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Patterns of spread and prognostic implications of lung cancer metastasis in an era of driver mutations

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ABSTRACT

Background In the present study, we examined the pattern of metastatic spread in patients with advanced non-small-cell lung cancer (NSCLC) and the effect of *EGFR* mutations.

Methods Patients were identified from a provincial cancer registry, and individual medical records were reviewed. Patients were included if they had stage IV NSCLC and underwent diagnostic *EGFR* mutation testing. Patients were divided into *EGFR* mutation-positive (*EGFR*+) and *EGFR* wild type (WT) cohorts. The primary endpoint was the cumulative incidence for each metastatic site: lung, bone, brain, liver, adrenal glands, distant nodes, and other. Cumulative incidence curves were estimated using a competing-risks method. The secondary outcome was survival.

Results Of the 543 identified patients, 121 (22.3%) tested as *EGFR*+, and 422 (77.7%) tested as *EGFR* WT. The incidence of brain (39.2% vs. 28.2%, $p = 0.038$) and lung (61.2% vs. 51.0%, $p = 0.048$) metastasis was higher in the *EGFR*+ cohort than in the *EGFR* WT cohort. In the *EGFR*+ cohort, a higher incidence of liver metastasis was associated with the exon 21 mutation subtype than with the exon 19 deletion subtype [23% vs. 7%, $p < 0.01$; hazard ratio (HR): 3.47]. Median survival was significantly longer for the *EGFR*+ cohort than for the *EGFR* WT cohort (22.4 months vs. 7.9 months, $p < 0.001$). In multivariable analysis, brain (HR: 1.73), liver (HR: 1.69), and bone (HR: 1.89) metastases were associated with worse survival.

Conclusions Rates of lung and brain metastases are higher in *EGFR* mutation carriers, even when adjusted for differences in survival. Brain, liver, and bone metastases are independent negative prognostic factors for survival.

Key Words *EGFR*, lung cancer, metastasis behaviour, population studies

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INTRODUCTION

The pattern of disease spread in non-small-cell lung cancer (NSCLC) has been described in several historic series[1,2]. Lung, bone, liver, and brain are frequent sites of metastatic involvement in cancer, and various hypotheses have attempted to explain this particular disposition. Paget[3] proposed that a hospitable environment at the metastatic site is most important for disease spread. Ewing[4] theorized that metastatic distribution relates to lymphatic or vascular flow patterns. Hellman and Weichselbaum[5] suggested that tumours gradually acquire the properties necessary for efficient and widespread metastatic spread, and that the likelihood, number, and sites of metastases might reflect the state of tumour development. Other factors are likely inherent to the biology of primary tumour. With the discovery of driver mutations, such as those affecting the epidermal growth factor receptor (EGFR), tumour genetics could play a significant role in metastatic behaviour.

The EGFR transmembrane receptor tyrosine kinase is involved in signal transduction, regulation of DNA synthesis, and cell proliferation. Mutations in the *EGFR* gene can result in constitutive activation of the tyrosine kinase that can lead to tumourigenesis[6]. Exon 19 deletions and

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exon 21 mutations account for 90% of the identified *EGFR* driver mutations. In NSCLC, overexpression of EGFR has an impact on the biologic behaviour of the disease, affecting survival and treatment response with EGFR tyrosine kinase inhibitors (TKIs)[7–9].

The presence of an *EGFR* mutation could have a significant effect on the pattern of metastatic disease spread. Further, differences in metastatic disposition could have a differential effect on morbidity and mortality. The aim of the present study was to examine the patterns of metastatic spread in NSCLC and whether it varies by *EGFR* mutation status. The resulting information could help to anticipate disease behaviour and to direct investigations or tailor therapy.

METHODS

Patient Selection

Patients for the years 2010–2012 were identified from a provincial (British Columbia) cancer registry. Patients were included if they had NSCLC that was stage IV at initial diagnosis (American Joint Committee on Cancer staging manual, 7th edition) and had undergone conclusive *EGFR* mutation testing. Patients were excluded if their histology was squamous or neuroendocrine. The study start date (2010) was set for the point at which *EGFR* mutation testing was available at our institution. Individual medical records were reviewed to obtain patient characteristics, disease characteristics, and locations of metastasis from the time of initial diagnosis to the time of death. Diagnostic imaging reports were used to identify the locations of metastatic sites and the time at which they were first detected. Diagnostic imaging was performed at the discretion of the treating physician and as clinically indicated. The study was approved by the institutional ethics review board of the BC Cancer Agency.

