

Give me a break: oncologists' perception of systemic treatment holidays

Fabiana M. Kreines¹, Elizabeth Will¹, Benjamin Margolis^{1,2}, Abigail Winkel¹, Leslie R. Boyd^{1,2,*}

¹Department of Obstetrics and Gynecology, New York University Langone Health, New York, NY 10016, USA

²Division of Gynecologic Oncology, Laura and Isaac Perlmutter Cancer Center, New York, NY 10016, USA

*Correspondence: leslie.boyd@nyulangone.org (Leslie R. Boyd)

DOI: [10.31083/j.ejgo4206160](https://doi.org/10.31083/j.ejgo4206160)

This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Submitted: 9 August 2021 Revised: 5 September 2021 Accepted: 14 September 2021 Published: 15 December 2021

Objective: To analyze physician opinions of, and experiences with patients who take a temporary break from treatment in the setting of metastatic primary or recurrent gynecologic cancer. **Methods:** An electronic survey was sent to the members of the Society of Gynecologic Oncology (SGO). A treatment holiday was defined as a planned temporary break from systemic treatment in a patient with recurrent or metastatic gynecologic malignancy. Descriptive statistics were calculated using Microsoft Excel, and continuous variables were compared using the Wilcoxon Rank Sum test. Free text responses were qualitatively analyzed. **Results:** Of the 1314 individuals invited to participate, 74 responded (5.6% response rate). Ninety-six percent of respondents had a patient take a treatment holiday. Ninety-five percent of respondents would offer a treatment holiday for ovarian cancer, 90% for endometrial cancer, 70% for cervical cancer, 57% for vulvar cancer, 52% for vaginal cancer, and 49% for sarcoma. Using a Likert scale, respondents identified life events (86.6%), fatigue from side effects (77.9%), schedule fatigue (67.6%) and desire for "life off treatment" (64.7%) as "very important" reasons for offering a treatment holiday. Patients resumed treatment for return of symptoms (62.9%), progression of disease (60.0%), end of pre-specified break (50%), patient anxiety (45.7%) and recommendation of the physician (11%). 6.8% of physicians experienced regret after a patient underwent a treatment holiday. Ninety-eight percent of respondents agreed that a treatment holiday can be valuable. **Conclusion:** The gynecologic and medical oncologists who responded to this survey almost uniformly offered their patients treatment holidays, were more likely to offer treatment holidays for ovarian and endometrial cancer, and were unlikely to express regret after the experience.

Keywords

Chemotherapy holiday; Gynecologic cancer; Treatment holiday

1. Introduction

Approximately 94,000 individuals are diagnosed with a gynecologic malignancy every year and many of these patients continue to live with advanced or recurrent disease [1]. The mainstay of treatment for patients with recurrent or advanced gynecologic cancer is systemic therapy which can include cytotoxic chemotherapy, biologic agents and/or immunotherapy. In the recurrent setting, systemic cancer treatments are generally palliative in nature and help achieve dis-

ease control, prolong survival, and improve quality of life. The duration of treatment in this setting is individualized and often involves extended time periods on treatment in the absence of a complete response.

In this setting, it is not uncommon for patients and physicians to make a decision to take a temporary break from treatment, often referred to as a "treatment holiday". There are a lack of data to support or advise against the decision to take a break from treatment in the setting of recurrent or metastatic gynecologic cancer. The reasons patients and their doctors elect to take treatment breaks have not been studied, but can include a desire to break from treatment schedules or treatment toxicities, planned events or vacations, or individualized reasons.

The purpose of this study is to understand physicians' decision-making process when it comes to recommending, supporting, or advising against a temporary break from cancer directed treatment in the setting of recurrent gynecologic cancer. The primary objective of this study is to analyze physician opinions of, and experiences with, patients who elect for a temporary break from treatment in the setting of metastatic primary or recurrent gynecologic cancer. The secondary objective is to analyze physicians' perceptions of patient experiences with treatment holidays.

2. Methods

A survey of physician opinions and experiences with treatment holidays in patients with gynecologic malignancies was used in this study. A treatment holiday was defined as a planned temporary break from treatment (cytotoxic chemotherapy, biologic therapy or immunotherapy) in a patient with metastatic primary or recurrent gynecologic malignancy. Our definition of treatment holiday excluded patients for whom the reason for a pause in treatment was progression of disease, switch to another treatment regimen, pursuit of hospice or best supportive care, or breach in a research protocol.

