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Comparative Age-Based Prospective Multi-Institutional Observations of 12,367 Patients Enrolled to the American College of Surgeons Oncology Group (ACOSOG) Z901101 Trials (Alliance)

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ABSTRACT

Background. The risk of surgery, particularly for older cancer patients with serious, extensive comorbidities, can make this otherwise curative modality precarious. Leveraging data from the American College of Surgeons Oncology Group, this study sought to characterize age-based comparative demographics, adverse event rates, and study completion rates to define how best to conduct research in older cancer patients.

Methods. This study relied on clinical data from 21 completed studies to assess whether older patients experienced more grade 3 or worse adverse events and were more likely to discontinue study participation prematurely than their younger counterparts.

Results. The study enrolled 12,367 patients. The median age was 60 years, and 36% of the patients were 65 years of age or older. Among 4008 patients with adverse event data, 1067 (27%) had experienced a grade 3 or worse event. The patients 65 years or older had higher rates of grade 3 or worse adverse events compared to younger patients [32% vs. 24%; odds ratio (OR), 1.5; 95% confidence interval (CI), 1.3–1.7; $p < 0.0001$]. This association was not observed in multivariate analyses. The study protocol was completed by 97% of the patients. No association was observed between age and trial completion (OR 0.8; 95% CI 0.7–1.1; $p = 0.14$). Only the older gastrointestinal cancer trial patients were less likely to complete their studies compared to younger patients (OR 0.50; 95% CI 0.30–0.70; $p < 0.0001$).

Conclusion. Despite higher rates of adverse events, the older patients typically completed the study protocol, thereby contributing relevant data on how best to render care to older cancer patients and affirming the important role of enrolling these patients to surgical trials.

Surgical extirpation of the cancer serves a pivotal role in rendering potentially curative therapy to patients with solid tumors. However, at times, the high risk of surgery, particularly for patients with serious, extensive comorbidities, makes this otherwise curative treatment modality precarious at best. This situation perhaps occurs most often with older cancer patients, or those 65 years of age or older. By 2030, these older patients will comprise an estimated 70% of the U.S. population of cancer patients.[1] Older cancer

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patients are underrepresented in clinical trials, often undertreated for their cancer, and, because of these shifting demographics, responsible for what is perceived as a crisis in health care.[2–4]

Admittedly, at times, advanced age has prompted less invasive but nonetheless effective surgical options. The omission of an axillary lymph node dissection with axillary radiation for older breast cancer patients with one to two tumor-positive sentinel nodes is an example of a more limited surgical approach that has resulted in comparable survival for older patients.[5] However, the preponderance of surgical data seems to suggest an increase in morbidity and mortality with increasing patient age.

Older patients with potentially curable gastrointestinal or thoracic malignancies often require complex surgeries and experience higher rates of postoperative complications than their younger counterparts.[6,7] For example, older patients with obstructive colorectal cancer are three times more likely to die postoperatively than younger patients.[8] Such data underscore the need for more prospective clinical research, both surgical interventional trials and other related studies, that focuses on older cancer patients. The current study was conducted in recognition of this need.

Building on multi-institutional U.S. government-funded prospective data, the current study sought to characterize age-based comparative demographics and outcomes as relevant to adverse event rates and prospective study completion of patients enrolled in prospective surgical oncology studies during a 15-year interval.

METHODS

Overview

The current study, referred to as ACOSOG Z901101, relied on clinical data from the American College of Surgeons Oncology Group (ACOSOG) founded in 1996 and later merged with other government-funded clinical trial infrastructure to form the Alliance for Clinical Trials in Oncology. Studies conducted by ACOSOG have included both therapeutic and non-therapeutic surgical investigations of patients with cancer of the breast, thorax, gastrointestinal area, and other organ sites. All 21 studies conducted by ACOSOG are included in the current report (Table 1).[9–26] Each participant signed an Institutional Review Board-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines.