Mutation Analysis

The study population was divided into those who were *EGFR* mutation–positive (*EGFR*+), and those who were *EGFR* wild type (WT). The *EGFR*+ cohort was further divided into exon 19 deletion and exon 21 mutation subgroups. Analysis of *EGFR* exon 19 in-frame deletions and exon 21 point mutations were performed with a minimum of 400 ng genomic DNA using polymerase chain reaction testing (the technique previously reported by Pan *et al.*[10]).

Study Endpoints

The primary endpoint was the cumulative incidence for each metastatic site. The secondary endpoints were overall survival (OS) and the prognostic implication of the site of metastasis.

Statistical Analysis

The Fisher exact and Kruskal–Wallis rank-sum tests were used to compare patient and disease characteristics between the *EGFR*+ and *EGFR* WT cohorts (categorical and continuous variables respectively). The time to metastasis was measured from the date of pathology diagnosis to the date of diagnostic imaging demonstrating metastasis at a given site. Cumulative incidence curves were estimated for each metastatic site by the competing-risks method. In the estimation of incidence, patient death before the development of metastasis at a given site was considered a competing-risk event. Patients who had not developed metastasis at a given site and had not died were censored at the time of last follow-up. Differences in the cumulative incidence curves between the two cohorts were assessed using the Gray test.

The associations between metastasis at a given site, *EGFR* mutation status, and patient characteristics were assessed using a proportional sub-distribution hazards model (Fine–Gray model). Overall survival was estimated by the Kaplan–Meier method and was compared using the log-rank test. The associations between OS, *EGFR* mutation status, and metastatic sites were assessed using a Cox proportional hazards model. Metastasis was treated as a time-dependent variable in the Cox regression analyses, in which the metastatic site was taken into account only after the date of diagnostic imaging demonstrating metastasis at that site. The model was tested for multicollinearity by estimating the variance inflation factor of the various variables. All reported p values are two-sided, with a p value less than 0.05 being set as the level of significance. Cox regression analysis was used to compute HRs with associated confidence intervals (CIs). All CIs are reported at 95%. Analyses were performed in the R software environment (version 2.1.5: The R Foundation, Vienna, Austria).

RESULTS

Patients

The initial search of the provincial cancer registry identified 1373 patients with stage IV NSCLC. After 746 patients without *EGFR* mutation testing and 84 with non-diagnostic results had been excluded, 543 patients were eligible for study. In the study group, 121 patients (22.3%) had *EGFR*+ cancers, and 422 (77.7%) had *EGFR* WT disease. In the *EGFR*+ cohort, 73 cancers (60%) had exon 19 deletions, and 48 (40%) had exon 21 mutations. Median follow-up duration for living patients was 34.9 months.

Table I presents baseline patient characteristics. Median age and sex were not different between the *EGFR* cohorts. A greater proportion of patients of Asian ethnicity and non-smokers had *EGFR*+ cancers. The proportions of patients who received any systemic therapy (chemotherapy or EGFR TKI, or both) were different in the *EGFR*+ and *EGFR* WT cohorts (90% vs. 50%, $p < 0.001$). The use of an EGFR TKI was significantly associated with *EGFR* mutation status, which aligns with the approved indication for an EGFR TKI as first-line treatment for metastatic *EGFR*+ NSCLC at our institution. However, only moderate collinearity was observed between *EGFR*+ status and use of an EGFR TKI (variance inflation factor: 1.8) because some patients who tested as *EGFR* WT received treatment with an EGFR TKI, and some patients who were *EGFR*+ did not receive an EGFR TKI. The first-line EGFR TKIs used were erlotinib (56.8% of patients) and gefitinib (40.5% of patients). Chemotherapy use was not different between the *EGFR* cohorts. Standard chemotherapy regimens were platinum doublets, most frequently cisplatin–gemcitabine (29.3%), carboplatin–gemcitabine (14.2%), and carboplatin–pemetrexed (12.1%).

