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Critical Review

American Society of Clinical Oncology 2021 Annual Meeting Highlights for Radiation Oncologists

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Abstract

The annual meeting of the American Society of Clinical Oncology is the largest multidisciplinary oncology-focused conference in the world. With more than 4900 total abstracts in 2021 alone, it is difficult for individuals to evaluate all the results. This article presents a review of 32 selected abstracts across all disease sites, focusing on those of greatest relevance to radiation oncologists.

Introduction

The annual meeting of the American Society of Clinical Oncology (ASCO) is the largest multidisciplinary oncology-focused conference in the world. In 2021, a total of 4900 abstracts were presented live (2450) or published online (2450). Given the wide breadth of presentations, it is difficult for individuals to evaluate all the results. Therefore, we reviewed the entire scientific library and narrowed down the abstracts to those we felt most applicable and of greatest interest to radiation oncologists. This article succinctly presents these 32 studies (Table 1), sorted alphabetically into sections by disease sites. Presentation types are denoted as plenary (**), oral (*), poster discussion (#), or poster (^).

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Breast

A novel biosignature identifies DCIS patients with a poor biologic subtype with an unacceptably high rate of local recurrence after breast conserving surgery and radiation therapy#,[1]

This study evaluated the DCISionRT biosignature and its response subtype (Rst) in 485 women with ductal carcinoma in situ (DCIS) in Sweden, the United States, and Australia who were treated with breast conservation with or without whole-breast radiation therapy (RT) from 1996 to 2011. Patients were classified into low-risk or elevated-risk groups to assess ipsilateral breast tumor recurrence and invasive breast recurrence. Patients in the elevated-risk groups were categorized as having a good Rst or a poor Rst. The investigators found that RT was associated with significantly reduced recurrence rates in the elevated-risk group among patients with a good Rst but not those with a poor Rst. A poor Rst, irrespective of RT, was associated with significantly higher recurrence rates than a good Rst. For patients in the low-risk group, no differences in recurrence were found in cohorts that

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Table 1 Selected presentations of interest to radiation oncologists from the American Society of Clinical Oncology 2021 annual meeting

Topic	Trial or study name	Authors	Session type	Abstract number
Breast	A novel biosignature identifies DCIS patients with a poor biologic subtype with an unacceptably high rate of local recurrence after breast conserving surgery and radiotherapy	Vicini et al	Poster discussion	513
Breast	A phase II trial of stereotactic radiation therapy and in situ oncolytic virus therapy in metastatic triple-negative breast cancer (mTNBC) patients followed by pembrolizumab (STOMP)	Sun et al	Poster	1079
CNS	EORTC 1709/CCTG CE.8: A phase III trial of marizomib in combination with temozolomide-based radiochemotherapy versus temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma	Roth et al	Oral	2004
CNS	A multisite clinical trial of spectroscopic MRI-guided radiation dose escalation for newly diagnosed glioblastomas	Shu et al	Poster discussion	2018
CNS	Gene expression signature to predict radiation response in lower-grade gliomas	Qian et al	Poster discussion	2019
CNS	A phase II trial combining nivolumab and stereotactic brain radiosurgery for treatment of brain metastases in patients with NSCLC	Wong et al	Poster discussion	2023
CNS	Phase 1, 2 trial of concurrent anti-PD1 and stereotactic radiosurgery for melanoma and non-small cell lung cancer brain metastases (NCT02858869)	Khan et al	Poster discussion	2022
GI	Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of Phase III RCT of CROSS versus periperative chemotherapy (Modified MAGIC or FLOT protocol)	Reynolds et al	Oral	4004
GI	Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) after neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577	Kelly et al	Oral	4003
GI	Multicenter, randomized phase II study of neoadjuvant pembrolizumab plus chemotherapy and chemoradiotherapy in esophageal adenocarcinoma (EAC)	Shah et al	Oral	4005
GI	Survival and organ preservation according to clinical response after total neoadjuvant therapy in locally advanced rectal cancer patients: A secondary analysis from the organ preservation in rectal adenocarcinoma (OPRA) trial	Thompson et al	Poster discussion	3509
GU (Prostate)	Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)	Morris et al	Plenary	LBA4
GU (Prostate)	Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: An updated safety analysis	Gillessen et al	Oral	5002
GU (Prostate)	Interim results of AASUR: A single arm, multicenter phase 2 trial of apalutamide (A) + abiraterone acetate + prednisone (AA + *P*) + leuprolide with stereotactic ultrahypofractionated radiation (UHRT) in very high risk (VHR), node negative (N0) prostate cancer (PCa)	McBride et al	Poster discussion	5012
GU (Prostate)	Radiation and androgen deprivation therapy with or without docetaxel in the management of non-metastatic unfavorable-risk prostate cancer: A prospective randomized trial	D'Amico et al	Poster discussion	5011
GU (Nonprostate)	Pembrolizumab (pembro) in combination with gemcitabine (Gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIBC): A multicenter phase 2 trial	Balar et al	Poster discussion	4504

(*continued on next page*)

Table 1 (*Continued*)