The current study sought to assess whether older cancer patients are able to participate in prospectively conducted surgery-based cancer studies safely and fully. The age cut-point of 65 years at trial enrollment was used for analyses because this age threshold meets the Medicare definition of older adult, but other analyses with an age cut-point of 70 years also were conducted and reported.

The first goal was to evaluate whether older patients who enrolled in therapeutic trials experienced more grade 3 or worse adverse events, as per Common Terminology Criteria Adverse Event (CTCAE), than their younger counterparts. The second goal was to evaluate whether older patients were more likely to discontinue study participation prematurely than their younger counterparts. For this second goal, premature discontinuation was defined as a patient's stopping short of fulfilling all aspects of therapy and monitoring as outlined in the clinical protocol for the study. For example, patients who withdrew from the study, declined further study treatment, or experienced adverse events that prompted treatment discontinuation were classified as having discontinued the study prematurely.

Data Reporting and Analyses

The characteristics of the patients are summarized descriptively. Uni- and multivariable logistic regression models were used to assess associations between patient demographics and study characteristics in terms of grade 3 or worse adverse events and study completion. A deliberate decision was made not to report survival outcomes due to the heterogeneous nature of the combined cohorts. Some patients had early-stage malignancies and therefore were expected to manifest long survival times. Early treatment-induced death was captured as a grade 5 adverse event. Although data were locked at different times based on the individual study, the last data lock occurred November 7 2013.

Both pooled and cancer-specific analyses were performed. These sets of analyses incorporated the following patient-based variables: age as a dichotomous variable, gender, race (white vs. other), and Eastern Cooperative Oncology Group performance score at study entry. These analyses also incorporated the following cancer-related variables: cancer type (breast, thoracic, gastrointestinal, or other), cancer stage for the respective cancer type as per the contemporaneous American Joint Committee on Cancer, treatment method (surgery, chemotherapy, radiotherapy, multimodality therapy, or other), and clinical trial type (therapeutic vs. non-therapeutic). Differences in baseline variables between groups were summarized as frequencies and proportions and compared with a Chi square test.

For all analyses, a p value lower than 0.05 was considered statistically significant. The Alliance Statistics and Data Center conducted the data collection and statistical analyses.

TABLE 1 Protocols

Protocol no.	Study protocol description	Study type	Cancer type	Total sample size/sample size ≥ 65 years/sample size ≥ 70 years
Z0010	This prospective trial determined factors important in locoregional recurrence of breast cancer with negative sentinel nodes; the study showed locoregional recurrences are rare	Non-therapeutic	Breast	5075/1361/811
Z0011	This prospective trial that sought to determine the effects of a complete axillary node dissection on survival of patients with sentinel lymph node metastasis of breast cancer; the study demonstrated that sentinel node dissection alone is comparable to complete axillary node dissection	Therapeutic	Breast	867/215/125
Z0020	This randomized trial aimed to determine whether the addition of tumor necrosis factor to melphalan-based hyperthermic isolated limb perfusion improved complete response for locally advanced extremity melanoma	Therapeutic	Melanoma	130/63/44
Z0030	This randomized trial determined whether mediastinal lymph node dissection improves survival compared with mediastinal lymph node sampling for patients undergoing resection for N0 or nonhilar N1, T1, or T2 non-small cell lung cancer; the study found that if careful node sampling is negative, then a mediastinal lymph node dissection does not improve survival for early-stage patients who were not staged radiographically	Therapeutic	Non-small cell lung	1111/713/464
Z0040	Although prior studies had suggested that occult metastases are associated with a poor prognosis, this study found that occult metastases in lymph nodes versus bone marrow were associated with worse survival	Non-therapeutic	Non-small cell lung	582/344/229
Z0050	This study sought to determine whether PET scans would detect cancer that would preclude resection of lung cancer; this imaging led to an avoidance of an unnecessary thoracotomy for 1 in 5 patients	Non-therapeutic	Non-small cell lung	335/180/117
Z0070	This trial examined outcomes from prostatectomy versus interstitial radiation closed early because of poor accrual. However, quality-of-life data suggest that adverse events and quality of life stabilized 3–5 years after therapy	Therapeutic	Genitourinary	54/16/4
Z0300	This trial showed the important role of stereotactic radiosurgery for patients with brain oligometastases	Therapeutic		70/23/15
Z0360	This trial examined sentinel lymph node biopsies for patients with early-stage head and neck cancer and found that sentinel lymph node biopsy with step sectioning and immunohistochemistry predicted a pathologically negative neck	Non-therapeutic	Head and neck	161/59/39
Z05031	This trial tested a novel interferon-based neoadjuvant approach for patients with pancreas cancer only to find that toxicity was too great to merit further development in the absence of notably regimen modification	Therapeutic	Gastrointestinal	89/24/11
Z05032	This study sought to determine the toxicity of hepatic arterial infusion with 5-fluorouracil and systemic irinotecan in patients with colorectal cancer liver metastases. Final results are not reported to date	Therapeutic	Gastrointestinal	11/2/1
Z1031	This trial showed that neoadjuvant aromatase inhibitor therapy improves outcome (tumor response) for patients with estrogen receptor + breast cancer	Therapeutic	Breast	622/325/221
Z1041	The trial tested a neoadjuvant regimen that included concurrent administration of trastuzumab and found that it offered no additional clinical benefit	Therapeutic	Breast	237/15/6
Z1071	This trial reported on a high false-negative rate among breast cancer patients with cN1 disease with sentinel lymph node dissection after neoadjuvant therapy	Non-therapeutic	Breast	726/72/29

