Impact of Provider Imaging Practices on Survival Outcomes in Advanced Ovarian Cancer

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ABSTRACT

Background: This study sought to describe how high- versus low-frequency surveillance imaging practices among providers at Memorial Sloan Kettering Cancer Center (MSKCC) impact overall survival (OS) and time to recurrence of patients with advanced epithelial ovarian cancer in first remission. **Methods:** The study cohort included patients with stage II–IV high-grade epithelial ovarian cancer diagnosed in January 2001 through January 2017 who experienced recurrence after initial platinum-based chemotherapy. To determine usual imaging practices for providers at MSKCC, median frequency of CT or MRI of the abdomen/pelvis was calculated among patients with a long-term remission (defined as at least 1 year) treated by each provider. Cox proportional hazards models were used to examine differences in OS and time to recurrence among patients treated by providers with high versus low imaging frequency practices, with additional subgroup analysis among patients with elevated CA-125 levels >35 U/mL at diagnosis. Chi-square tests were used to examine differences in the proportion of patients who enrolled in clinical trials or underwent secondary cytoreductive surgery (SCS) by imaging frequency. **Results:** A total of 543 patients were treated by providers with high imaging frequency (>1 scan every 12 months) and 141 were treated by providers with low imaging frequency (≤1 scan every 12 months). Time to recurrence was shorter among patients treated by providers with high versus low imaging frequency (18.0 vs 19.2 months; hazard ratio, 1.33; P=.003). Results were similar when restricted to patients with elevated CA-125 levels at diagnosis. There was no significant difference in OS, clinical trial enrollment, or SCS by imaging practice. **Conclusions:** Within the limitations of this retrospective analysis, patients with advanced ovarian cancer treated by high-frequency-imaging providers had earlier detection of recurrence. Future analyses in a larger population are warranted to elucidate the risks versus benefits of surveillance imaging.

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Background

The Society for Gynecologic Oncology, as part of ASCO's Choosing Wisely Campaign, recommended against routine posttreatment surveillance imaging in patients with advanced epithelial ovarian cancer in first remission due to a lack of supporting evidence that it improves outcomes.[1,2] Yet imaging, either in response to patient symptoms or for surveillance, is common in the management of patients with ovarian cancer in first remission among providers at academic medical centers.[3] In a study by Esselen et al[3] in 2016, patients treated at NCI-designated cancer centers received an average of 1.7 CT scans during a 12-month surveillance period.

Imaging in patients with advanced ovarian cancer in first remission is primarily obtained for the evaluation of new symptoms, in the presence of an increasing CA-125 level, or for routine scheduled surveillance in the absence of either symptoms or a change in CA-125 level. Routine surveillance imaging may allow for earlier detection of recurrence that can then facilitate initiation of systemic therapy before the development of complications that could preclude optimal intervention. Although recurrent ovarian cancer is rarely curable, patients often achieve durable responses to subsequent therapy. A small proportion of patients with recurrent ovarian cancer may also be candidates for secondary cytoreductive surgery (SCS) for low-volume, isolated disease, which may be missed without routine surveillance imaging. Recent data suggest that among patients with a good prognosis for resectability, SCS portends a significant progression-free survival benefit of several months, although final overall survival (OS) data are pending.[4] However, the potential disadvantages of surveillance imaging include excess costs,[3,5] intervention for inconsequential incidental findings,[6,7] and heightened patient anxiety.[8,9]

Previous studies attempted to elucidate whether earlier detection of ovarian cancer recurrence and

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intervention ultimately impact patient survival. A randomized prospective study in Europe by Rustin et al[10] in 2010 showed no difference in survival among patients who had early initiation of second-line therapy after detection of an increasing CA-125 level versus later initiation with symptomatic recurrence documented with imaging. However, it is uncertain if this analysis is generalizable to patients with ovarian cancer treated in the United States, where SCS referral is more common and second-line chemotherapy regimens differ. It also remains unclear whether intervention after the development of radiographically visible disease is more consequential than intervention based on microscopic, serologically apparent disease. In a small retrospective analysis by Tanner et al, [11] patients showed a survival benefit if their disease recurrence was detected at a regular follow-up visit versus symptomatically with an unscheduled visit or hospital admission, but the influence of routine imaging on this association was not assessed.