Topic	Trial or study name	Authors	Session type	Abstract number
GU (Nonprostate)	Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy (RT) in patients (pts) with localized muscle invasive bladder cancer (MIBC) treated with a selective bladder preservation approach: IMMUNOPRESERVE-SOGUG trial	Garcia Del Muro et al	Poster discussion	4505
GU (Nonprostate)	Programmed death ligand-1 (PD-L1) expression in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with nivolumab (NIVO) in combination with stereotactic body radiotherapy (SBRT) in NIVES study	Masini et al	Poster	4558
GU (Nonprostate)	Phase II trial of stereotactic ablative radiation (SAbR) for oligoprogressive kidney cancer	Hannan et al	Poster	4564
GYN	Adjuvant chemotherapy after chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274)	Mileshkin et al	Plenary	LBA3
Head and neck	A randomized phase II trial of diffusion-weighted MR imaging-guided radiotherapy plus chemotherapy versus standard chemoradiotherapy in locoregional advanced nasopharyngeal carcinoma	Liu et al	Poster discussion	6018
Hematology	CALGB 50801 (Alliance): PET adapted therapy in bulky stage I/II classic Hodgkin lymphoma (cHL)	LaCasce et al	Oral	7507
Pediatrics	Mortality among 5-year survivors of childhood cancer: Results over 5 decades of follow-up in the Childhood Cancer Survivor Study	Dixon et al	Oral	10013
Pediatrics	Low-dose radiation to cardiac substructures and late-onset cardiac disease: A report from the Childhood Cancer Survivor Study (CCSS)	Bates et al	Poster discussion	10027
STS	Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the 62092-22092 STRASS trial	Haas et al	Poster	11566
STS	Preliminary results of phase 2 trial of preoperative image guided intensity modulated proton radiation therapy (IMPT) with simultaneously integrated boost (SIB) to the high-risk margin for retroperitoneal sarcomas (RPS)	DeLaney et al	Poster	11550
Thoracic	Phase 3 comparison of high-dose once-daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG	Bogart et al	Oral	8505
Thoracic	Stereotactic ablative radiotherapy in operable stage I NSCLC patients: Long-term results of the expanded STARS clinical trial	Chang et al	Oral	8506
Thoracic	Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial	Spigel et al	Poster discussion	8511
Thoracic	NRG-RTOG 1106/ACRIN 6697: A phase IIR trial of standard versus adaptive (midtreatment PET-based) chemoradiotherapy for stage III NSCLC—Results and comparison to NRG-RTOG 0617 (nonpersonalized RT dose escalation)	Kong et al	Poster	8548
The profession	Impact of machine learning-directed on-treatment evaluations on cost of acute care visits: Economic analysis of SHIELD-RT	Natesan et al	Poster discussion	1509
The profession	Specialty representation on national comprehensive cancer network guideline committees	Odei et al	Poster	11041

Abbreviations: CNS = central nervous system; DCIS = ductal carcinoma in situ; EORTC = European Organisation for Research and Treatment of Cancer; GI = gastroenterology; GU = genitourinary; GYN = gynecology; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SBRT = stereotactic body radiation therapy; STS = soft tissue sarcoma.

received or did not receive RT. Validation of these findings is needed to identify groups of patients in whom treatment intensification or deintensification is required.

A phase II trial of stereotactic radiation therapy and in situ oncolytic virus therapy in patients with metastatic triple-negative breast cancer (mTNBC) followed by pembrolizumab (STOMP)[2,^]

In this single-arm phase 2 trial, investigators assessed sequential treatment with viral vector-based gene therapy using an adenovirus-mediated expression of herpes simplex virus thymidine kinase (ADV/HSV-tk) plus ganciclovir, stereotactic body radiation therapy (30 Gy in 5 fractions), and pembrolizumab in the hope that this combination may enhance the antitumor activity of pembrolizumab alone in metastatic triple-negative breast cancer. Twenty-eight heavily pretreated patients (64.3% of whom were PD-L1 negative) received this regimen, with 9 experiencing adverse events of grade 3 to 4. Clinical benefit was noted in 21% of the patients, with a median duration on treatment of more than 1 year. A significant association was seen between immune markers and clinical responses.

Central nervous system

EORTC 1709/CCTG CE.8: A phase III trial of marizomib in combination with temozolomide-based radiochemotherapy versus temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma[3,*]

Marizomib is a novel, irreversible, and brain-penetrating panproteasome inhibitor with encouraging findings in preclinical models and early-stage clinical trials for patients with glioblastoma (GBM). In this phase 3 superiority trial across Europe and North America, a total of 749 patients with newly diagnosed GBM and a Karnofsky performance status greater than 70 were randomized to receive standard temozolomide-based chemoradiation therapy with or without concurrent and adjuvant marizomib. The addition of marizomib did not improve overall survival (15.7 vs 15.9 months) or progression-free survival (6.2 vs 6.1 months) but did result in a doubling in the rate of toxic events of grade 3 to 4 (43% vs 21%).

A multisite clinical trial of spectroscopic MRI-guided radiation dose escalation for newly diagnosed glioblastomas[4,#]

Radiation therapy (RT) dose escalation using conventional and stereotactic radiation surgery techniques have failed to improve outcomes in glioblastoma (GBM). In this multi-institutional feasibility trial, investigators assessed the feasibility and safety of focal RT dose escalation to areas at high risk for GBM recurrence based on high ratios of Choline to N-acetyl aspartate identified on magnetic resonance spectroscopy. Gross tumor volumes (GTVs) 1 and 2 were contoured as per standard protocol, whereas the GTV 3 was generated by the union of the residual tumor and the area of a high ratio of Choline to N-acetyl aspartate. Margins of 5 mm were added to create clinical tumor volumes (CTVs) 1 and 2 (CTV 3 = GTV 3) with an additional 3-mm margin expansion for planning target volumes 1, 2, and 3. These targets received 50.1, 60, and 75 Gy in 30 fractions, respectively. Thirty adult patients with GBM were evaluated (9 MGMT methylated and 28 IDH-wild type). At a median follow-up of 21.4 months, the median overall survival was 23.0 months. Eleven patients experienced toxic events of grade 3 or greater, with the majority (7) attributed to temozolomide. A phase 2 randomized trial is planned by the ECOG-ACRIN Cancer Research Group (EAF211).

Gene expression signature to predict radiation response in lower-grade gliomas[5,#]

In this analysis, investigators used the Cancer Genome Atlas and Chinese Glioma Genome Association databases to identify and validate patterns of gene expression associated with differential outcomes in patient with low-grade glioma treated with maximal safe resection and adjuvant radiation therapy. Five genes with prognostic implication (*MAP3K15*, *MAPK10*, *CCL3*, *CCL4*, and *ADAMTS1*) were identified as being involved in MAP kinase activity, T cell chemotaxis, and cell cycle transition. A high genomic risk score, defined as being in the top third of scores, was significantly associated with worse outcomes independent of age, sex, glioma histology, World Health Organization cancer grade, IDH mutation, 1p/19q codeletion, and chemotherapy status.