TABLE 1 continued

Protocol no.	Study protocol description	Study type	Cancer type	Total sample size/sample size ≥ 65 years/sample size ≥ 70 years
Z4031	This study found that PET scans perform poorly in diagnosing early-stage lung cancer	Non-therapeutic	Non-small cell lung	1032/561/356
Z4032	This phase 3 trial showed that postoperative brachytherapy did not reduce local recurrence rates after a sublobar resection for lung cancer	Therapeutic	Non-small cell lung	223/162/122
Z4033	This single-arm phase 2 trial showed that radiofrequency ablation for biopsy-proven stage 1A lung cancer appears to provide an acceptable rate of local control and survival for patients deemed to be poor surgical candidates	Therapeutic	Non-small cell lung	52/49/37
Z6041	This single-arm phase 2 trial showed that neoadjuvant chemoradiotherapy followed by local excision might provide an organ-preserving option for select T2N0 patients who are not candidates for transabdominal resection	Therapeutic	Gastrointestinal	90/39/27
Z9000	This comparative phase 2 trial showed that surgically treated high-risk gastrointestinal stromal tumor patients live longer with adjuvant imatinib	Therapeutic	Gastrointestinal stromal tumor	109/36/18
Z9001	This translational study used tumor specimens from a larger trial to show that tumor size, location, and mitotic rate, but not tumor type, are predictive of tumor behavior	Non-therapeutic	Gastrointestinal stromal tumor	778/248/151
Z9031	This phase 3 study attempted to determine whether preoperative radiation improves survival for patients with retroperitoneal sarcoma but was terminated early because of poor accrual	Therapeutic	Sarcoma	13/3/2

PET positron emission tomography

RESULTS

Patient Characteristics

A total of 12,367 patients are the focus of this report. The median age of the entire pooled cohort was 60 years at trial entry, with only 36% of the patients 65 years of age or older. Across the studies, only a minority of patients were older, with only one exception. Z4033 was a single-arm phase 2 trial that examined radiofrequency ablation for patients with biopsy-proven early-stage lung cancer deemed unfit for surgery. In this 52-patient trial, 94% of the patients were 65 years of age or older.[23] Because 61% of the patients were enrolled in breast cancer studies, women comprised 80% of the entire pooled cohort.

Age-based comparisons showed marked differences in patient demographics (Table 2). The older patients manifested worse performance scores at trial entry and were more likely to have been enrolled in a study for an early-stage cancer. At the time of data analyses, the majority of the patients were still alive regardless of their age-based cohort (Table 2).