A survey of gynecologic oncology physicians was performed using an electronic mailing list obtained with permis-

sion from the Society of Gynecology Oncology. The survey was sent out to all “gynecologic oncologist” and “medical oncologist” members of the Society for Gynecologic Oncology, which included 1269 and 45 members, respectively. The survey was generated by the authors after a discussion of the relevant topics related to physician experiences with and opinions of treatment holidays. The aim was to achieve a 10–15% response rate, which would allow for analysis from approximately 130 participants. Two follow up recruitment emails after the initial email were sent to maximize participation. The survey was open to physicians for three weeks total.

The survey was created in RedCap and included multiple choice questions and free-form responses. Survey results were recorded online through the survey website and were transferred to a Microsoft Excel document for analysis. Responses were gathered both in categorical form and in free responses. Free form response questions addressed reasons for treatment holiday acceptance or refusal by patient or physician, perceived treatment holiday risks and benefits and perceived medico-legal concerns. Descriptive statistics were calculated using Microsoft Excel, and continuous variables were compared using the Wilcoxon Rank Sum test on Microsoft Excel. Free response data were analyzed by two authors (B.M., F.K). Each author separately coded free text responses inductively by assigning overarching themes to the response content. An inductive coding method was chosen due to a desire to allow unanticipated decision-making reasons to emerge from the data. Authors then reviewed codes and achieved mutual agreement on code assignments including merging of independently generated similar codes into parent codes. Authors then developed the themes through serial discussions and selected representative quotes to communicate the relevant themes.

3. Results

Of the 1314 individuals invited to participate, 74 (5.6%) completed the survey. The characteristics of respondents are displayed in Table 1. Of those who responded, 51% (38/74) self-identified as physicians at an academic institution. The remainder identified as academic-affiliated (26%, 19/74), private (13%, 10/74), military (3%, 2/74), retired (3%, 2/74), and other (4%, 3/74). Ninety-one percent (68/74) self-identified as gynecologic oncologists, 8% (6/74) as medical oncologists, and 1% (1/74) as other. Geographically, 41% of respondents (30/74) were from the Southern US, 23% (17/74) from the Northeastern states, 20% (15/74) from the Western states, and 16% (12/74) from the Midwestern states. The median number of years since fellowship of respondents was 12 years (IQR 4–24).

All respondents reported familiarity with the term “treatment holiday” or “chemotherapy holiday” as applied to patients with recurrent gynecologic cancers and 96% (70/73) reported having had a patient of theirs take a treatment holiday. The average number of patients reported on treatment at any given time was 29 (IQR 10–40). The average num-

ber of patients reported currently on treatment holiday was 2 (IQR 0–3). The average number of patients reported to have taken a treatment holiday in the last 6 months was 4 (IQR 1–5). The calculated average percentage of patients in a respondent’s practice who are currently on treatment holiday was 6.8% (IQR 0–11.8%). There was a significant difference by type of physician on the percentage of patients currently on treatment holiday (gynecologic oncologists 6.2% versus medical oncologists 20.8%, $p = 0.03$). Most respondents (83%) estimated the average length of treatment holiday was 2–3 months for all patients who previously underwent a treatment holiday. When asked about the length of the treatment holiday taken by their most recent patient, the average reported time was 4.6 months. Of the three respondents who reported not having a patient of theirs take a treatment holiday, the average years from fellowship training was 4 and two of these three respondents separately acknowledged the possible benefits of a treatment holiday, while one respondent cited no potential benefit.

Ninety-five percent of respondents (66/69) reported that they would offer a treatment holiday for ovarian cancer, 90% (62/69) for endometrial cancer, 70% (48/69) for cervical cancer, 57% (39/69) for vulvar cancer, 52% (36/69) for vaginal cancer, and 49% (34/69) for sarcoma (Fig. 1). Ninety-three percent (69/74) reported that they had suggested a patient take a treatment holiday, whereas 81% (60/74) also reported a patient had suggested one. Of note, no respondents answered that they had never suggested that a patient take a treatment holiday. Twenty-eight percent of respondents (21/74) reported that someone other than themselves or the patient had suggested a treatment holiday; Family members (spouse, child, partner, family member) were the most commonly reported as suggesting the holiday.