A phase II trial combining nivolumab and stereotactic brain radiosurgery for treatment of brain metastases in patients with NSCLC[6,#]

This single-arm clinical trial reported the results of upfront stereotactic radiation surgery (SRS) (15-21 Gy) with nivolumab in 22 patients with brain metastases less than 10 cm^3 (median [range], 2 [1-9] cm^3) from non-small cell lung cancer. The median treatment was 4.3 months and the follow-up duration was 11 months. The investigators found the median intracranial progression-free survival (primary endpoint), extracranial progression-free survival, and overall survival to be 5.0, 2.9, and 14 months, respectively. Accounting for death as a competing risk, the 1-year cumulative incidence of intracranial relapse was 17.4%. Only 2 patients experienced grade 3 adverse events related to nivolumab or SRS. In addition, freedom from neurocognitive decline (Hopkins Verbal Learning Test total recall) was 89% by 4 months, and quality-of-life scores (FACT-Br) improved from baseline within 2 to 4 months.

Phase 1, 2 trial of concurrent anti-PD1 and stereotactic radiosurgery for melanoma and non-small cell lung cancer brain metastases (NCT02858869)[7,#]

In this study, 4 patients with non-small cell lung cancer and 21 with melanoma who had 1 to 10 (mean, 2.7) brain metastases and 1 or more extracranial lesions were treated with pembrolizumab and stereotactic radiation surgery (6 received 30 Gy in 5 fractions, 12 received 27 Gy in 3 fractions, and 5 received 18-21 Gy in 1 fraction). The primary endpoint was met because no central nervous system toxic events of grade 3 had occurred at 3 months. Two patients experienced toxic events of grade 3 or greater (none experienced events of grade 5). The median overall survival (OS) was 32.8 months. The rates of 1-year OS, local control, intracranial progression-free survival, and extracranial progression-free survival were 67.8%, 95.7%, 57.5%, and 43.6%, respectively. Clinical benefit, defined as a best overall response of stable disease or better according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1, occurred in 12 patients (48%). Early activation of CD8+PD+Ki67+ T cells (within 3 weeks of starting stereotactic radiation surgery and anti-PD1) correlated with clinical benefit.

Gastrointestinal

Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol)[8,*]

Recent trials of gastric or gastroesophageal junction (GEJ) adenocarcinoma have shown efficacy of perioperative chemotherapy.[9,10] The Neo-AEGIS trial is the first randomized controlled trial to assess perioperative chemotherapy (modified MAGIC, and later, FLOT) vs standard-of-care neoadjuvant chemoradiation therapy (CRT) (CROSS[11]) in resectable, locally advanced esophageal and GEJ cancer. Notably, the trial was designed based on a 10% overall survival (OS) superiority of CROSS but was modified after the first futility analysis to a noninferiority margin of 5%. A total of 377 patients with cT2-3, N0-3 esophageal or GEJ adenocarcinoma were included. In the perioperative chemotherapy arm, 85% of patients received the modified MAGIC regimen. At a median follow-up of approximately 2 years, no difference in OS was noted between CRT and perioperative chemotherapy (approximately 56% each). Other cancer-related outcomes were not reported; however, there was significant improvement in surrogates of local recurrence in the CRT arm, including R0 margins (95% vs 82%), ypN0 (60% vs 45%), tumor regression of grade 1 to 2 (42% vs 12%), and pathologic complete response (16% vs 5%). Furthermore, perioperative chemotherapy was associated with higher rates of toxic events such as grade 3 to 4 neutropenia (14% vs 3%), neutropenic sepsis (approximately 3% vs approximately 1%), and postoperative pneumonia (20% vs 16%) but lower acute respiratory distress syndrome (0.6% vs 4.3%). We eagerly await reporting of full results of this trial.

Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577[12,13,*]

The CheckMate 577 trial[13] showed that the escalation of therapy with nivolumab doubled progression-free survival (median, 22 vs 11 months) in patients with stage 2 to 3 esophageal or gastroesophageal cancer with residual pathologic disease (minimum ypT1 or ypN1) after neoadjuvant chemoradiation therapy (CRT) and R0 resection. Expanded data were presented at the 2021 American Society of Clinical Oncology annual meeting. Nivolumab was associated with significantly decreased rates of distant recurrence (29% vs 39%) and locoregional recurrence (12% vs 17%). The median distant metastases-free survival (28.3 vs 17.6 months) and progression-free survival (not reached vs 32.1 months) was also significantly improved with nivolumab. Safety data in the nivolumab arm were acceptable. Furthermore, no detriment to quality of life (FACT-ECS, FACT-G7) was noted with immunotherapy. When evaluating these results in context with the Neo-AEGIS trial, neoadjuvant CRT followed by resection and adjuvant immunotherapy in cases without pathologic complete response represents possibly the most potent paradigm for these patients.

Multicenter, randomized phase II study of neoadjuvant pembrolizumab plus chemotherapy and chemoradiotherapy in esophageal adenocarcinoma (EAC)[14,*]

This multi-institutional, randomized phase 2 study evaluated the role of adding immunotherapy as part of definitive treatment in esophageal cancer in a neoadjuvant setting and concurrent with chemoradiation therapy (CRT). Forty patients with cT3-4Nx or T2N1 adenocarcinoma of the esophagus or gastroesophageal junction (GEJ) were randomized to receive induction carboplatin and paclitaxel with or without pembrolizumab followed by CRT (41.4 Gy in 23 fractions; carboplatin and paclitaxel) and concurrent pembrolizumab. After resection, patients received adjuvant pembrolizumab for 1 year. The primary endpoint was met because 50% of patients showed a major pathologic response (MPR) that exceeded the 30% threshold based on historical controls. An MPR was associated with superior 1-year disease-free survival (100% vs 32% without an MPR; $P = .002$). Esophageal or GEJ type I cancers had higher rates of MPR than type II-III cancers, which may have been

associated with important differences in the baseline immune microenvironment of the tumor.