Study Protocol Characteristics

The clinical trials in this study included 14 therapeutic studies, with the remaining trials comprising non-therapeutic studies (Table 1). These studies were heavily focused on more prevalent cancers such as breast cancer and lung cancer, both of which comprised the majority of the studies.

Age and Adverse Events

Among the 4008 patients with available adverse event data, 1067 patients (27%) who participated in clinical trial protocols experienced a grade 3 or worse adverse event. The patients 65 years of age or older had higher rates of grade 3 or worse adverse events than the younger patients (32% vs. 24%; univariate odds ratio [OR], 1.5; 95% CI, 1.3–1.7; $p < 0.0001$; Table 3), although this statistically significant association with age was not observed in the multivariate analyses. The uni- and multivariable analyses of adverse events based on age yielded differing results based on cancer type (see supplemental tables). However, even in the investigation of specific cancer types, the older patients appeared overall to manifest worse adverse event profiles.

TABLE 2 Patient characteristics, including mortality data

	All patients (n = 12,367)	≥65 Years of age (n = 4510) n (%)	< 65 Years of age (n = 7857) n (%)	p value	≥ 70 Years of age (n = 2838) n (%)	< 70 Years of age (n = 9529) n (%)	p value
Median age: years (range)	60 (18.5–95.5)	72 (65–95.5)	53.9 (18.5–65.0)	–	75.1 (70.0–95.5)	56.1 (18.5–70.0)	–
Sex							
Male	2501	1305 (52)	1196 (48)	< 0.0001	850 (34)	1651 (66)	< 0.0001
Female	9862	3204 (33)	6658 (68)		1987 (20)	7875 (80)	
Race							
White	9992	3829 (38)	6163 (62)		2454 (25)	7538 (75)	
Other	1395	364 (26)	1031 (74)	< 0.0001	189 (14)	1206 (87)	< 0.0001
Performance score							
0	673	75 (11)	598 (89)	< 0.0001	33 (5)	640 (95)	< 0.0001
1	2854	1205 (42)	1649 (58)		738 (26)	2116 (74)	
2	1074	634 (59)	440 (41)		451 (42)	623 (58)	
3	128	88 (69)	40 (31)		68 (53)	60 (47)	
4	2	1 (50)	1 (50)		1 (50)	1 (50)	
Cancer type							
Breast	7527	1988 (26)	5539 (74)	< 0.0001	1192 (16)	6335 (84)	< 0.0001
Gastrointestinal	1077	349 (32)	728 (68)		208 (19)	869 (81)	
Thoracic	3335	2009 (60)	1326 (40)		1334 (40)	2001 (60)	
Other	428	164 (38)	264 (62)		104 (24)	324 (76)	
Cancer stage (per cancer type)							
1	5302	2277 (43)	3025 (57)	< 0.0001	1446 (27)	5302 (55)	< 0.0001
2	3296	941 (29)	2355 (72)		569 (17)	3296 (34)	
3	923	273 (30)	650 (70)		171 (19)	923 (10)	
4	100	30 (30)	70 (70)		20 (20)	100 (1)	
Tested therapeutic intervention							
Surgery	4479	1964 (44)	2515 (56)	< 0.0001	1251 (28)	3228 (72)	< 0.0001
Chemotherapy	1887	689 (37)	1198 (64)		441 (23)	1446 (77)	
Radiation	52	49 (94)	3 (6)		37 (71)	15 (29)	
Multiple	539	267 (50)	272 (51)		181 (34)	358 (66)	
Other	5410	1541 (29)	3869 (72)		928 (17)	4482 (83)	
Patient insurance							
Medicare	3706	3339 (90)	367 (10)	< 0.0001	2192 (59)	1514 (41)	< 0.0001
Other	8656	1170 (14)	7486 (87)		645 (8)	8011 (93)	
Type of study[a]							
Therapeutic	3678	1685 (46)	1993 (54)	< 0.0001	1097 (30)	2581 (70)	< 0.0001
Non-therapeutic	8689	2825 (33)	5864 (68)		1741 (20)	6948 (80)	
Vital status at time of analyses							
Alive	8910	3070 (35)	5840 (65)	–	1860 (21)	7050 (79)	–
Dead	1703	1011 (59)	692 (41)		726 (43)	977 (57)	
Death within 30 days after study registration							
Yes	46	32 (70)	14 (30)	–	26 (57)	20 (44)	–
No	10567	4049 (38)	6518 (62)		2560 (24)	8007 (76)	
Death within 6 months after study registration							
Yes	180	120 (67)	60 (33)	–	97 (54)	83 (46)	–
No	10433	3961 (38)	6472 (62)		2489 (24)	7944 (76)	