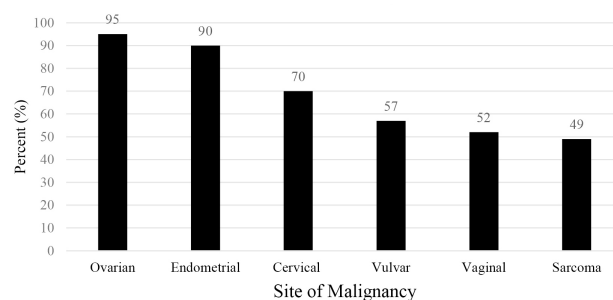


Fig. 1. Percentage of respondents who would offer treatment holiday by site of malignancy.

Using a five-point Likert scale, respondents identified life events (86.6%, 58/67), fatigue from side effects (77.9%, 53/67), schedule fatigue (67.6%, 46/67) and desire for “life off treatment” (64.7%, 44/67) as “very important” reasons their patients decided to take a treatment holiday. A thematic evaluation of free responses regarding reasons patients or physicians recommended for or against treatment holidays

Table 1. Respondent demographics and practices.

Characteristic	Number (%)
Medical training	
Gynecologic Oncologist	67 (90.5)
Medical Oncologist	6 (8.1)
Other	1 (1.4)
Practice setting	
Academic	38 (51.4)
Academic-affiliated private	19 (25.7)
Private	10 (13.5)
Military	2 (2.7)
Retired	2 (2.7)
Other	3 (4.1)
Region	
South (DE, FL, GA, MD, NC, SC, VA, DC, WV, AL, KY, MS, TN, AR, LA, OK, TX)	30 (40.5)
Northeast (CT, ME, MA, NH, RI, VT, NJ, NY, PA)	17 (23.0)
West (AZ, CO, ID, MT, NV, NM, UT, WY, AK, CA, HI, OR, WA)	15 (20.8)
Midwest (IL, IN, MI, OH, WI, IA, KS, MN, MO, NE, ND, SD)	12 (16.2)
Years of practice since fellowship	
Median (interquartile range)	12 (4–24)
Range	1–46
Percent of patients currently on treatment holiday*	
Median (interquartile range)	6.8 (0–11.8)
Number of patients in one's practice who have taken a treatment holiday in the last 6 months	
Median (interquartile range)	2.5 (1–5)
Range	0–25

*Calculated as the number of patients in a respondent's practice on a treatment holiday divided by the total number of patients reported in that respondent's practice on treatment plus the number on a treatment holiday.

and perceived risks and benefits of treatment holidays is displayed in Table 2. The two most frequently reported reasons for physicians to recommend a treatment holiday were a holiday/vacation/special life event (19/58 free text respondents) and need for a physical or mental break from treatment (14/58 free text respondents). Alternatively, the two most frequently reported reasons for patients to agree to a treatment holiday were need for a physical or mental break from treatment (44/58 free text respondents) and stable or slow-growing tumor (22/58 free text respondents). Although only three respondents cited reasons for a patient to decline a treatment holiday, all three listed anxiety as the reason. Similarly, only five respondents offered circumstances for which they disagreed with the idea for a treatment holiday suggested by a patient, and the most common reason was good response to cancer treatment (3/5 respondents). All of these physicians had patients who had previously taken treatment holidays.

Respondents reported the following were reasons their patients had resumed treatment: return of symptoms (62.9%, 44/70), progression of disease (60.0%, 42/70), end of pre-specified break (50%, 35/70), patient anxiety (45.7%, 32/70) and recommendation of physician (11%, 8/70). Qualitative analysis of responses regarding benefits of taking treatment holidays revealed the most frequently reported perceived benefit to be improved quality of life (58/65 free text respondents), including fewer visits/interventions, fewer side ef-

fects, and psychological recovery. The most frequently reported perceived risk of treatment holiday among respondents was progression of disease (46/65 free text respondents).