TABLE I Patient characteristics by *EGFR* mutation status

Characteristic	Overall	*EGFR* WT	*EGFR*-positive	*p* Value
Patients (*n*)	543	422	121	
Age at diagnosis (years)				
Median	66	67	66	0.75[a]
IQR	58–74	58–73	55–77	
ECOG PS [*n* (%)]				
0	23 (4)	14 (3)	9 (7)	0.008[b]
1	229 (42)	166 (39)	63 (52)	
2	160 (29)	129 (31)	31 (26)	
3	116 (21)	100 (24)	16 (13)	
4	15 (3)	13 (3)	2 (2)	
Asian ethnicity [*n* (%)]				
Yes	123 (23)	64 (15)	59 (49)	<0.001[b]
No	420 (77)	358 (85)	62 (51)	
Sex				
Women	327 (60)	247 (59)	80 (66)	0.14[b]
Men	216 (40)	175 (41)	41 (34)	
Smoking (pack–years)				
Median	21	30	0	<0.001[a]
IQR	0–40	10–40	0–5	
Chemotherapy				
Yes	267 (49)	208 (49)	59 (49)	1[b]
No	276 (51)	214 (51)	62 (51)	
EGFR TKI				
Yes	222 (41)	117 (28)	105 (87)	<0.001[b]
No	321 (59)	305 (72)	16 (13)	

[a] Calculated using the Kruskal–Wallis rank-sum test.
[b] Calculated using the Fisher exact test.
WT = wild type; IQR = interquartile range; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

Incidence of Metastases

Table II presents the 10 most frequent sites of metastasis at initial diagnosis. The metastatic sites were lung (including pleura), bone (including vertebral spine), brain (including intracranial leptomeninges), liver, adrenal glands, distant (extrathoracic) lymph nodes, soft tissue, pericardium, spleen, and kidney. At presentation, no difference in metastatic involvement for any organ site was observed for the *EGFR*+ and EGFR WT cohorts. Of the patients overall, 323 (59.5%) presented with a single-organ site of metastasis, and 220 (40.5%), with multiple organ metastases.

Table II also presents the 3-year cumulative incidence rates for each metastatic site. The most common sites of metastasis were lung, bone, and brain (in 53%, 40%, and 31% of patients respectively). The cumulative incidences for lung (61.2% vs. 51.0%, $p = 0.048$) and brain (39.2% vs. 28.2%, $p = 0.038$) metastasis were significantly higher in the *EGFR*+ cohort than in the *EGFR* WT cohort. With respect to the other metastatic sites, the incidence of metastatic involvement was not significantly different between the cohorts.

TABLE II Metastatic sites: frequency at initial diagnosis and three-year cumulative incidence rate[a] by *EGFR* mutation status

Site	Frequency							Cumulative incidence (%)						
	Overall		*EGFR* WT		*EGFR*-positive		*p* Value[b]	Overall		*EGFR* WT		*EGFR*-positive		*p* Value[c]
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)		Rate	95% CI	Rate	95% CI	Rate	95% CI	
Lung	287	52.9	215	50.9	72	59.5	0.10	53.2	48.9 to 57.3	51.0	46.1 to 55.6	61.2	51.8 to 69.2	0.048
Bone	211	38.9	167	39.6	44	36.4	0.60	40.4	36.2 to 44.5	40.8	36.1 to 45.4	38.9	30.2 to 47.6	0.65
Brain	118	21.7	89	21.1	29	24.0	0.53	30.7	26.8 to 34.6	28.2	23.9 to 32.6	39.2	30.4 to 47.9	0.038
Liver	62	11.4	48	11.4	14	11.6	1.00	12.4	9.8 to 15.3	12.1	9.2 to 15.4	13.2	7.9 to 20	0.74
Adrenal gland	59	10.9	49	11.6	10	8.3	0.41	11.1	8.6 to 13.9	11.9	9 to 15.1	8.3	4.2 to 14	0.27
Distal nodes	56	10.3	44	10.4	12	9.9	1.00	10.7	8.3 to 13.5	10.9	8.2 to 14.2	9.9	5.4 to 16	0.75
Soft tissue	22	4.1	17	4.0	5	4.1	1.00	4.8	3.2 to 6.8	4.8	3 to 7.1	5.0	2 to 9.9	0.93
Pericardium	15	2.8	10	2.4	5	4.1	0.34	3.1	1.9 to 4.9	2.6	1.4 to 4.5	5.0	2 to 9.9	0.19
Spleen	6	1.1	4	0.9	2	1.7	0.62	1.1	0.5 to 2.3	0.9	0.3 to 2.3	1.7	0.3 to 5.3	0.51
Kidney	2	0.4	1	0.2	1	0.8	0.40	0.4	0.1 to 1.3	0.2	0 to 1.3	0.8	0.1 to 4.1	0.35