At Memorial Sloan Kettering Cancer Center (MSKCC), the gynecologic medical oncology group advocates routine surveillance imaging after first remission in patients with ovarian cancer, but variability in imaging practices exists. Although all providers at MSKCC monitor CA-125 levels with follow-ups every 3 months, the frequency of surveillance imaging varies. If CA-125 is a reliable biomarker, providers may choose to perform imaging only if the CA-125 level is increasing or symptoms develop, whereas other providers perform imaging at routine intervals. Patients with normal CA-125 levels at diagnosis, however, generally receive routine imaging, but the interval may differ among providers.

We hypothesized that more-frequent surveillance imaging allows for timely initiation of therapy before the development of complications, resulting in improved OS. To test this hypothesis, we sought to describe the impact on OS and time to recurrence of high- versus low-frequency surveillance imaging practices among providers at MSKCC. To do so, we first characterized typical annual imaging practices among providers within our institution among a subset of patients with remission lasting at least 1 year. We then examined whether time to recurrence and survival outcomes among patients with ovarian cancer in first remission differed by provider imaging practice.

Methods

Study Population

We included patients with stage II–IV high-grade epithelial ovarian cancer initially diagnosed in January 2001 through January 2017 treated at MSKCC. Patients were included if they developed an ovarian cancer recurrence at least 3 months after completion of 6 cycles of initial platinum-based chemotherapy. Recurrence was defined by initiation of a subsequent line of chemotherapy after completion of initial platinum-based chemotherapy. Patients were excluded if they did not complete first-line therapy or were not diagnosed with a recurrence due to death, cure, or loss to follow-up. Patients who were enrolled on a clinical trial protocol for first-line or maintenance therapy were also excluded from the analyses because the protocol would dictate imaging frequency.

Surveillance Practices for Providers

We determined usual imaging practices for each provider in the first year of follow-up after completion of chemotherapy among the subpopulation of patients with a time to recurrence of at least 1 year. The cohort was restricted to patients with a remission of at least 1 year in order to have a sufficient time period to assess providers' typical imaging practice. Imaging among patients experiencing a cancer recurrence <1 year after completion of chemotherapy may not reflect usual provider practices because of the short window of observation. Alternatively, in the case of a prolonged remission (such as ≥ 2 years), providers may ultimately decrease the frequency interval of imaging. One year of remission for ovarian cancer is a sufficient time frame to determine a provider's tendency to order imaging (eg, every 3 months, every 6 months, annually, or not routinely). Because patients at our institution may transfer care after initial consultation to providers at MSKCC regional centers, primary providers were assigned to each patient using an algorithm to distinguish the oncologist who had the most frequent appointments with the patient in follow-up. Cancer-related follow-up is rarely, if ever, shared with an outside provider, particularly in the first year of follow-up. During this period, we expect that patients receive surveillance imaging within our institution and not through an outside provider or hospital.

Frequency of unique events for CT or MRI of the chest, abdomen, and/or pelvis in the year after completion of first-line chemotherapy was calculated for patients beginning 1 month after completion to exclude standard postchemotherapy imaging. Any combination of imaging within 7 days of each other was counted as 1 scan. Excluded images were chest radiographs, abdominal radiographs, and brain CT/MRI scans. For each provider, the median number of scans per year was calculated among all patients treated by that provider. Although counted imaging also included imaging tests obtained for the evaluation of symptoms or increasing CA-125 levels, we assumed that this practice was similar among MSKCC providers and thus variability in imaging frequency would be primarily attributed to differences in surveillance imaging practices.

Statistical Analyses

Provider imaging practices were dichotomized as high versus low based on clinically relevant cut points. Kaplan-Meier estimates and Cox proportional hazards models were used to examine differences in median OS and median time to recurrence in the overall cohort of patients treated by providers with high- versus low-frequency imaging practice. Patients who subsequently enrolled in clinical trials after recurrence were excluded from the OS analysis. A chi-square test was used to examine differences in the proportion of patients enrolled on clinical trials and the proportion of patients who underwent SCS by imaging practices. Characteristics between patients treated by high- versus low-frequency imaging providers were compared using chi-square tests for discrete variables and *t* tests for continuous variables. Because CA-125 monitoring may impact imaging frequency, we performed a secondary analysis restricted to only patients with elevated CA-125 levels at diagnosis. Provider imaging practices were reevaluated in the restricted cohort using the same methodology as described earlier, and median OS and time to recurrence by imaging practice were recalculated.