Only 6.8% of physicians (5/74) reported ever experiencing regret after a patient of theirs underwent a treatment holiday. The most common reason for regret was rapid progression of the patient's disease. Two of 74 respondents (3%) endorsed concerns related to medico-legal implications of patients taking a treatment holiday. Ninety-eight percent of respondents (72/74) strongly agreed or agreed to the following statement: 'A treatment holiday for an individual patient who desires a break from treatment can be valuable even though the impact on that patient's disease progression and prognosis is unknown'.

4. Discussion

This study is the first to describe factors that affect physician decision making when it comes to recommending treatment holidays in gynecologic malignancies. All respondents had heard of the term "treatment holiday" or "chemotherapy holiday". The vast majority of respondents were in favor of offering treatment holidays in the setting of recurrent gynecologic cancers, although fewer respondents were supportive of treatment holidays in vulvar cancer, vaginal cancer and sarcomas. The lowest support of a treatment holiday in sar-

Table 2. Treatment holiday decision making responses organized by theme and frequency.

Code	Free text response theme	Response frequency	Representative quotes
Reasons patients agreed to or declined treatment holiday (58 free text respondents)			
A1	Break from symptoms/psychological break	44	"If patients are truly aware of their prognosis, they are often willing to accept time off chemo for quality of life in exchange for theoretical loss of longevity. . . Most accept as it's a balance between QOL and quantity"
A2	Stable or slow-growing tumor	22	"Stable disease over many cycles but having significant side effects . . . I suggest for indolent biology tumors in which treatment effect is likely to be modest"
A3	Holiday/vacation/special life event	21	"They desire break to travel or for special events; these circumstances are usually short and only 1–2 months typically. . . . Upcoming wedding, birth of grandchild, cruise, anniversary party"
A4	Little anticipated benefit of treatment/cure not possible	9	"Goal of subsequent lines of treatment are palliative and if patient wants to take a break then she should. . . Patients with plateau of response to chemo, and some level of toxicity frequently agree to a holiday"
A5	Fatigue from office visits	3	"Tired of coming to office"
A6	Planned medical procedure	2	"Patients who have . . . other medical procedures/conditions that arise are ones where treatment holidays are suggested"
D1	Patient anxiety	3	"Patients who decline a treatment holiday typically do so because they are anxious about being off of treatment for any time at all or have mistaken beliefs about the benefit of continual therapy"
Reasons physicians agreed to or declined treatment holiday (37 free text respondents)			
A1	Holiday/vacation/special life event	19	"I have frequently had patients who want to go on vacation with their families. I always give them a month off (enough time before, during and after to avoid side effects)"
A2	Break from symptoms/psychological break	14	"I suggest for intermediate biology tumors in which the patient is experiencing appreciable treatment toxicity with only modest clinical benefit from treatment, they have always accepted"
A3	Little anticipated benefit of treatment/cure not possible	5	"Most patients with recurrent cancer have more benefit than risk of a 3–6 month treatment break"
A4	Stable or slow-growing tumor	3	"The biology of tumor seems slow growing or senescent at that time"
A5	Fatigue from office visits	1	"Fatigue from treatment schedule"
D1	Curative intent treatment	3	"I would generally disagree with any kind of holiday in first line treatment with curative intent, regardless of tumor type"
D2	Minimal side effects	1	"Responding well and minimal side effects, aka no 'need' for holiday"
Perceived risks/benefits of treatment holiday (65 free text respondents)			
B1	Better quality of life	58	"Offer a needed respite and the promise that treatment will resume once a certain condition has been met (time, progression, symptoms etc). . . Peace! Joy! Laughter! Hair growth! . . . Mental and physical well-being"
B2	Ability to travel and go to important events	8	"Ability to go on a planned vacation without side effects of chemo on board. . . Spending time with family and friends that live afar. Some form of normalcy"
B3	More perceived patient control	2	"Perceived control over treatment for a 'chronic disease'"
B4	Less creation of resistant biology	1	"Potentially less induction of resistant biology"
B5	Increased survival	1	"Sometimes live longer"
R1	Progression of disease	46	"The risk is progression that becomes symptomatic in a manner that may compromise one's ability to take future treatments . . . occasional pts will have rapid progression of disease, though I suspect they would not have benefited greatly from continuing therapy"
R2	Resistance to treatment/compromising future treatment	6	"Decreased efficacy of treatment if return to same therapy"
R3	Second guessing choice/regret	4	"Emotional risks of second guessing choice to go on holiday"
R4	Shortened survival	2	"Decreased survival if disease progression affects performance status or an organ function"
R5	Lack of predicted holiday benefit	1	"Lack of expected improvement"

