; P = 0.47). Among whole population, patients who achieve CB with previous nSAI treatment tended to show a lower CBR than that of patients who had not achieved CB with no statistical significance (24.6% vs 44.4%; P = 0.06). Since CBR was affected by age and achieving CB with the previous nSAI on univariate analysis with p <0.10, these two variables were applied as multivariate analysis. Achieving CB with the previous nSAI treatment remained as a significant predictor for CBR with exemestane treatment in the multivariate analysis (Odds ratio = 2.85, P = 0.04; Table 3).

With a median follow-up of 50.3 months (range, 20.2–82.8), all patients experienced disease progression and 70 patients (79.5%) died with a median PFS of 3.0 months (95% CI, 1.99–4.01) and an OS of 21.5 months (95% CI, 17.96–25.04). Patients who achieved CB lived significantly longer than those who did not (29.6 vs 17.9 months; P = 0.002; Figure 1). None of factors affected to PFS in our analysis (Table 3).

Table 3. Analysis of Predictive Factors for CBR and PFS

Variables	CBR						PFS		
	Univariate				Multivariate		Univariate		
	No.	%	OR (95% CI)	P value	OR (95% CI)	P value	mo	HR(95% CI)	P value
Age				0.08		0.05			0.13
< 60 yr	66	25.8	1		1		2.9	1.45 (0.89-2.37)	
≥ 60 yr	22	45.5	2.4 (0.88-6.56)		2.84 (0.99-8.15)		3.6	1	
Menopausal status				0.99					0.92
Pre-menopausal	13	30.8	1				3	0.97 (0.54-1.76)	
Post-menopausal	75	30.7	0.99 (0.28-3.57)				4.1	1	
Disease free interval				0.62					0.67
< 2 yr	36	27.8	1				2.9	1.09 (0.71-1.69)	
≥ 2 yr	52	32.7	1.26 (0.50-3.21)				3.1	1	
Adjuvant hormone therapy				0.62					0.96
No	36	27.8	1				2.9	1.01 (0.66-1.55)	
Yes	52	32.7	1.26 (0.50-3.21)				3.2	1	
Number of prior chemotherapy				0.59					0.56
≥ 2	33	27.3	1				2.3	1.13 (0.73-1.76)	
< 2	55	32.7	1.29 (0.50-3.36)				3.6	1	
Exemestane as hormone therapy				0.39					0.47
2nd line	70	28.6	1				3	1.21 (0.71-2.07)	
3rd line	18	38.9	1.59 (0.54-4.69)				3.6	1	
Visceral disease (lymphangitic lung or liver)				0.64					0.84
Yes	12	25	1				2.9	0.93 (0.49-1.78)	
No	76	31.6	1.38 (0.34-5.58)				3	1	
Number of involved organs				0.86					0.34
≥ 2	63	30.2	1				2.8	1.25 (0.78-2.02)	
< 2	25	32	1.09 (0.40-2.96)				4.1	1	
Time since last nSAI				0.69					0.52
< 6 months	58	29.3	1				2.9	0.86 (0.55-1.35)	
≥ 6 months	30	33.3	1.21 (0.47-3.11)				3.2	1	
Response of prior nSAI				0.06		0.04			0.23
CR, PR, SD ≥ 24 weeks	61	24.6	1		1		2.8	1.32 (0.84-2.09)	
SD < 24 weeks, PD	27	44.4	2.45 (0.94-6.39)		2.85 (1.05-7.76)		4.8	1	

No; number, mo; months, Yr; year

Table 4. Relationship of Tumor Responses to Exemestane and Previous nSAI

	CR or PR N (%)	SD ≥ 24wks N (%)	CBR N (%)	SD < 24wks N (%)	PD N (%)	Total N (%)
CR or PR	0	0	0	0	0	0
SD≥ 24wks	4 (4.5)	11 (12.5)	15 (17.0)	4 (4.5)	8 (9.1)	27 (30.7)
CBR	4 (4.5)	11 (12.5)	15 (17.0)	4 (4.5)	8 (9.1)	27 (30.7)
SD <24wks	2 (2.3)	4 (4.5)	6 (6.8)	2 (2.3)	1 (1.1)	9 (10.2)
PD	8 (9.1)	32 (36.4)	40 (48.5)	6 (6.8)	6 (6.8)	52 (59.1)
Total	14 (15.9)	47 (53.4)	61 (69.3)	12 (13.6)	15 (17.0)	88 (100)

Efficacy of previous nSAI treatment

We also assessed the responses to the previous nSAI treatment. The median PFS was 7.8 months (95% CI, 5.41–10.19) and the overall response rate was 15.9%. Sixty-one patients (69.3%) achieved CB with a median CB duration of 11.9 months (range, 6.1–44.6). In particular, 27 patients who achieved CB with subsequent exemestane had following clinical efficacies with previous nSAI treatment: 0 CR, 4 PR, 11 SD ≥ 24 weeks, 4 SD < 24 weeks, and 8 progressive disease. Therefore, 12 of 27 patients who did not benefit from their previous nSAI therapy achieved CB when treated with exemestane (Table 4).