Results

A total of 684 patients with advanced ovarian cancer were included in the overall analysis (Figure 1). Most patients had stage III or IV (97.5%) cancer, and 89% had elevated CA-125 levels at diagnosis. Four patients had endometrioid adenocarcinoma and 680 patients had serous adenocarcinoma. No patients had clear-cell carcinoma.

Median frequency of imaging for providers calculated among patients with time to recurrence of at least 1 year (n=294) was 2 scans per year (1 scan every 6 months), with a range from 1 scan per year (1 scan every 11.9 months) to 4.1 scans per year (1 scan every 2.9 months) (Figure 2). Providers were dichotomized as high imaging frequency (>1 scan per year; 23 providers, 543 patients) versus low imaging frequency (≤1 scan per year; 4 providers, 141 patients). There was no significant difference in age (mean, 63 years for high vs 62 years for low; *P*=.20), stage, histology, or proportion of patients with elevated CA-125 at diagnosis between the high- and the low-imaging-frequency groups (Table 1).

Time to recurrence was significantly shorter among patients treated by providers with high versus low imaging frequency (Figure 3; 18.0 vs 19.2 months; hazard ratio [HR], 1.33; 95% CI, 1.10–1.60; *P*=.003). No significant difference was seen in OS among patients treated by providers with high versus low imaging frequency (Figure 4; 51.8 vs 60.7 months; HR, 1.10; 95% CI, 0.87–1.37; *P*=.43). There were 247 patients in our study population who enrolled in a clinical trial for treatment of recurrent disease and were excluded from the OS analysis. No difference was seen in clinical trial enrollment among patients treated by providers with high versus low imaging frequency (low, 29.8%; high, 37.8%; *P*=.10), and no difference was seen in the proportion of patients undergoing SCS (low, 12.0%; high, 10.4%; *P*=.77).

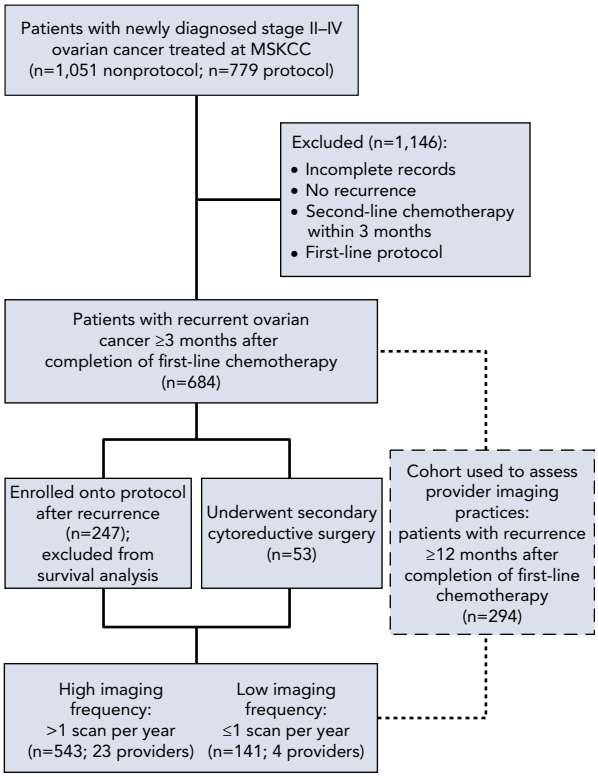

Figure 1. Patient selection flow diagram.
Abbreviation: MSKCC, Memorial Sloan Kettering Cancer Center.

In the analysis restricted to patients with elevated CA-125 levels at diagnosis (n=606), results were similar. Time to recurrence remained shorter among patients treated by providers with high versus low imaging frequency (HR, 1.30; 95% CI, 1.03–1.61; *P*=.02), whereas no significant difference in OS was seen between the groups (HR, 1.2; 95% CI, 0.89–1.62; *P*=.20).