QOL, quality of life; R#, risk; B#, benefit; A#, agree; D#, decline.

comas likely reflect their known aggressive behavior. In addition, there are fewer effective treatment options for sarcomas, so a delay which could promote chemotherapy resistance may be more consequential. Respondents were most comfortable offering treatment holidays for ovarian and endometrial cancer patients. This may reflect general comfort level with treating these common malignancies, and that there are a multitude of effective regimens making chemotherapy resistance a less concerning outcome. Very few respondents reported any regret in offering a holiday to their patients. Medical oncologists reported a higher percentage of patients on treatment holiday, however the total number of medical oncologist respondents was low (6) and makes this comparison subject to bias or a stochastic event.

The biggest driving factors for physicians offering treatment holidays were quality of life issues such as important life events, relief from treatment side effects, and an understanding of the risk/benefit of pausing treatment. Respondents described real world practice in their discussion of reasons they and their patients elected to proceed with treatment holidays, often raising the importance of “stable disease over many cycles” or “senescent” biology. The “balance between quality of life and quantity” was an overarching theme as respondents discussed their support of their patients attending a “wedding, birth of a grandchild, cruise, [or] anniversary party”. These priorities during treatment that lead to the joint decision to take a treatment holiday fall in line with qualitative data from a focus group of ovarian cancer patients showing that quality of life and minimization of side effects were among the most important aspects of care and were valued over incremental survival benefits [2].

Although very few respondents reported physician or patient reluctance in offering treatment holidays to patients, the most common reason for this was anxiety surrounding progression of disease. The only respondents who voiced regret in their decision to offer a treatment holiday did so because of progression of disease that was subsequently hard to control. This was also seen in the perceived risks of a treatment holiday, as concerns over “progression that becomes symptomatic... that may compromise one’s ability to take future treatments” were raised. This highlights the importance of thorough counseling for patients who take a treatment break including the possibility of disease progression off treatment and its implications.

Literature from colorectal, urologic and breast cancer addresses intermittent treatment holidays with the goal of avoiding cumulative toxicity and preserving quality of life [3–7]. Onishi *et al.* [6] studied patients with advanced urothelial carcinoma who were subjected to intermittent chemotherapy after induction chemotherapy and observed a 90% clinical benefit rate after re-introduction of chemotherapy. In prostate cancer, intermittent chemotherapy was associated with improvement of fatigue and decreased toxicity for patients without sacrificing sensitivity to treatment [7]. Randomized trials from colorectal cancer also support the use

of intermittent chemotherapy in patients with advanced, metastatic cancer [8]. In patients with metastatic breast cancer, intermittent chemotherapy administration, while it did not impact overall survival outcomes, did lead to shorter progression free intervals.

In the colorectal literature it has been proposed that treatment holidays may reduce the emergence of acquired resistance to chemotherapy [3]. Pre-clinical data in ovarian cancer raises opposite concerns. Vassileva *et al.* [4] have shown decreased efficacy to paclitaxel with intermittent administration in mouse xenograft models compared to continuous administration. In their theory, tumor repopulation between chemotherapy administration leads to a poorer response. Clinical evidence is lacking in gynecologic oncology to guide decisions with respect to treatment holidays. In a 2019 ASCO educational document that addressed maintenance chemotherapy and treatment holidays in gynecologic cancer care, no evidence was provided with regards to treatment holidays [9]. Additionally, to our knowledge, despite these few studies regarding treatment holidays in other types of malignancies, there are no data regarding decision making on this topic. The aforementioned studies do not address how physicians or patients decide whether or not to take a treatment holiday.