Discussion

In Exemestane, an orally administered, active, irreversible SAI, has demonstrated efficacy as a second- or third-line hormonal therapy after the failure of nSAI, with a reported CBR of 20%–55% (Lonning et al., 2000),(Chin et al., 2007) and a median PFS of 3.7–4.5 months (Steele et al., 2006),(Chia et al., 2008). The results of this study support exemestane as an effective therapy for nSAI pretreated MBC patients by showing similar clinical outcomes to those reported by others (Lonning et al., 2000; Gennatas et al., 2006; Steele et al., 2006; Chin et al., 2007; Chia et al., 2008). When exemestane was used as a first-line therapy, the response rate was 46%, with a PFS of 9.9 months (Paridaens et al., 2008), which is similar to the first-line efficacy of nSAIs according to other reports (Bonneterre et al., 2000; Nabholtz et al., 2000; Mouridsen et al., 2003). The current data show similar efficacies for previous nSAI treatments. Although the overall PFS was worse, the median duration of CB was similar by exemestane treatment to previous nSAI treatment (10.0 vs 11.9 months). This indicates that a selected fraction of patients could achieve full benefit from sequential hormonal therapies for metastatic disease. However, few studies have examined the reverse sequence, with third-generation nSAI administered after SAI failure. One study by Bertelli et al. (2005) reported a 55% response rate in 18 patients who received anastrozole or letrozole after previous exposure to exemestane. Although the exact mechanism has not been clarified, the binding of the SAI to different parts of the aromatase enzyme, the kinetics of reversibility, and an androgen-agonistic effect exerted by SAI potentially explain the lack of cross-resistance (Lonning, 2009).

The clinical factors that predict a greater likelihood of a response to hormonal therapy are positivity of ER and/or PgR, age, menopausal status, soft-tissue disease, longer DFI, and a previous response to hormonal therapy (Santen et al., 1990; Muss, 1992). Few data are available regarding the response association between exemestane and nSAIs, although tamoxifen responsiveness is thought to be an important predictor of subsequent endocrine responsiveness (Santen et al., 1990; Muss ,1992; Kurebayashi et al., 2000). In a phase II study of exemestane given as the third- or fourth-line therapy, Lønning et al. (2000) showed that the efficacy of exemestane in 241 patients depended on their response to the previous hormonal therapy. CBR was 25.2% in patients who received clinical benefit from the previous hormonal therapy and 24.7% in patients who did not. The previous hormonal therapies included aminoglutethimide in 56.4%, anastrozole in 19.1%, letrozole in 16.6%, and vorozole in 7.9% of patients. The data suggest that previous responses to hormonal therapy do not predict the response to subsequent hormone therapy. In the present study, whereas the CBR achieved with exemestane was 24.6% in patients who had achieved CB with previous nSAI, it was 44.4% in those patients who had not achieved CB with the previous nSAI. The median PFS tended to be also longer in patients who had not achieved CB than in those who had. Two inferences can be drawn from these findings. First, the overall efficacy of exemestane is modest in patients who benefited fully from previous nSAI therapy. It is possible that prolonged treatment with nSAIs results in high levels of aromatase and the resumption of estrogen biosynthesis in the presence of estrogen depletion, which may contribute to the development of resistance to exemestane (Miller et al., 2008). Second, a fair number of patients who did not benefit from previous hormone therapy achieved CB from consecutive hormonal therapy. This is most likely attributable to the differential sensitivity of individual tumors to nSAI and SAI. Structural functional studies of aromatase have demonstrated proteins that appear resistant to an SAI (formestane) while maintaining their sensitivity to nSAIs (Miller et al., 2003). Another explanation involves the androgenic properties of SAIs. A few lines of preclinical evidence have demonstrated that the estrogen depletion induced by AIs further sensitizes breast cancer cells to the antiproliferative effects of androgens, suggesting an additional and complementary

anticancer mechanism for SAIs (Macedo et al., 2006; Suzuki et al., 2007). These findings challenge the dogma that further endocrine therapy should not be offered to patients who do not show an initial response to hormonal therapy. Additional markers, including molecular biological markers, are therefore required to improve our ability to predict these responses. In a recent prospective study involving fulvestrant and exemestane after the failure of nSAI, fulvestrant and exemestane were equally active, with CBRs of approximately 32% and median times to progression (TTPs) of 3.7 months for both agents (Chia et al., 2008). However, patients who were deemed to be sensitive to the previous nSAI tended to have longer TTPs with fulvestrant than with exemestane (HR = 0.73; 99.8% CI, 0.45–1.19). The best sequence of treatment and the optimal population for hormonal therapy after the failure of nSAI are still unclear.