[a] Estimated using a competing-risks method.
[b] Calculated using the Fisher exact test.
[c] Calculated using the Gray test.
WT = wild type; CI = confidence interval.

In an analysis of the 6-month incidence rates for each metastatic site (full data not shown), the findings were the same, with lung ($p = 0.048$) and brain ($p = 0.038$) metastasis being higher in the *EGFR*+ cohort. Within the *EGFR*+ cohort, the incidence of liver metastasis was significantly higher in patients with an exon 21 mutation than in those with an exon 19 deletion (23% vs. 7%, $p < 0.01$; HR: 3.47). No other differences in metastatic spread were observed between the exon subtypes.

Survival

Median OS duration was 22.4 months for the *EGFR*+ cohort and 7.9 months for the *EGFR* WT cohort ($p < 0.001$). Figure 1 presents a forest plot of the univariable and multivariable analyses for OS. In the multivariable analysis, *EGFR*+ status ($p < 0.001$; HR for death: 0.58), younger age ($p = 0.05$; HR: 0.86), chemotherapy use ($p < 0.001$; HR: 0.57), and use of EGFR TKI ($p < 0.001$; HR: 0.63) were significant factors for longer survival. Poor functional status was significant for worse survival ($p < 0.001$). Female sex was significant for survival in the univariable analysis, but not in the multivariable analysis ($p = 0.13$). In the multivariable analysis, the development of brain ($p < 0.001$; HR: 1.73), bone ($p < 0.001$; HR: 1.89), and liver ($p < 0.001$; HR: 1.69) metastasis was significant for worse survival.

In a multivariable analysis including only *EGFR*+ patients, the only metastatic site significant for worse survival was liver ($p < 0.04$; HR: 1.83). For the study population, the median survival durations after a diagnosis of brain, bone, and liver metastasis were 6.5 months (CI: 5.1 to 8.6 months), 7.9 months (CI: 6.1 to 9.8 months), and 4.3 months (CI: 3.1 to 9.8 months) respectively. Figure 2 shows survival after a diagnosis of brain, bone, liver, and lung metastasis by *EGFR* mutation status. In the figure, patients represented on each Kaplan–Meier curve might have had more than 1 site of metastasis, and patients with multiple metastases might be represented on more than one curve. In a time-dependent Cox regression analysis, no difference in survival was observed for single compared with multiple organ sites of metastasis.

DISCUSSION

To our knowledge, the present study is the largest to use a cohort of patients of mixed Asian and non-Asian ethnicity to examine the metastatic behaviour of NSCLC and the influence of *EGFR* mutations. Our study also examined patient subgroups by metastasis site and treatment type to identify factors associated with survival. Based on clinical evaluation, the metastatic sites of highest incidence for both *EGFR* cohorts were lung, brain, and bone. Those sites are likely to have the greatest clinical impact in terms of management resources during the course of a patient's advanced disease.

Differences in the pattern of metastatic spread are observed depending on *EGFR* mutation status. We observed a higher cumulative incidence of lung and brain metastasis in the *EGFR*+ cohort compared with the *EGFR* WT cohort. That observation supports emerging evidence suggesting characteristic differences in metastases from *EGFR*+ cancers compared with those from EGFR WT cancers. For instance, Laack *et al.*[11] described a miliary pattern of pulmonary metastasis strongly associated with *EGFR* exon 19 deletion in 5 patients. Sekine *et al.*[12] reported that patients with exon 19 deletion were more likely to have multiple and smaller brain metastases. Our study found a significant