Survival and organ preservation according to clinical response after total neoadjuvant therapy in locally advanced rectal cancer patients: A secondary analysis from the organ preservation in rectal adenocarcinoma (OPRA) trial[15,#]

The OPRA trial randomized patients with stage II-III rectal adenocarcinoma identified by magnetic resonance imaging to 4 months of FOLFOX or CAPEOX either before or after standard-of-care chemoradiation therapy. Patients with complete clinical response (cCR) or near complete response (nCR) were offered a watch and wait approach, whereas those with incomplete clinical response (iCR) were recommended total mesorectal excision (TME). Results of 294 patients who underwent this 3-tiered clinical response assessment were presented. Of these patients, 42.2% were categorized as cCR, 38.4% as nCR, and 19.4% as iCR. Significant differences in organ preservation (79% vs 52% vs 9%; $P < .0001$), disease-free survival (84% vs 76% vs 52%; $P < .0001$) and TME-free disease-free survival (72% vs 44% vs 4%; $P < .0001$) were noted based on the response. This information can be used to counsel physicians and patients who may be considering a watch-and-wait approach.

Genitourinary—prostate

Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)[16,17,**]

Lutetium-177-PSMA-617 (Lu-PSMA-617) is a targeted radioligand therapy that delivers β-particle radiation to cells expressing prostate-specific membrane antigen (PSMA), which are highly expressed in metastatic castrate-resistant prostate cancer (mCRPC) lesions. In the VISION trial, 831 patients with mCRPC were randomized 2:1 to receive ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks × 4-6 cycles) and investigator-determined standard of care (SOC) vs SOC only. Patients had to have been treated previously with 1 or more androgen receptor pathway inhibitors and 1 to 2 taxane regimens and have had a PSMA-positive gallium-68-labeled PSMA-11 positron emission tomography scan that was positive. At a median follow-up of 21 months, both primary endpoints were significantly improved with the addition of Lu-PSMA-617 (median radiographic progression-free survival, 8.7 vs 3.4 months; $P < .001$; median overall survival, 15.3 vs 11.3 months; $P < .001$). The secondary endpoints of overall response rate (29.8% vs 1.7%) and time to first symptomatic skeletal event (89.0% vs 66.7%) were also improved. A higher rate of toxic events, including grade 3 to 5 events, occurred in the Lu-PSMA-617 arm (28.4% vs 3.9%). Specific increased adverse events included bone marrow suppression and xerostomia as well as nausea and emesis. One key limitation of this trial was that SOC options excluded chemotherapy, immunotherapy, radium (Ra)-223, and investigational drugs. Nonetheless, this groundbreaking study supported the adoption of Lu-PSMA-617 as a new standard of care for mCRPC.

Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: An updated safety analysis[18,*]

Skeletal fractures are a frequent adverse event of systemic treatment of advanced prostate cancer. Owing to a higher-than-expected rate of fractures, particularly at sites without metastases, and to deaths associated with abiraterone and radium (Ra)-223, the ERA-223 trial[19] was prematurely unblinded. Use of bone-protecting agents (BPAs) was low (40%); however, post hoc analyses suggested benefits in preventing fracture. Therefore, the parallel EORTC-1333-GUCG trial, which was assessing the addition of Ra-223 to enzalutamide, was amended to mandate the use of BPAs. A total of 253 patients (134 after BPAs were mandated) were randomized. With a median follow-up of 36.7 months before the amendment and 23.1 months after it, a total of 39 patients reported a fracture. Among them, 30 patients (20 in the enzalutamide and Ra-223 arm) did not receive BPAs and 9 (4 in the enzalutamide and Ra-223 arm) received BPAs. Of interest, in both arms, the risk was almost abolished by a preventive continuous administration of BPAs, thus stressing the importance of complying with international recommendations in terms of giving BPAs to patients with metastatic prostate cancer.

Interim results of AASUR: A single arm, multicenter phase 2 trial of apalutamide (A) + abiraterone acetate + prednisone (AA + P) + leuprolide with stereotactic ultrahypofractionated radiation (UHRT) in very high-risk (VHR), node negative (N0) prostate cancer (PCa)[20,#]

In this trial, investigators assessed whether treatment intensification of androgen deprivation therapy (ADT) via apalutamide and abiraterone acetate plus prednisone for 6 months with concomitant ultrahypofractionated radiation therapy (RT) (7.5-8 Gy in 5 fractions) to the prostate and seminal vesicles would improve clinical outcomes in very high-risk, clinically node-negative prostate cancer. Very high-risk was defined by a Gleason score of 9 to 10, more than 4 Gleason scores of 8, or 2 high-risk features (including rT3-4 disease). The authors hypothesized that a reduction in 3-year biochemical recurrence (BCR) from 25% to 10% would be seen. A total of 64 patients were enrolled, of which 63 (98.4%) achieved an undetectable nadir prostate-specific antigen (PSA) level. Only 7 patients developed BCR. The median follow-up

for patients without BCR was 30 months. The 2- and 3-year BCR-free survival rates were 95.0% and 89.7%, respectively. For the 57 patients without BCR, 56 (98.2%) had noncastrate testosterone (>150 ng/mL) at the last follow-up. As of the last follow-up, the median PSA level was 0.10 ng/mL. Grade 3 toxic events were rare and transient. Intensified, short-course androgen deprivation with dual androgen blockage and ultrahypofractionated RT represents an attractive alternative to the standard 18 to 36 months of ADT and longer courses of RT in men with very high-risk, node-negative prostate cancer.