This study has several limitations. The data were obtained retrospectively and not all patients received exemestane consecutively to nSAI. Because the sample size was small, none of the predefined predictive factors were statistically significant.

In conclusion, exemestane showed activity in patients with progression after previous treatment with nSAIs. The OS was better in the patients with CB from exemestane. Whereas the efficacy of exemestane was worse in patients who had fully benefited from previous nSAI, a fair number of patients who had not benefited from nSAI achieved CB with exemestane. Further study is required to clarify the optimal population for the receipt of sequential hormonal therapy.

References

BBertelli G, Garrone O, Merlano M, et al (2005). Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology*, **69**, 471-7.

Bonneterre J, Thurlimann B, Robertson J F, et al (2000). Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol,* **18**, 3748-57.

Chia S, Gradishar W, Mauriac L, et al (2008). Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol,* **26**, 1664-70.

Chin Y S, Beresford M J, Ravichandran D, et al (2007). Exemestane after non-steroidal aromatase inhibitors for post-menopausal women with advanced breast cancer. *Breast*, **16**, 436-9.

Gennatas C, Michalaki V, Carvounis E, et al (2006). Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on letrozole or anastrozole. A phase II trial conducted by the Hellenic Group of Oncology (HELGO). *Tumori,* **92**, 13-7.

Kurebayashi J, Sonoo H, Inaji H, et al (2000). Endocrine therapies for patients with recurrent breast cancer: predictive factors for responses to first- and second-line endocrine therapies. *Oncology*, **59**, Suppl 1, 31-7.

Lonning P E (2009). Lack of complete cross-resistance between different aromatase inhibitors; a real finding in search for an explanation? *Eur J Cancer*, **45**, 527-535.

Lonning P E, Bajetta E, Murray R, et al (2000). Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol,* **18**, 2234-44.

Macedo L F, Guo Z, Tilghman S L, et al (2006). Role of androgens on MCF-7 breast cancer cell growth and on the inhibitory effect of letrozole. *Cancer Res*, **66**, 7775-82.

McShane L M, Altman D G, Sauerbrei W, et al (2005). Reporting recommendations for tumor marker prognostic studies. *J Clin Oncol*, **23**, 9067-72.

Miller W R, Anderson T J, Evans D B, et al (2003). An integrated view of aromatase and its inhibition. *J Steroid Biochem Mol Biol,* **86**, 413-421.

Miller W R, Bartlett J, Brodie A M, et al (2008). Aromatase inhibitors: are there differences between steroidal and nonsteroidal aromatase inhibitors and do they matter? *Oncologist*, **13**, 829-37.

Mouridsen H, Gershanovich M, Sun Y, et al (2003). Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol,* **21**, 2101-9.

Muss H B (1992). Endocrine therapy for advanced breast cancer: a review. *Breast Cancer Res Treat*, **21**, 15-26.

Nabholtz J M, Buzdar A, Pollak M, et al (2000). Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol*, **18**, 3758-67.

Nam B H, Kim S Y, Han H S, et al (2008). Breast cancer subtypes and survival in patients with brain metastases. *Breast Cancer Res*, **10**, R20.

Paridaens R J, Dirix L Y, Beex L V, et al (2008). Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol*, **26**, 4883-90.

Santen R J, Manni A, Harvey H, et al (1990). Endocrine treatment of breast cancer in women. *Endocr Rev*, **11**, 221-65.

Smith I E, Dowsett M (2003). Aromatase inhibitors in breast cancer. *N Engl J Med*, **348**, 2431-42.

Steele N, Zekri J, Coleman R, et al (2006). Exemestane in metastatic breast cancer: effective therapy after third-generation non-steroidal aromatase inhibitor failure. *Breast*, **15**, 430-6.

Suzuki T, Miki Y, Moriya T, et al (2007). 5Alpha-reductase type 1 and aromatase in breast carcinoma as regulators of in situ androgen production. *Int J Cancer*, **120**, 285-91.

Therasse P, Arbuck S G, Eisenhauer E A, et al (2000). New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*, **92**, 205-16.