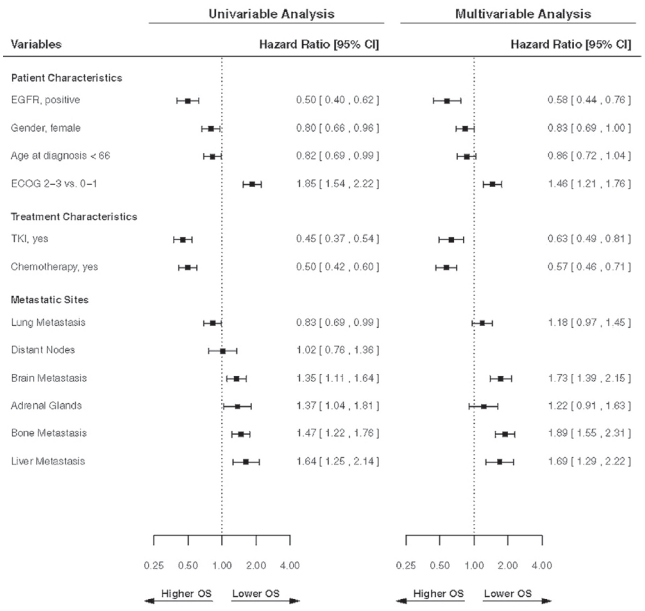

FIGURE 1 Forest plots showing the univariable and multivariable analyses for overall survival (OS). Hazard ratios were estimated in a Cox proportional hazards regression model. The multivariable analysis was limited to variables that showed significance in the univariate analysis. All metastatic sites were analyzed as time-dependent variables. CI = confidence interval; EGFR = epidermal growth factor receptor; ECOG = Eastern Cooperative Oncology Group; TKI = tyrosine kinase inhibitor.

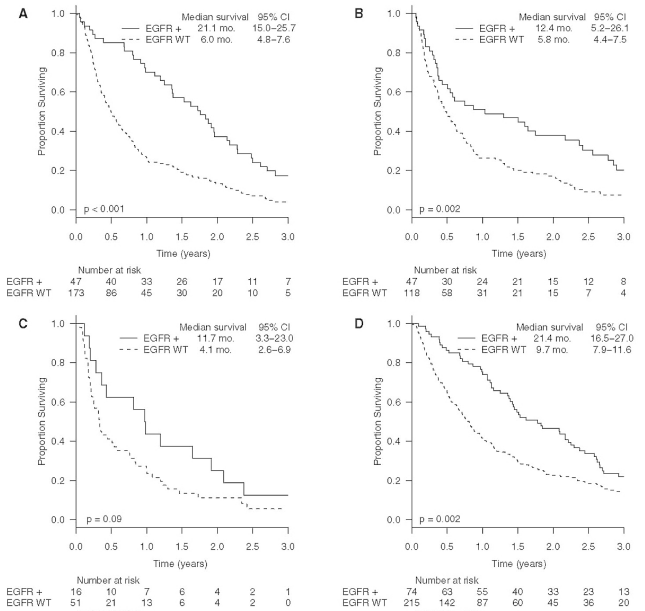

FIGURE 2 Kaplan–Meier curves showing survival after the diagnosis of (A) bone, (B) brain, (C) liver, and (D) lung metastases by *EGFR* mutation status. CI = confidence interval; WT= wild-type.

difference in the incidence of liver metastasis between the *EGFR* exon 19 deletion and exon 21 mutation subtypes. One explanation is a predisposition for liver spread in exon 21–mutant disease. An alternative explanation comes from case reports associating exon 19 deletion with a particular pattern of tiny and innumerable metastases in lung and brain resembling a miliary pattern[11–13]. A presentation of that kind in the liver would make the metastases more difficult to detect on computed tomography or magnetic resonance imaging[14] and could explain our finding of fewer liver metastases in our exon 19 subgroup. Future studies using detailed and dedicated liver imaging will be needed to investigate that hypothesis. The results from our study could affect surveillance strategies for brain or liver depending on *EGFR* mutation status.

