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

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Abstract

Background: The risk of surgery – particularly in older cancer patients with serious, extensive comorbidities – can make this otherwise curative modality precarious. Leveraging data from ACOSOG, we 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 1) developed more grade 3 or worse adverse events and 2) were more likely to discontinue study participation prematurely compared to their younger counterparts.

Results: Among 12,367 patients, the median age was 60 years; 36% were >/= 65 years of age. Among 4008 patients with adverse event data, 1067 (27%) experienced a grade 3 or worse event. Patients >/=65 years had higher rates of grade 3 or worse adverse events compared to younger patients (odd ratio (OR) = 1.5; 95% confidence interval (CI): 1.3–1.7; 32% versus 24%, p<0.0001); this association was not observed in multivariate analyses. Ninety-seven percent of

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patients completed their study protocol; no association was observed between age and trial completion (OR=0.8; 95% CI: 0.7 − 1.1; p=0.14). Only 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, 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.

INTRODUCTION

Surgical extirpation of the cancer serves a pivotal role in rendering potentially curative therapy to patients with solid tumors. Yet, at times, the high risk of surgery – particularly in patients with serious, extensive comorbidities – makes this otherwise curative treatment modality precarious at best. This situation occurs perhaps most often in older cancer patients, or those who are 65 years of age or older; by 2030, these older patients will comprise an estimated 70% of the United States' (US) population of cancer patients [1]. Older cancer 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 healthcare [2–4]. because of these shifting demographics, responsible for what is perceived as a crisis in healthcare [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 in older breast cancer patients with 1 to 2 tumor-positive sentinel nodes is an example of a more limited surgical approach that has resulted in comparable survival in 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 compared to 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 as well as other related studies — that focus on older cancer patients.

The current study was undertaken in recognition of this need. Building on multi-institutional, US 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 over a fifteen-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), which was founded in 1996 and which later merged with other government-funded clinical trial infrastructure to form

the Alliance for Clinical Trials in Oncology. ACOSOG had conducted both therapeutic and non-therapeutic surgical studies in patients with cancer of the breast, thoracic, gastrointestinal area as well as of other organ sites. ACOSOG undertook 21 studies, all of which are included in the current report [9–26](Table 1). 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, based on the fact that this age threshold meets the Medicare definition of older adult, but other analyses with an age cut point of 70 years were also conducted and reported. The first goal was to evaluate whether older patients who enrolled in therapeutic trials developed more grade 3 or worse adverse events, as per Common Terminology Criteria Adverse Event (CTCAE), compared to their younger counterparts. The second goal was to evaluate whether older patients were more likely to discontinue study participation prematurely compared to 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 prematurely.

Data Reporting and Analyses.

Patient characteristics are summarized descriptively. Univariable and multivariable logistic regression models were used to assess associations between patient demographics and study characteristics with 1) grade 3 or worse adverse events and 2) study completion. A deliberate decision was made not to report survival outcomes because of the heterogeneous nature of the combined cohorts; the fact that some patients had early-stage malignancies and therefore were expected to manifest long survival times; and, with respect to this previous point, the fact that early treatment-induced death would be captured as grade 5 adverse events. 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 versus 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 modality (surgery, chemotherapy, radiotherapy, multimodality therapy, or other); and clinical trial type (therapeutic versus 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 <0.05 is considered statistically significant. The Alliance Statistic and Data Center conducted data collection and statistical analyses.

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 patients age 65 years 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 who had biopsy-proven early-stage lung cancer and who were deemed unfit for surgery; in this 52-patient trial, 94% of patients were 65 years of age or older [23]. Because 61% of patients were enrolled to breast cancer studies, women comprised 80% of the entire pooled cohort.

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

Study Protocol Characteristics.

Fourteen of the included studies were therapeutic clinical trials, and the remainder non-therapeutic (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 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. Patients who were 65 years of age or older had higher rates of grade 3 or worse adverse events compared to younger patients (univariate odds ratio (OR) =1.5; 95% CI: 1.3.1.7; 32% versus 24%, $p<0.0001$; (Table 3)), although this statistically significant association with age was not observed in multivariate analyses. Univariable and multivariable analyses of adverse events based on age yielded differing results based on cancer type (see supplemental tables); however, even when looking at specific cancer types, older patients appeared overall to manifest worse adverse event profiles.

Additional multivariable logistic regression models were fit for adverse events with stratification based on tested therapeutic intervention (surgery versus chemotherapy versus multiple versus radiation/other/none) with similar results as described above.