Percentages may not sum to 100% because of rounding

[a]Therapeutic trials refer to those specifically designed to provide cancer treatment, whereas non-therapeutic trials sought to understand outcomes based on disease- or other-related factors. See Table 1 for characterization of each trial based on these categories

TABLE 3 Uni- and multivariable models predicting grade 3 or worse adverse events

	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age				
> 65 Years versus younger	1.5 (1.3–1.7)	< 0.0001	0.8 (0.6–1.1)	0.24
Gender				
Male versus female	1.5 (1.3–1.7)	< 0.0001	1.3 (0.9–1.8)	0.11
Performance score: 0 and 1 versus other	0.5 (0.5–0.6)	< 0.0001	0.7 (0.5–1.0)	0.02
Race				
White versus other	1.5 (1.2–2.0)	< 0.001	1.4 (1.0–1.9)	0.08
Cancer				
GI versus breast	2.2 (1.8–2.6)	< 0.0001	165.5 (68.4–	< 0.0001
Thoracic versus breast	1.8 (1.5–2.1)	< 0.0001	400.5)	< 0.0001
Other versus breast	2.3 (1.8–2.9)	< 0.0001	13.6 (8.5–21.9)	< 0.0001
Cancer stage				
Stages 1 and 2 versus 3+	1.3 (1.0–1.6)	0.02	7.4 (3.1–17.6)	0.03
Insurance				
Medicare versus other	1.5 (1.3–1.7)	< 0.0001	1.0 (0.7–1.4)	0.97
Tested therapeutic intervention				
Chemotherapy versus surgery	2.4 (2.0–2.9)	< 0.0001	9.6 (6.6–14.1)	< 0.0001
Multiple treatment methods versus surgery	6.0 (4.7–7.5)	< 0.0001	1.0 (0.7–1.5)	0.91
Radiation/other/none versus surgery	0.3 (0.2–0.5)	< 0.0001	1.1 (0.6–2.1)	0.77
Study type				
Therapeutic versus non-therapeutic[a]	4.9 (4.2–5.8)	< 0.0001	–	–

OR odds ratio, *CI* confidence interval, *GI* gastrointestinal

The referent group is the last group (e.g., for "male vs. female," female is the referent

[a]Therapeutic trials refer to those specifically designed to provide cancer treatment, whereas non-therapeutic trials sought to understand outcomes based on disease- or other-related factors. See Table 1 for characterization of each trial based on these categories

Additional multivariable logistic regression models were fit for adverse events with stratification based on tested therapeutic intervention (surgery vs. chemotherapy vs. multiple vs. radiation/other/none), and the results were similar to those described earlier.

Parenthetically, and in view of scarce data on the "oldest of the old," data on the patients 75 years of age or older are provided descriptively. In these trials, 1467 (12%) of the 12,367 patients were 75 years older. A further breakdown showed that 583 (8%) of 7527 patients in this older age range were included in breast cancer trials, that 116 (11%) among 1077 of these patients were included in gastrointestinal cancer trials, and that 719 (22%) among 3335 of these patients were included in thoracic trials. Notably, 33% of the patients 75 years of age or older had a grade 3 or worse adverse event compared with 26% of the younger patients ($p < 0.001$).