The small response rate observed in this survey study raises the risk of selection bias. Physicians who are familiar with and supportive of treatment holidays could have been more likely to respond to this survey leading to answers that were more likely to represent positive opinions of treatment holidays. While the lack of universal representation of the physician population is a limitation, the goal of this study was to characterize the decision making regarding offering treatment holidays. As with all survey studies, reporting bias may impact information that respondents reported from memory. For example, the majority of respondents reported an average treatment holiday duration of 2–3 months but reported an average treatment holiday duration for their most recent patient of 4.6 months. The generation of free text responses by a survey platform could also have been influenced by the content of the survey, as example reasons for treatment holiday decisions were included in the survey questions. Another limitation is the lack of the patient perspective in this work, as physician commentary on patient experience could differ from the patient perspective. There are currently no published studies to the authors’ knowledge on treatment holidays from the patient perspective, however the authors have undertaken simultaneous research on this topic which will be presented separately.

Although this study offers an important window into decision making surrounding treatment holidays for recurrent gynecologic cancers, future research is needed. This study suggests that chemotherapy holidays are common in real world clinical practice. It is important to investigate patient opinions and experiences with treatment holidays, as this study offered only physician perception of patient experi-

ences. Additionally, future studies regarding outcomes with treatment holidays in recurrent gynecologic cancers will be very important to help guide decision making both for physicians and patients.

5. Conclusions

Despite a limited sample size, this study offers valuable insight into the decision making of physicians in recommending for or against treatment holidays for gynecologic malignancies. We highlight an overall positive opinion which physicians have of treatment holidays, given that gynecologic and medical oncologists surveyed almost uniformly offer their patients treatment holidays. Oncologists were most comfortable offering treatment holidays to patients with ovarian and endometrial cancers. This is the first description of physician decision making with regards to treatment holidays in gynecologic cancer, and additional studies are needed to confirm our findings.

Author contributions

FK and BM conceived of and designed the surveys with input and guidance from LB and AW. FK and BM collected and analyzed the data. FK, EW, BM, AW, and LB prepared the manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. Completion of the survey, after explanation of the survey, implied consent to take part in the study; no protected health information of patients was used. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee at NYU Grossman School of Medicine (study number S19-01055).

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Centers for Disease Control and Prevention, US Department of Health and Human Services: Gynecologic Cancer Incidence, United States–2012–2016. U.S. Cancer Statistics Data Brief: Atlanta, GA. 2019. No 11.
- [2] Frey MK, Philips SR, Jeffries J, Herzberg AJ, Harding-Peets GL, Gordon JK, *et al.* A qualitative study of ovarian cancer survivors' perceptions of endpoints and goals of care. *Gynecologic Oncology*. 2014; 135: 261–265.
- [3] Tonini G, Imperatori M, Vincenzi B, Frezza AM, Santini D. Rechallenge therapy and treatment holiday: different strategies in management of metastatic colorectal cancer. *Journal of Experimental & Clinical Cancer Research*. 2013; 32: 92.
- [4] Vassileva V, Allen CJ, Piquette-Miller M. Effects of sustained and intermittent paclitaxel therapy on tumor repopulation in ovarian cancer. *Molecular Cancer Therapeutics*. 2008; 7: 630–637.
- [5] Muss HB, Case LD, Richards F, White DR, Cooper MR, Cruz JM, *et al.* Interrupted versus Continuous Chemotherapy in Patients with Metastatic Breast Cancer. *New England Journal of Medicine*. 1991; 325: 1342–1348.
- [6] Onishi T, Sasaki T, Hoshina A. Intermittent Chemotherapy is a Treatment Choice for Advanced Urothelial Cancer. *Oncology*. 2012; 83: 50–56.
- [7] Beer TM, Garzotto M, Henner WD, Eilers KM, Wersinger EM. Intermittent chemotherapy in metastatic androgen-independent prostate cancer. *British Journal of Cancer*. 2003; 89: 968–970.
- [8] Tournigand C, Cervantes A, Figuer A, Lledo G, Flesch M, Buyse M, *et al.* OPTIMOX1: a Randomized Study of FOLFOX4 or FOLFOX7 with Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—a GERCOR Study. *Journal of Clinical Oncology*. 2006; 24: 394–400.
- [9] Madariaga A, Rustin GJS, Buckanovich RJ, Trent JC, Oza AM. Wanna Get Away? Maintenance Treatments and Chemotherapy Holidays in Gynecologic Cancers. *American Society of Clinical Oncology Educational Book*. 2019; 107: e152–e166.