Of parenthetical note and in view of a paucity of data on the “oldest of the old,” data on patients 75 years of age and older are provided descriptively. Within these trials, 1467/12367 (12%) of patients were ≥75 years old. Further breakdown showed that 583/7527 (8%) patients within this older age range were included in breast cancer trials; 116/1077 (11%) were included on gastrointestinal cancer trials; and 719/3335 (22%) were included on thoracic trials. Of note, 33% of patients who were ≥75 years of age had a grade 3 or worse adverse event compared to 26% of younger patients ($p<0.001$).

Age and Trial Completion.

Across the entire cohort, 97% of patients completed their respective study per protocol (8607 of 8895 subjects with trial completion data) (Tables 4 and 5). Ninety-seven percent (95% CI: 95.7%, 97%) of patients ≥ 65 years of age and 97% (95% CI: 96.5%, 97.4%) of patients <65 years of age, respectively, completed the study into which they had enrolled. No association between age and trial completion (OR=0.8; 95% CI: 0.7 − 1.1; p=0.14) was observed.

Additional multivariable logistic regression models were fit for trial completion with stratification based on tested therapeutic intervention (surgery versus chemotherapy versus multiple versus radiation/other/none) with similar results.

Of note, older gastrointestinal cancer trial participants were less likely to complete their respective trials compared to younger patients: odds ratio of 0.50 (95% confidence interval: 0.30–0.70; p<0.0001). (Supplemental Table 2b with cancer-specific data in the other supplemental tables).

Age-based reasons for premature study discontinuation show no apparent age-based differences (Table 5).

DISCUSSION

The current study is comprised of 12,367 patients — perhaps the largest age-focused report of prospectively-gathered data — and sought to understand comparative demographics and adverse events/study completion rates of older cancer patients enrolled to surgical trials. This effort generated three salient conclusions. First, although the United States' population of cancer patients is rapidly growing, only 36% of the entire cohort enrolled to these surgical oncology protocols were 65 years of age or older. This percentage does not reflect the proportion of older cancer patients who live 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 that approaches 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 render care to a group who comprise the majority of those diagnosed with cancer.

Second, in keeping with previous non-surgical studies, rates of adverse events were higher in older cancer patients compared to their younger counterparts [27–28], although statistically significant associations between older age and higher adverse event rates were observed only in univarate and not multivariate analyses. 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 in gastrointestinal cancer protocols, which often entail 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 above observations underscore the feasibility and relative safety of enrolling older patients to cancer surgical protocols; these observations should be pursued with the goal of learning how best to provide this growing population 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.

Of note, 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 for grade 3 or worse adverse events, significant interactions were observed between older age and type of therapeutic intervention employed (for example, multimodality therapy versus surgery alone) as well as between older age and study type (therapeutic versus 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 (for example, surgery versus multimodality therapy, and between age by study type (therapeutic versus 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 has both strengths and limitations. The strengths include a considerably large sample size generated from 15 years of prospectively-gathered, multi-site clinical trials. 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 5 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' co-morbidities outside of what was necessary to meet trial eligibility. Because comorbidities often co-migrate with age, this lack of information is 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 better inform patients 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 oncological endpoints as disease-free and overall survival. In an effort to circumvent some aspects of this limitation, we have 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, the use of the 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 while seeking healthcare, into the clinical experience. Perhaps future research should attempt to make use of lay navigators to help with the enrollment of older cancer patients to clinical trials. Of paramount importance is the need to enroll more older patients to cancer surgical trials with the goal of not only understanding the risks of surgery but of testing novel surgical approaches that might make life-prolonging or curative surgery easier for older cancer patients. More surgical oncology research in older patients is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009; 27:2758–65. [PubMed: 19403886]
2. Freedman RA, Foster JC, Seisler DK, et al. Accrual of older patients with breast cancer to Alliance systemic therapy trials over time: protocol A151527. J Clin Oncol 2017; 35:421–431. [PubMed: 27992272]
3. Witherby SM, Muss HB. Special issues related to breast cancer adjuvant therapy in older women. Breast 2005; 14:600–11. [PubMed: 16198568]
4. http://nationalacademies.org/hmd/Reports/2013/Delivering-High-Quality-Cancer-Care-Charting-a-New-Course-for-a-System-in-Crisis/Press-ReleaseMR.aspx; last accessed June 18, 2019.
5. Shah-Khan M, Boughey JC. Evolution of axillary node staging in breast cancer: clinical implications of the ACOSOG Z0011 trial. Cancer Control 2012; 19:267–76. [PubMed: 23037494]
6. Khan S, Sclabas G, Lombardo KR, et al. Pancreatoduodenectomy for ductal adenocarcinoma in the very elderly; is it safe and justified? J Gastrointest Suer 2010; 14:1826–31.
7. Detillon DDEMA Veen EJ. Postoperative outcome after pulmonary surgery for non-small cell lung cancer in elderly patients. Ann Thorac Surg 2018; 105:287–293. [PubMed: 29132701]
8. Waldron RP, Donovan IA, Drumm J, et al. Emergency presentation and mortality from colorectal cancer in the elderly. Br J Surg 1986; 73:214–6. [PubMed: 3947921]
9. Hunt KK, Ballman KV, McCall LM, et al. Factors associated with local-regional recurrence after a negative sentinel node dissection: results of the ACOSOG Z0010 trial. Ann Surg 2012; 256:428–36. [PubMed: 22868365]
10. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection versus no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305:569–75. [PubMed: 21304082]
11. Cornett WR, McCall LM, Petersen RP, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosisfactor: American College of Surgeons Oncology Group Trial Z0020. J Clin Oncol 2006; 24:4196–201. [PubMed: 16943537]

12. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial.
13. Rusch VW, Hawes D, Decker PA, et al. Occult metastases in lymph nodes predict survival in resectable non-small cell lung cancer: report of the ACOSOG Z0040 trial. J Clin Oncol 2011; 29:4313–9. [PubMed: 21990404]
14. Reed CE, Harpole DH, Posther KE, et al. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. J Thoracic and Cardiovascular Surgery 2003; 126:1943–1951.
15. Crook JM, Gomez-Iturriaga A, Wallace K, et al. Comparison of health-related quality of life 5 years after treatment for men who either chose or were randomized to radical prostatectomy or brachytherapy after a SPIRIT Trial education session. Brachytherapy 2010; 9:S23.
16. Civantos FJ, Zitsch RP, Schuller DE, et al. Sentinel lymph node biopsy accurately stages the regional lymph nodes for T1–T2 oral squamous cell carcinomas: results or a prospective multi-institutional trial. J Clin Oncol 2010; 28:1395–400. [PubMed: 20142602]
17. Picozzi VJ, Abrams RA, Decker PA, et al. Multicenter phase 2 trial of adjuvant therapy for resected pancreatic cancer using cisplatin, 5-fluorouracil, and interferon-alpha-2b-based chemoradiation: ACOSOG trial Z05031. Annals of Oncol 2011; 22:348–54.
18. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase 2 neoadjuvant comparison between letrozole, anastrazole, and exemestane for postmenopausal women with estrogen receptive-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype — ACOSOG Z1031. J Clin Oncol 2011; 29:2342–9. [PubMed: 21555689]
19. Buzdar AU, Suman VJ, Meric-Berstam F, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomized, controlled, phase 3 trial. Lancet Oncol 2013; 14:1317–25. [PubMed: 24239210]
20. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinal lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. The ACOSOG (Alliance) Clinical Trial. JAMA 2013; 310:1455–1461. [PubMed: 24101169]
21. Grogan EL, Deppen SA, Ballman KV, et al. Accuracy of fluorodeoxyglucose-positron emission tomography within the clinical practice of the American College of Surgeons Oncology Group Z4031 trial to diagnose clinical stage 1 non-small cell lung cancer. Ann Thorac Surg 2014; 97:1142–8. [PubMed: 24576597]
22. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. Impact of brachytherapy on local recurrence after sublobar resection: results from ACOSOG Z4032 (Alliance), a phase 3 randomized trial for high-risk operable non-small cell lung cancer. J Clin Oncol 2014; 32:2456–62. [PubMed: 24982457]
23. Dupuy DE, Fernando HC, Hillman S, et al. Radiofrequency ablation of stage 1A non-small cell lung cancer in medically inoperable patients: results from the American College of Surgeons Oncology Group Z4033 (Alliance) trial. Cancer 2015; 121:3491–8. [PubMed: 26096694]
24. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol 2015; 16:1537–1546. [PubMed: 26474521]
25. DeMatteo RP, Ballman KV, Antonescu CR, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Ann Surg 2013; 258:422–9. [PubMed: 23860199]
26. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014; 32:1563–70. [PubMed: 24638003]
27. Schild SE, Mandrekar SJ, Jatoi A, et al. The value of combined-modality therapy in elderly patients with stage III nonsmall cell lung cancer. Cancer 2007; 110:363–8. [PubMed: 17542000]

28. Tallarico M, Foster JC, Seisler D, et al. Frequency and impact of grade three or four toxicities of novel agents on outcomes of older patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma (A151611). J Geriatr Oncol 2018; 9:321–328. [PubMed: 29673807]

Synopsis:

This study showed that older patients had higher rates of adverse events but nonetheless were typically able to complete the study protocol and thereby contribute relevant data on how best to render care to older patients with cancer.