Radiation and androgen deprivation therapy with or without docetaxel in the management of nonmetastatic unfavorable-risk prostate cancer: A prospective randomized trial[21,22,#]

The addition of docetaxel to radical prostatectomy or radiation therapy (RT) and androgen deprivation therapy (ADT) for men with unfavorable-risk nonmetastatic prostate cancer has been studied in 7 randomized controlled trials, with negative or inconclusive results in 6 of them. Of note, some benefit was seen in the small subset of patients with high-grade, low prostate-specific antigen (PSA) cancers. In addition, because docetaxel even at low doses (ie, 20 mg/m^2) is a potent radiosensitizer, the authors felt it plausible that docetaxel may help sterilize cells that survive RT-induced damage and later develop into RT-induced cancers. Therefore, this phase 3 trial randomly assigned 350 men with unfavorable-risk prostate cancer (meeting any of the following criteria: T2c-4 or T1b-T2b and PSA level >20 ng/mL or a Gleason score [GS] ≥4 + 3 or tertiary grade 5 or biopsy GS 3 + 4 and ≥50% positive cores or PSA velocity >2 ng/mL/y or seminal vesicle invasion) to RT plus ADT with or without docetaxel. At a median follow-up of 10.2 years, overall survival (OS) was not significantly increased in the docetaxel arm (restricted mean survival time over 10 years of 9.11 vs 8.82 years; $P = .22$). Exploratory analysis in men with a PSA level <4 ng/mL vs 4 to 20 ng/mL showed that docetaxel resulted in a reduction of prostate cancer–specific mortality and OS. Caution must be taken when analyzing these results, because only 27 men had a PSA level <4 ng/mL. Interestingly, an OS benefit without a concomitant prostate cancer specific mortality benefit was seen in men with a PSA level >20 ng/mL vs 4 to 20 ng/mL. Notably, the investigators noted a significant reduction in the 10-year rate of RT-induced cancers in the docetaxel arm: 0.61% vs 4.9% ($P = .46$). Caution must be taken when interpreting these results, considering that (1) the incidence was very small (1 vs 8), (2) there was no comparator arm without RT, and (3) much larger data sets such as ProtecT[23] showed no difference in secondary malignancies between RT, radical prostatectomy, and active monitoring.

Genitourinary—nonprostate

Pembrolizumab (pembro) in combination with gemcitabine (Gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIBC): A multicenter phase 2 trial[24,#]

Trimodality bladder preservation therapy for muscle-invasive bladder cancer consists of maximal transurethral resection of the bladder tumor (TURBT) followed by chemoradiation therapy (CRT). The optimal systemic therapy regimen has not been elucidated yet. In addition, a recent meta-analysis of individual patient data showed superior locoregional control with hypofractionated radiation therapy.[25] This single-arm trial assessed the safety and efficacy of neoadjuvant pembrolizumab followed by maximal TURBT and adjuvant hypofractionated gemcitabine-based CRT (52 Gy in 20 fractions to the whole bladder) with concurrent pembrolizumab. A 6-patient, phase 1 safety lead-in was designed in which only 1 patient developed a dose-limiting toxic event (grade 2 immune-related diarrhea, which was treated with corticosteroids). This was followed by a phase 2 efficacy cohort of 48 patients. The primary endpoint was a 20% absolute improvement in the 2-year bladder-intact disease-free survival (BIDFS) rate over the 60% historical rate.[26] At 12 weeks after CRT, the complete response rate was 59% in the overall cohort. At a median follow-up of 14.6 months, the 1-year BIDFS rate was 88% in the efficacy cohort. Also in the efficacy cohort, 35% of patients had treatment-emergent adverse events (TEAEs) of grade 3 or greater. Notable pembrolizumab-related TEAEs of grade 3 or greater included 3 patients with grade 3 gastrointestinal toxic events and 1 patient with a grade 4 colonic perforation. Overall, this regimen showed promising efficacy and toxicity in this early analysis.

Phase II trial of durvalumab plus tremelimumab with concurrent radiation therapy (RT) in patients (pts) with localized muscle invasive bladder cancer (MIBC) treated with a selective bladder preservation approach: IMMUNOPRESERVE-SOGUG trial[27,#]

Preclinical studies have shown that the combination of radiation and dual-checkpoint blockade may have synergistic antitumor activity in muscle-invasive bladder cancer (MIBC). In this phase 2 study, 32 patients with T2-4aN0 MIBC who desired bladder preservation or were ineligible for cystectomy were treated with initial transurethral resection of the bladder tumor followed by durvalumab plus tremelimumab and subsequent radiation therapy (RT) (46 Gy to the minor pelvis and 64-66 Gy to the bladder). Patients with residual or relapsed MIBC were offered salvage cystectomy. The primary endpoint was complete response, defined as the absence of MIBC at the posttreatment tumor site biopsy. Complete

response at the posttreatment biopsy was documented in 26 patients (81%). After a median follow-up of 6.1 months, 2 patients underwent salvage cystectomy owing to MIBC and T1 relapses, respectively. The estimated 6-month rates for disease-free survival with bladder intact, disease-free survival, and overall survival were 76%, 80%, and 93%, respectively. Grade 3 or 4 adverse events were reported in 31% patients, including gastrointestinal toxicity (12.5%), acute kidney failure (6%), and hepatitis (6%). This trial adds to the data suggesting promising results of immunotherapy with RT-based bladder-preservation approaches.

Programmed death ligand-1 (PD-L1) expression in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with nivolumab (NIVO) in combination with stereotactic body radiation therapy (SBRT) in NIVES study[28,^]

The NIVES study prospectively evaluated combined nivolumab and stereotactic body radiation therapy in pretreated metastatic renal cell carcinoma. Although the study did not meet the primary endpoint of objective response rate, the treatment combination did show a faster time to treatment response and a long progression-free survival and median duration of response without increasing toxic effects. This exploratory analysis tested the correlation between PD-L1 expression, as evaluated by 4 commercial kits, and overall survival (OS) in 44 patients from the NIVES study. Twenty-two patients were PD-L1 negative (all tumor cells unstained), 14 were PD-L1 weakly positive (<1% positive tumor cells in ≥1 kit), and 8 were PD-L1 strongly positive (>1% to 50% or >50%). The median OS was not significantly different between patients who were PD-L1 negative vs PD-L1 positive (21 vs 18 months; $P = .56$). PD-L1 expression may not be a predictive biomarker for selecting patients to receive nivolumab-based treatment, with the main limitation being that this result is based on a very small sample size.