Discussion

This study examined variability in surveillance imaging practices among providers at MSKCC and assessed its impact on outcomes in patients with advanced ovarian cancer. Within the limitations of this retrospective analysis, we found that patients treated by providers with high imaging frequency had earlier detection of recurrence as expected, but there was no evidence of improved OS. In addition, the proportion of patients who subsequently enrolled on clinical trials or underwent SCS was similar among those treated by providers with high versus low imaging frequency. In patients whose CA-125

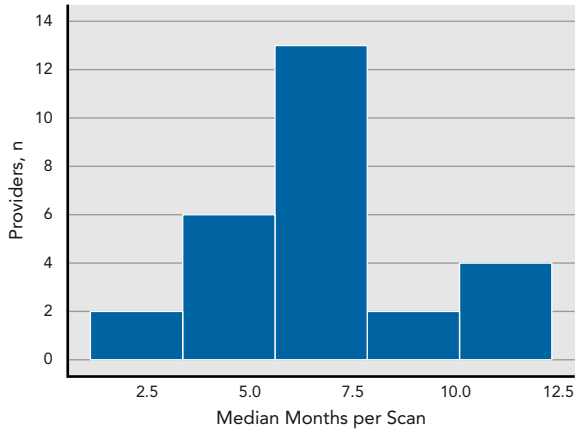

Figure 2. Provider imaging frequency among patients with advanced ovarian cancer with remission lasting ≥12 months.

level is elevated at diagnosis, providers may monitor these levels to inform the decision for imaging and reduce reliance on routine scans. Given the influence of this biomarker on imaging practices, we restricted our analysis to patients with elevated CA-125 levels at diagnosis and found no difference in the results.

We were unable to differentiate which scans were specifically for surveillance and which were prompted by symptoms or increasing CA-125 levels; however, the subset of patients used to determine imaging practices had prolonged remission, and scanning based on increasing CA-125 levels or symptoms was similar among providers at MSKCC, thus the observed variability was expected to result from differences in surveillance. This variation illustrates the debate in the field regarding the appropriate surveillance strategy in patients with ovarian cancer who experience a complete response after initial therapy.

The goal of surveillance imaging after primary cancer therapy is to identify asymptomatic disease, based on the assumption that earlier intervention has a favorable impact on cancer morbidity or mortality. The published literature to date regarding the optimal surveillance approach is limited and has mixed findings. Our results are consistent with those of Rustin et al,[10] demonstrating that earlier detection of recurrent disease, biochemically or radiographically, does not confer a survival advantage despite earlier intervention. In contrast, a retrospective analysis by Tanner et al[11] showed that symptomatic recurrence leading to an unscheduled appointment or hospitalization was associated with worse survival compared with detection through routinely scheduled examination, CA-125 monitoring, and/or imaging among patients treated at 2 US academic cancer centers. Optimal SCS was more often performed in the asymptomatic group as well.[11] However, the impact of

Table 1. Characteristics of Patients Treated by Providers With High Versus Low Imaging Frequency

	High Imaging Frequency (>1 Scan/Year) n (%)	Low Imaging Frequency (≤1 Scan/Year) n (%)	*P* Value
Total, n	543	141	
Mean age, y	63	62	.20
Stage at diagnosis			.47
II	12 (2.2)	5 (3.5)	
III	347 (63.9)	94 (66.7)	
IV	184 (33.9)	42 (29.8)	
Histology			1.00
Serous	540 (99.4)	140 (99.3)	
Endometrioid	3 (0.6)	1 (0.7)	
Clear	0 (0)	0 (0)	
CA-125 level at diagnosis			.36
>35 U/mL	487 (89.7)	122 (86.5)	
≤35 U/mL	56 (10.3)	19 (13.5)	

routine surveillance imaging, common in the study population, on prevention of symptomatic recurrences diagnosed at an unscheduled visit or on the rates of SCS could not be assessed, and it is possible that the survival differences reported were primarily caused by disease biology.

Median imaging frequency in our study (every 6 months, or 2 scans per year) was higher than at other NCI-designated cancer centers among patients with ovarian cancer.[3] Most patients with ovarian cancer experience recurrence after first-line therapy, and predictive factors for recurrence at diagnosis before therapy are poorly defined, which likely motivates more frequent scanning due to the high-risk nature of the disease. In addition, progression-free survival in ovarian cancer is regarded as an acceptable surrogate endpoint for OS,[12] and therefore documenting time to recurrence with imaging is a critical prognostic marker.