Table 1:

Protocols

Protocol Number	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 loco-regional recurrence of breast cancer with negative sentinel nodes; showed loco-regional 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; this study demonstrated that sentinel node dissection alone is comparable to complete axillary node dissection	therapeutic	breast	867/215/125
Z0020	This randomized trial 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 that determined whether mediastinal lymph node dissection improves survival compared with mediastinal lymph node sampling in patients undergoing resection for N0 or nonhilar N1, T1, or T2 non-small cell lung cancer; this study found that if careful node sampling is negative, then a mediastinal lymph node dissection does not improve survival in early stage patients who were not staged radiographically	therapeutic	non-small cell lung	1111/713/464
Z0040	Although prior studies had suggested occult metastases are associated with a poor prognosis, this study found that occult metastases in lymph nodes as opposed to the 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 in 1 in 5 patients.	non-therapeutic	non-small cell lung	335/180/117
Z0070	This trial that 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 in patients with brain oligometastases.	therapeutic		70/23/15
Z0360	This trial examined sentinel lymph nodes biopsies in 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 in 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 not yet reported.	therapeutic	gastrointestinal	11/2/1
Z1031	This trial showed that neoadjuvant aromatase inhibitor therapy improves outcome (tumor response) in patients with estrogen receptor + breast cancer.	therapeutic	breast	622/325/221
Z1041	The trial tested neoadjuvant regimen that included concurrent administration of trastuzumab 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

Protocol Number	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 III trial showed 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 in patients deemed poor surgical candidates.	therapeutic	non-small cell lung	52/49/37
Z6041	This single arm phase 2 trial that showed neoadjuvant chemoradiotherapy followed by local excision might provide an organ-preserving option in select T2N0 patients who are not candidates for transabdominal resection.	therapeutic	gastrointestinal	90/39/27
Z9000	This comparative phase II 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 III study attempted to determine whether preoperative radiation improved survival in patients with retroperitoneal sarcoma but was terminated early because of poor accrual.	therapeutic	sarcoma	13/3/2

Table 2:

Patient Characteristics, Including Mortality Data *

	All patients N=12367	>/= 65 years of age N=4510 (%)	< 65 years of age N=7857 (%)	p-value	>/= 70 years of age N=2838 (%)	< 70 years of age N=9529 (%)	p-value
Median age (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)	<0.0001	2454 (25)	7538 (75)	< 0.0001
Other	1395	364 (26)	1031 (74)		189 (14)	1206 (87)	
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 **							
Therapeutic	3678	1685 (46)	1993 (54)	<0.0001	1097 (30)	2581 (70)	<0.0001

	All patients N=12367	>/= 65 years of age N=4510 (%)	< 65 years of age N=7857 (%)	p-value	>/= 70 years of age N=2838 (%)	< 70 years of age N=9529 (%)	p-value
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 of 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 of 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.

**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:

Univariable and Multivariable Models Predicting Grade 3 or Worse Adverse Events *

	UNIVARIABLE		MULTIVARIABLE	
	odds ratio (95% confidence intervals)	**p-value**	**odds ratio (95% confidence intervals)**	**p-value**
AGE				
>/65 years of age 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				
gastrointestinal versus breast	2.2 (1.8, 2.6)	<0.0001	165.5 (68.4, 400.5)	<0.0001
thoracic versus breast	1.8 (1.5, 2.1)	<0.0001	13.6 (8.5, 21.9)	<0.0001
other versus breast	2.3 (1.8, 2.9)	<0.0001	7.4 (3.1, 17.6)	<0.0001
CANCER STAGE				
Stage 1 and 2 versus 3+	1.3 (1.0, 1.6)	0.02	0.7 (0.5, 1.0)	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 modalities 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 **	4.9 (4.2, 5.8)	<.0001	-	-

* The referent group is last group; for example, with “male versus female,” female is the referent.

** 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 4:

Univariable and Multivariable Models Predicting Study Completion *

	UNIVARIABLE		MULTIVARIABLE	
	odds ratio (95% confidence intervals)	**p-value**	**odds ratio (95% confidence intervals)**	**p-value**
AGE				
>/65 years of age 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				
gastrointestinal 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 modalities 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 **	0.8 (0.6, 1.0)	0.08		

* The referent group is last group; for example, with “male versus female,” female is the referent.

** 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 (%)	>/= 65 years of age (%)	< 65 years of age (%)	>/= 70 years of age (%)	< 70 years of age (%)
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.