Phase II trial of stereotactic ablative radiation (SAbR) for oligoprogressive kidney cancer[29,^]

This phase 2, single-arm study evaluated the role of stereotactic ablative radiation (SAbR) in controlling oligoprogressive metastatic renal cell carcinoma with a goal of extending ongoing systemic therapy by more than 6 months in 4% of patients. The investigators included 20 patients who showed an initial response to systemic therapy with subsequent radiographic progression at 3 or fewer sites who then received SAbR to all 36 progressive sites. At a median follow-up of 8.3 months, SAbR extended the duration of the ongoing systemic therapy by more than 6 months in 12 patients (71%). LC was 100%. Three patients received repeat SAbR to a new site for sequential disease control. Thirteen of 20 patients progressed with a median progression-free survival of 8.7 months. Overall survival was not reached. Of importance, no grade 3 toxic effects were reported, and no significant decline in quality of life was detected. These data support further evaluation of SAbR for oligoprogressive metastatic renal cell carcinoma in a prospective randomized setting.

Gynecology

Adjuvant chemotherapy after chemoradiation as primary treatment for locally advanced cervical cancer compared with chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274)[30,**]

A significant percentage of women with locally advanced cervical cancer develop distant metastatic disease and subsequently die despite definitive chemoradiation therapy (CRT). The randomized phase 3 OUTBACK trial investigated whether the addition of 4 cycles of adjuvant carboplatin and paclitaxel chemotherapy to standard-of-care CRT and vaginal brachytherapy would improve outcomes for these patients. A total of 919 women were eligible and included in the analysis. Seventy-eight percent assigned to the adjuvant chemotherapy group received treatment. No improvement in overall survival at 5 years (the primary endpoint) was observed with the addition of adjuvant chemotherapy (72% vs 71%). No benefit was seen in progression-free survival between the 2 arms (63% vs 61%). Patterns of disease recurrence were similar in the 2 treatment groups. Adjuvant chemotherapy resulted in an increase in grade 3 to 5 adverse events within a year of randomization (81% vs 62%), although not beyond 1 year. Alternative strategies are needed to improve outcomes in this disease.

Head and neck

A randomized phase II trial of diffusion-weighted MR imaging-guided radiation therapy plus chemotherapy versus standard chemoradiotherapy in locoregional advanced nasopharyngeal carcinoma[31,#]

This phase 2 trial randomized 256 patients to receive standard computed tomography–based chemoradiation therapy (CRT) or diffusion-weighted magnetic resonance imaging (DWI)–guided dose-painting radiation therapy (DP-RT). Both groups received 3 cycles of induction chemotherapy followed by cisplatin-based CRT. In the DP-RT group, a gross tumor volume subvolume was determined based on an apparent diffusion coefficient (ADC) less than the mean ADC. This structure received 75.2 Gy in 32 fractions in patients with T1-2 disease and 77.55 Gy in 33 fractions for T3-4 disease. DWI-guided DP-RT significantly improved 2-year local recurrence-free survival (100% vs 95%), distant metastasis-free survival

(93% vs 87%), and overall survival (100% vs 95%). DWI-guided DP-RT was a significant independent prognostic factor on multivariate analysis for distant metastasis-free survival and disease-free survival. No significant differences in toxic effects were seen.

Hematologic

CALGB 50801 (Alliance): PET adapted therapy in bulky stage I/II classic Hodgkin lymphoma (cHL)[32,*]

In this landmark prospective study, patients with stage IA-IIB classical Hodgkin lymphoma with bulky disease greater than 10 cm or a maximum intrathoracic diameter greater than 0.33 on chest x-ray received 2 cycles of Adriamycin, Bleomycin, Vinblastine, Dacarbazine followed by a positron emission tomography (PET) scan. A negative PET scan was defined as Deauville 1 to 3. Patients with a negative PET scan (PET2−) received 4 additional cycles of Adriamycin, Bleomycin, Vinblastine, Dacarbazine chemotherapy without consolidative radiation therapy (RT). Patients with a positive PET scan (PET2+) received 4 cycles of escBEACOPP plus 30 Gy involved-site RT. Among 94 evaluable patients, 73 became PET2−. Three-year progression-free survival (PFS) was 93.1% in patients who were PET2− and 89.7% in patients who were PET2+. The protocol-defined primary endpoint was met because the PFS hazard ratio for PET2+ vs PET2− was less than 4.1 (1-sided $P = .04$). Thus, the PET-adapted approach proved successful in omitting RT in most patients while allowing for escalation of therapy in PET-positive patients to avoid inferior outcomes.

Pediatrics

Mortality among 5-year survivors of childhood cancer: Results over 5 decades of follow-up in the Childhood Cancer Survivor Study[33,*]

In this report, all-cause, cause-specific, and late health-related mortality (HRM) more than 5 years from diagnosis were evaluated in 34,230 survivors diagnosed at younger than 21 years of age between 1970 and 1999. All-cause mortality by time from diagnosis showed a U-shaped distribution: 10.1 deaths per 1000 person-years at 5 to 9 years after diagnosis, largely owing to recurrence of the primary cancer, decreased to 4.1 deaths per 1000 person-years at 15 to 19 years after diagnosis before increasing to 18.5 deaths per 1000 person-years at 40 to 48 years after diagnosis, attributable to an increasing mortality rate from HRM (2.3 deaths per 1000 person-years at 5-9 years after diagnosis compared with 17.0 at 40-48 years after diagnosis). Of 5916 deaths, 51.2% were attributable to health-related causes including subsequent neoplasm (1458 deaths), cardiac causes (504 deaths), and pulmonary causes (238 deaths). HRM was significantly higher among the youngest group of survivors (0-4 years at diagnosis), non-Hispanic Black individuals, and those who received radiation therapy to the brain, chest, or total body or who were exposed to anthracycline or to alkylating or platinum chemotherapy. In summary, aging survivors consistently remain at higher risk of all-cause mortality compared with the general aging population, primarily owing to a persistent 4-fold increased risk of HRM. This study highlights the importance of continued late-effects surveillance and reduction of therapies associated with long-term morbidity and mortality.