Age and Trial Completion

Across the entire cohort, 97% of the patients completed their respective study per protocol (8607 of 8895 subjects had trial completion data; Tables 4 and 5). The patients completing the trial in which they had enrolled included 97% (95% CI, 95.7–97%) of the patients 65 years of age older and 97% (95% CI, 96.5–97.4%) of the patients younger than 65 years of age. No association between age and trial completion was observed (OR, 0.8; 95% CI, 0.7–1.1; $p = 0.14$).

Additional multivariable logistic regression models were fit for trial completion with stratification based on tested therapeutic intervention (surgery vs. chemotherapy vs. multiple vs. radiation/other/none) and showed similar results. Notably, the older gastrointestinal cancer trial participants were less likely to complete their respective trials than the younger patients (OR, 0.50; 95% CI, 0.30–0.70; $p < 0.0001$; Table S2b, with cancer-specific data in the other supplemental tables). Age-based reasons

TABLE 4 Uni- and multivariable models predicting study completion

	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age				
>/65 Years versus younger	0.8 (0.7–1.1)	0.14	0.7 (0.5–1.1)	0.12
Gender				
Male versus female	0.6 (0.4–0.7)	< 0.0001	1.5 (1.1–2.0)	0.02
Performance score				
0,1 versus other	0.8 (0.5–1.1)	0.12	–	–
Race				
White versus other	2.1 (1.4–3.0)	< 0.0001	–	–
Cancer				
GI versus breast	(0.1–0.1)	< 0.0001	(0.0–0.4)	0.01
Thoracic versus breast	2.4 (1.4–4.0)	< 0.001	3.5 (1.9–6.6)	< 0.0001
Other versus breast	0.6 (0.3–1.3)	0.19	0.4 (0.0–3.3)	0.37
Cancer stage				
1 and 2 versus other	1.6 (0.7–3.6)	0.21	–	–
Insurance				
Medicare versus other	0.8 (0.6–1.0)	0.08	0.9 (0.6–1.3)	0.5821
Tested therapeutic intervention				
Chemotherapy versus surgery	(0.1–0.1)	< 0.0001	2.8 (0.4–22.3)	0.33
Multiple treatment methods versus surgery	(0.1–0.3)	< 0.0001	2.1 (0.3–15.9)	0.48
Radiation/other/none versus surgery	1.1 (0.7–1.6)	0.68	2.0 (1.3–3.1)	< 0.01
Study type				
Therapeutic versus non-therapeutic[a]	0.8 (0.6–1.0)	0.08	–	–

OR odds ratio, *CI* confidence interval, *GI* gastrointestinal

The referent group is the last group (e.g., for "male vs. female," female is the referent

[a]Therapeutic trials refer to those specifically designed to provide cancer treatment, whereas non-therapeutic trials sought to understand outcomes based on disease- or other-related factors. See Table 1 for characterization of each trial based on these categories

TABLE 5 Reasons for premature study discontinuation

Reasons for discontinuation	All patients *n* (%)	≥ 65 years of age *n* (%)	< 65 years of age *n* (%)	≥ 70 years of age *n* (%)	< 70 years of age *n* (%)
Patient declined	179 (2)	60 (2)	119 (2)	37 (2)	142 (2)
Adverse events	109 (1)	57 (2)	52 (1)	39 (2)	70 (1)
Cancer progression	72 (1)	27 (1)	45 (1)	18 (1)	54 (1)

Cancer progression is not a reason for premature study discontinuation, but is nonetheless included in this listing

for premature study discontinuation showed no apparent age-based differences (Table 5).

DISCUSSION

The current study investigated 12,367 patients perhaps the largest age-focused report of prospectively gathered data and sought to understand comparative demographics as well as adverse events and study completion rates of older cancer patients enrolled in surgical trials.

This effort generated three salient conclusions. First, although the U.S. population of cancer patients is growing rapidly, only 36% of the entire cohort enrolled in these surgical oncology protocols were 65 years of age or older. This percentage did not reflect the proportion of older cancer patients who lived or had lived in the United States during recruitment to these studies. In a manner commensurate with real-time, age-based demographics, older patients should be enrolled to surgical protocols.