Nonbeneficial imaging could result in harm, including unnecessary downstream procedures, increased anxiety, and higher costs of care. Evaluating the disadvantages of surveillance imaging that may supersede potential benefits is an area of future research. There may be subsets of patients with ovarian cancer who do benefit from more frequent imaging. Among candidates for maintenance PARP inhibitors after first-line chemotherapy or patients participating on clinical trials, earlier detection of cancer recurrence would reduce the duration of exposure to toxicities related to therapy. It is also possible that a survival benefit exists among patients

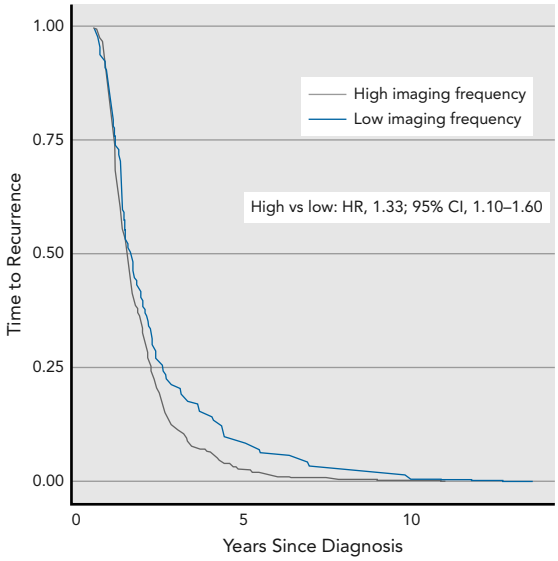

Figure 3. Time to recurrence among patients treated by providers with high- versus low-frequency imaging practices.
Abbreviation: HR, hazard ratio.

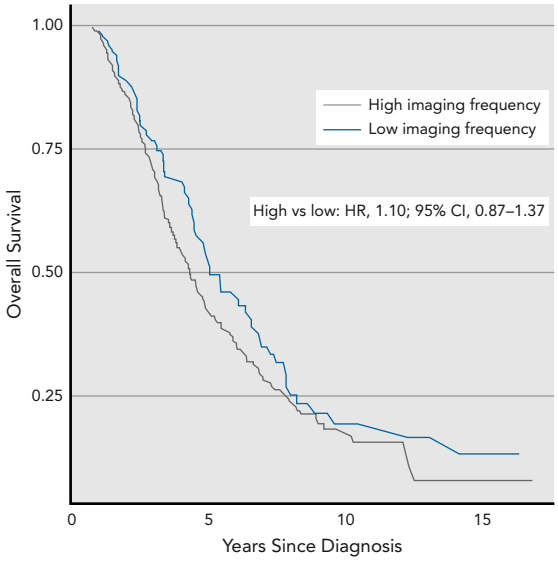

Figure 4. Overall survival among patients treated by providers with high- versus low-frequency imaging practices.
Abbreviation: HR, hazard ratio.

without an informative biomarker (eg, normal CA-125 level despite presence of disease), but sample size limitations precluded this analysis.

Our analysis has several important methodological limitations. First, it may be underpowered to detect a significant difference in survival among patients treated by providers with high versus low imaging frequency if a difference does exist. Second, this study was retrospective in nature, and patients were not randomized to high or low surveillance imaging frequency. However, there was sufficient provider variability in standard surveillance imaging practices at our institution, and patients are for the most part randomly assigned to providers based on scheduling constraints. At the same time, there could have been other unaccounted provider-specific factors associated with imaging frequency and survival that could have confounded our observed results. For example, there may have been variability among providers in the dosing frequency of paclitaxel and the use of intraperitoneal and postprogression regimens, which was not accounted for in the analysis, although this is unlikely. Third, we did not include data on the extent of original surgery, a critical prognostic factor for ovarian cancer, which may be imbalanced between the groups. Although patients with suboptimal debulking surgery may ultimately receive more frequent surveillance, the extent of debulking should not be associated with a patient's medical oncology provider in this analysis. Fourth, recurrence was categorized based on receipt of second-line chemotherapy rather than date of image-documented disease. Thus, the true date of recurrence was likely earlier in all patients but would not be differentially associated with assigned provider or imaging frequency.

Conclusions

Our findings showed that provider surveillance imaging practices varied within our institution. Imaging more than once annually did not confer a significant survival benefit compared with imaging once a year or less among patients with recurrent, advanced ovarian cancer in remission. There may be subgroups of patients who clinically benefit from more frequent scanning, and ultimately, if practice shifts toward maintenance therapy with PARP inhibitors or bevacizumab for all patients with advanced ovarian cancer, routine imaging may become the norm. Our study offers a research framework for future retrospective analyses in a larger cohort, because resources to fund prospective studies addressing this topic are unlikely. Thus, we recommend future research using a larger, multi-institutional database to further elucidate the risks versus benefits of surveillance imaging in patients with advanced ovarian cancer and to help guide practice recommendations.

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