Compared with their *EGFR* WT counterparts, patients with *EGFR*+ NSCLC experience longer survival and therefore a longer period at risk for metastatic spread. We used the competing-risks method to adjust for the difference in survival duration between the cohorts, with death as a competing-risk event. Compared with the Kaplan–Meier method, the competing-risks method provides a better estimation of incidence when death rates are high[15,16]. Our findings using that analysis methodology make it likely that the underlying biology of *EGFR* mutation is responsible for the differences in incidence. Further, the differences in incidence for lung and brain metastasis were seen at 6 months, indicating that the competing-risks curves separate early for the *EGFR*+ and *EGFR* WT patients during the course of their disease. Additionally, if the higher incidence for lung and brain metastasis came solely from longer survival, it would be expected that the incidences for most other metastatic sites would be higher as well, and heightened metastasis at those sites was not observed.

We also looked at the differential effect of metastasis on outcomes. Lung metastasis was most frequent in our population, but our analysis did not find that patients with lung metastasis did significantly worse than patients without metastasis at that site. That observation could be the result of a better systemic therapy response for malignant lung disease or available options for focused treatment with radiotherapy. In contrast, the incidence of liver metastasis was notably lower, and patients with liver involvement experienced significantly worse survival. In fact, patients with liver metastasis were seen to have the shortest survival duration after diagnosis. That finding is congruent with other NSCLC series reporting that liver metastasis predicts for poor survival[17,18].

Brain and bone metastasis were both common and independent negative prognostic factors. Other literature about brain and bone metastasis in NSCLC support that finding[19–21]. As an adverse prognostic event, bone metastasis could relate to secondary complications such as pathologic fracture, spinal cord compression, and morbidity from other skeletal-related events. Another possibility is less sensitivity to cytotoxic therapy than is seen with visceral organ metastasis[22].

We also investigated how survival relates to the number of metastatic sites. In our analysis, the specific organ of metastatic involvement and not the number of sites involved is significantly associated with survival.

Our findings complement results from prior autopsy series[23,24]. However, a clinically-based study such as ours has advantages over post-mortem data. Our analyses were able to examine metastasis at various sites as time-dependent variables, allowing for a better evaluation of metastasis as a prognostic factor. Furthermore, autopsy studies are more likely to capture micrometastatic disease that might not be clinically significant.

As in all retrospective analyses, interpretation of the results is limited by bias. Many of the patients in our population were excluded from the study because they had not undergone *EGFR* mutation testing. It is possible that exclusions could have affected the accounting of metastatic spread. However, the large size of the two *EGFR* cohorts makes it less likely that our findings are a result of chance. We examined only *EGFR* mutations because of the available data at our institution. It is possible that other driver mutations also affect the pattern of metastatic spread. However, the frequencies of other driver mutations are comparatively low, and multiple driver mutations are rarely found concurrently in the same tumour.

Given the retrospective nature of our study, diagnostic imaging was obtained at the discretion of the treating physician; no routine interval imaging was performed. It is possible that asymptomatic or small-volume metastasis during the patient's disease trajectory was not detected. Nonetheless, it is unlikely that any future prospective study examining metastatic behaviour in a time-dependent model with routine imaging protocols would be undertaken in this palliative population. Treatment with chemotherapy or EGFR TKI could affect patterns of spread such that they become different from the natural history of the disease. With that caveat, our study reports real-world findings with contemporary chemotherapy regimens and molecularly-targeted agents.

Into the future, the information gained from our study could be used to help develop tools for estimating survival that consider *EGFR* mutation status and sites of metastatic spread. Current survival nomograms, such as the diagnosis-specific graded prognostic assessment for brain metastases[25], will have to be updated to account for survival differences for patients with driver mutations. Differences in the characteristics of metastasis might provide clues to the presence of driver mutations or disease behaviour.

CONCLUSIONS

The most frequent sites of metastatic spread from NSCLC are lung, brain, and bone. Mutations in *EGFR* affect the metastatic behaviour of disease, resulting in a higher incidence of lung and brain metastasis, even when adjusted for differences in survival. The incidence of detected liver metastasis is significantly different between the *EGFR* exon 19 deletion and exon 21 mutation subtypes. The effect on survival duration varies depending on the site of metastatic involvement, with the prominent negative prognostic factors being brain, liver, and bone metastasis.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: FH has received a research grant from Varian Medical Systems; AN has received a research grant and speaker honorarium from Varian Medical Systems; CH has received grants and honoraria from Boehringer Ingelheim, Eli Lilly, Roche, AstraZeneca, Bayer, and Pfizer outside the submitted work; and ADC, DA, and TT have no conflicts to disclose.

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