With a study completion rate approaching 100%, regardless of patient age, the current report shows that older cancer patients are able to engage fully in clinical research. Thus, engaging these older patients promises to provide direction on how best to give care to a group who comprise the majority of those diagnosed with cancer.

Second, in keeping with previous nonsurgical studies, the rates of adverse events were higher for the older cancer patients than for their younger counterparts,[27,28] although statistically significant associations between older age and higher adverse event rates were observed only in the univarate analysis and not in the multivariate analysis. When the risks of curative treatment are high in the setting of an otherwise fatal disease such as cancer, it is important to provide patients with balanced discussions that allow them to make informed decisions about surgery.

Third, despite relatively high rates of adverse events, the current study found that the vast majority of older patients were able to complete all aspects of the study protocol. The exception occurred with gastrointestinal cancer protocols, which often entailed multimodality therapy with highly complex surgeries. These findings suggest that surgical protocols that require patients to have highly complex and aggressive treatment should ensure the necessary supportive care and appropriate treatment modifications. Nonetheless, the aforementioned observations underscore the feasibility and relative safety of enrolling older patients for cancer surgical protocols. These observations should be pursued with the goal of learning how best to provide this growing population with optimal cancer care and how best to present to them their best therapeutic options. These older patients have shown that they are able to complete their respective study protocols and thereby enhance our understanding of how best to render cancer care to older patients.

Notably, it is important not to oversimplify the concept of older age and to acknowledge that several other outcome-driving factors are associated with age. For example, in exploratory analyses of grade 3 or worse adverse events, significant interactions were observed between older age and type of therapeutic intervention used (e.g., multimodality therapy vs. surgery alone) as well as between older age and study type (therapeutic vs. non-therapeutic).

Similarly, when examining associations between age and study completion, we observed significant interactions between age and gender, between age and cancer type, between age and tested therapeutic intervention (e.g., surgery vs. multi-modality therapy), and between age by study type (therapeutic vs. non-therapeutic). In essence, age is not an isolated determinant of outcomes but ostensibly a component of a more complex set of variables.

The current study had both strengths and limitations. The strengths included a considerably large sample generated from 15 years of prospectively gathered, multi-site clinical trials.

The limitations include a lack of detailed information on older patients. These studies did not require a geriatric assessment, which provides a wealth of data within five domains and in the setting of other cancer trials has been effective in providing correlative data on chemotherapy-induced toxicity. Moreover, these studies did not require a methodical assessment of patients' comorbidities besides what was necessary to meet trial eligibility. Because comorbidities often co-migrate with age, this lack of information was a shortcoming of the current study. Such supplemental information on older patients would be of value for future surgical oncology trials, serving to address the need to inform patients better about surgical risk, especially when surgery offers the only chance for longer-term benefit.

A second limitation is the heterogeneity between all the studies captured in this report and the fact that the design of the current study pooled these data. This heterogeneity posed challenges when studies were analyzed in aggregate, thus precluding our ability to examine such important oncologic end points as disease-free and overall survival. In an effort to circumvent some aspects of this limitation, we included supplementary tables that focus on specific cancer types and provide tumor-based models of adverse event prediction and premature study discontinuation.

A third limitation is the fact that these trials likely recruited a select group of older patients who might not be representative of the older population of cancer patients at large. Thus, we are unable to conclude that our results are widely generalizable.

Finally, this report highlights opportunities for future research in geriatric surgical oncology. As mentioned earlier, the use of geriatric assessment promises to provide rich data that in turn can help identify factors to help patients better understand the risks and untoward consequences of surgery. Similarly, cancer centers are integrating lay navigators, or people who provide individual assistance to patients who need help and direction in the clinical experience while seeking health care. Perhaps future research should attempt to make use of lay navigators to help with the enrollment of older cancer patients in clinical trials. Of paramount importance is the need to enroll more older patients in cancer surgical trials with the goal not only of understanding the risks of surgery, but also of testing novel surgical approaches that might make life-prolonging or curative surgery easier for older cancer patients. More surgical oncology research of older patients is needed.

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