Low-dose radiation to cardiac substructures and late-onset cardiac disease: A report from the Childhood Cancer Survivor Study (CCSS)[34,#]

A deeper understanding of associations between the radiation therapy (RT) dose to cardiac substructures and the risk of specific cardiac outcomes is needed. In this study, fields were reconstructed on an age-scaled computational phantom for more than 12,000 survivors of childhood cancer (median age of diagnosis, 6.1 years, with a median follow-up of 30 years) who received RT. Mean doses to the entire heart, cardiac chambers, valves, and left main anterior descending (LAD), circumflex, and right coronary (RCA) arteries were estimated and associations between the mean RT dose to each structure and patient outcomes were evaluated using piecewise exponential models (including the cumulative anthracycline dose). Mean doses less than 5 Gy were not associated with increased risk of coronary artery disease (CAD), heart failure, or valvular disease. Mean doses of 5 to 9.9 Gy to the RCA, LAD, and left ventricle but not to the whole heart were associated with increased risk of CAD. Mean doses of 5 to 9.9 Gy to the aortic valve and tricuspid valve but not to the whole heart were associated with risk of valvular disease. There was no association between RT at a mean dose of 5 to 9.9 Gy to any cardiac structure with increased risk of heart failure. Mean doses of 10 Gy or greater to nearly all substructures and the entire heart were associated with increased risk of CAD, heart failure, or vascular disease.

Soft-tissue sarcoma

Critical impact of radiation therapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the 62092-22092 STRASS trial[35,^]

The STRASS trial[36] failed to detect superiority with the addition of neoadjuvant radiation therapy (RT) in patients with resectable retroperitoneal sarcoma; however, significant limitations[37-39] in the trial design, RT techniques, and RT compliance were noted that could have masked the potential benefit of RT. Of importance,

low RT protocol compliance was initially reported (65%), including a 26% major deviation rate, which has been associated with inferior outcomes in multiple malignancies.[40-43] Therefore, these authors examined the effect of RT compliance on patient outcomes in the STRASS trial. Patients were classified into 2 groups: RT compliant and RT noncompliant. After final review, 75% of patients were deemed to have RT-compliant plans; the majority of errors were due to incorrect target volume delineations. Patients with RT-compliant plans had significant improvement in 3-year abdominal recurrence-free survival compared with those without compliance (67.2% vs 48.4%). In addition, a trend toward improved 3-year overall survival was also noted in favor of the RT-compliant plan group (89.9% vs 75.4%; $P = .07$). Future studies comparing protocol-compliant RT vs no RT are warranted.

Preliminary results of phase 2 trial of preoperative image guided intensity modulated proton radiation therapy (IMPT) with simultaneously integrated boost (SIB) to the high-risk margin for retroperitoneal sarcomas (RPS)[44,^]

The risk of local recurrence of retroperitoneal sarcoma (RPS) is often greatest at the posterior margin. Dose-escalated radiation therapy (RT) using a simultaneous integrated boost (SIB) is a strategy that can potentially help reduce this risk; however, nearby dose-limiting organs limit the extent of escalation that is possible. Proton RT has the advantage of no exit dose and provides an opportunity to overcome this specific limitation. In this phase 2 study, investigators combined these 2 techniques and administered preoperative intensity modulated proton therapy to a uniform dose of 50.4 GyRBE in 28 fractions with a SIB of 63.0 GyRBE to the posterior margin to 60 patients. Of these, 51 underwent surgery and an additional 5 were awaiting surgery. Four patients developed distant metastases before surgery. With an approximately 2-year median follow-up from the start of RT, only 2 local recurrences were observed. Some perioperative morbidity was noted but not beyond the historical expected range for RPS. Given these results, further study integrating RT into treatment for RPS is warranted.

Thoracic

Phase 3 comparison of high-dose once-daily (QD) thoracic radiation therapy (TRT) with standard twice-daily (bid) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG[45,*]

The standard of care for limited-stage small cell lung cancer (LS-SCLC) is radiation therapy (RT) administered twice daily with concurrent chemotherapy[46]; however, the inconvenience of twice-daily treatment limits its application in favor of once-daily RT. The CALGB 30610/RTOG 0538 trial randomized 638 patients with LS-SCLC to receive thoracic RT at a dosage of either 45 Gy twice daily (313 patients) or 70 Gy once daily (325 patients). After a median follow-up of approximately 3 years, once-daily treatment compared with twice-daily treatment did not result in a significant difference in overall survival (median, 30.5 months vs 28.7 months) or progression-free survival. Grade 3+ hematologic and nonhematologic AEs were similar between cohorts including febrile neutropenia, dyspnea, esophageal pain, and dysphagia. Grade 5 AEs were reported in 3.7% of the once-daily cohort and 1.7% of the twice-daily cohort. Similar to the conclusions of the CONVERT[47] study of BID vs QD RT, the authors concluded that despite failing to show superiority, the favorable outcomes of this trial supported high-dose RT once daily as an acceptable option in patients with LS-SCLC. The findings of future trials evaluating dose escalated, twice-daily,[48] hypofractionated RT[49] and/or adjuvant immunotherapy[50] may represent potential options to improve outcomes in patients with LS-SCLC.

Stereotactic ablative radiation therapy in operable stage I NSCLC patients: Long-term results of the expanded STARS clinical trial[51,52,*]

The pooled analysis of the STARS and ROSEL trials[53] showed improved overall survival (OS) with stereotactic ablative radiation (SAbR) versus lobectomy with mediastinal lymph node dissection (LND) in operable stage I non-small cell lung cancer (NSCLC); however, the limited sample size (58 patients) limits any definitive conclusions. Given the challenges in accrual, investigators expanded the STARS protocol to a single-arm SAbR trial (54 Gy in 3 fractions, peripheral; 50 Gy in 4 fractions, central) and compared the results with those of a published, longitudinally followed institutional cohort of 229 patients with stage IA NSCLC who received video-assisted thoracoscopic surgery (VATS)-LND. Key inclusion criteria included tumors less than 3 cm, N0M0, and staging by positron emission tomography and/or computed tomography and endobronchial ultrasound. The study was designed to test noninferiority of SAbR, specified as a 3-year OS not lower than 12% than the historical VATS-LND cohort. With a median follow-up of 61 months, the 3-year OS and progression-free survival (PFS) rates were 91% and 87%, respectively, and the 5-year OS and PFS rates were 80% and 77%, respectively. After propensity score matching, no significant differences were observed between SAbR or VATS-LND in terms of PFS, lung cancer–specific survival, or cumulative incidence rates of local, regional, or distant failures. The SABR arm was associated with significantly higher 3-year and 5-year OS compared with VATS-LND (3-year, 91% vs 87%; 5-year, 82% vs 72%; $P = .01$ from a log-rank test). Although the results are promising, fully

completed trials of SAbR versus surgery in operable stage IA disease remain necessary.

Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial[54,#]

The landmark PACIFIC trial[55] established consolidation durvalumab after concurrent chemoradiation therapy as a new standard of care for unresectable stage III non-small cell lung cancer. In the latest update, with a median follow-up duration of 34.2 months, the median overall survival (47.5 vs 29.1 months) and progression-free survival (16.9 vs 5.6 months) remained consistently in favor of durvalumab. The 60-month rates of overall survival and progression-free survival were 42.9% and 33.1%, respectively, with durvalumab and 33.4% and 19.0%, respectively, with placebo. This represents unprecedented progress in this disease.

NRG-RTOG 1106/ACRIN 6697: A phase IIR trial of standard versus adaptive (midtreatment PET-based) chemoradiotherapy for stage III NSCLC—Results and comparison to NRG-RTOG 0617 (nonpersonalized RT dose escalation)[56,^]

This phase 2 randomized trial studied whether adaptive chemoradiation therapy (CRT) using midtreatment fludeoxyglucose–positron emission tomography (after approximately 40 Gy) to personalize radiation therapy (RT) dose intensification simultaneously with field reduction would improve outcomes compared with CRT (60 Gy; carboplatin plus paclitaxel). Of note, no patients received consolidative immunotherapy. A total of 127 patients were randomized 2:1 to receive adaptive CRT (increase to daily fraction, 2.2-3.8 Gy up to 80.4 Gy in 30 fractions; median actual dose, 71 Gy). The 2-year local-regional-progression freedom was 59.5% for standard RT versus 54.6% for adaptive RT (P = .66); the 3-year OS rates were 49.1% versus 47.5% (P = .80). An exploratory analysis of 2-year in-field local primary tumor control and local-regional tumor control (institution-assessed) were 58.5% and 55.6%, respectively, for standard RT and 75.6% and 66.3%, respectively, for adaptive RT. No detrimental toxic effects on OS or cardiac events occurred with adaptive dose escalation. More studies are needed to refine personalized RT while incorporating immunotherapy.

The Profession

Impact of machine learning-directed on-treatment evaluations on cost of acute care visits: Economic analysis of SHIELD-RT[57,#]

In this analysis of the System for High-Intensity Evaluation During Radiation Therapy (SHIELD-RT), patients who received radiation therapy (RT) during a 6-month time span at Duke University Medical Center were evaluated by a machine learning algorithm to identify high-risk courses (defined as >10% risk of an acute emergency room [ER] visit during RT). High-risk patients were then randomized to weekly (standard [S]) or twice weekly [TW] intervention) evaluation during RT. Cost data associated with acute ER visits were obtained and compared between cohorts. Of 311 high-risk RT courses evaluated, the 154 patients in the TW arm had fewer hospitalizations (29 vs 41) and ER visits (18 vs 33) than did the 157 patients in the S arm. The mean (SD) cost associated with acute ER visits was significantly lower in the TW arm ($1939 [$5912]) compared with the S arm ($4002 [$11,568]). SHIELD-RT represents a tangible application of machine learning to improve financial toxicity for patients.

Specialty representation on national comprehensive cancer network guideline committees[58,^]

This study aimed to assess whether there was adequate representation of radiation oncologists (ROs) on National Comprehensive Cancer Network (NCCN) committees (NCMs). Fifty-seven Category 1 or 2A recommendations for radiation therapy (RT) were analyzed, from which a total of 1284 committee members were identified. Overall, 42.2% were medical oncologist, 23.9% were surgical oncologists (SOs), and 11.5% were ROs. The representation of ROs was highest for head and neck cancer NCMs (38.8%) and prostate cancer NCMs (25.8%). Forty-two percent of the NCMs recommending RT had less than 10% representation of ROs; 17% of guidelines recommending RT had input from 1 or no ROs, including guidelines from 4 NCMs that did not have a single RO committee member. Efforts to ensure more proportional representation of ROs on NCCN guideline committees, particularly in those where RT is a Category 1 recommendation, are warranted, including exploring potential barriers to committee leadership.

References

1. Vicini F, Shah C, Whitworth PW, et al. A novel biosignature identifies DCIS patients with a poor biologic subtype with an unacceptably high rate of local recurrence after breast conserving surgery and radiotherapy. *J Clin Oncol*. 2021;39. 513-513.
2. Sun K, Ensor JE, Xu Y, et al. A phase II trial of stereotactic radiation therapy and in situ oncolytic virus therapy in metastatic triple-negative breast cancer (mTNBC) patients followed by pembrolizumab (STOMP). *J Clin Oncol*. 2021;39. 1079-1079.
3. Roth P, Gorlia T, Reijneveld JC, et al. EORTC 1709/CCTG CE.8: A phase III trial of marizomib in combination with temozolomide-based radiochemotherapy versus temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma. *J Clin Oncol*. 2021;39:2004.
4. Shu H-KG, Mellon EA, Kleinberg L, et al. A multisite clinical trial of spectroscopic MRI-guided radiation dose escalation for newly-diagnosed glioblastomas. *J Clin Oncol*. 2021;39:2018.

5. Qian DC, Marascio JA, Neill SG, et al. Gene expression signature to predict radiation response in lower-grade gliomas. *J Clin Oncol*. 2021;39:2019.
6. Wong P, Florescu M, Plourde M-E, et al. A phase II trial combining nivolumab and stereotactic brain radiosurgery for treatment of brain metastases in patients with NSCLC. *J Clin Oncol*. 2021;39:2023.
7. Khan MK, Nasti T, Kleber T, et al. Phase 1, 2 trial of concurrent anti-PD1 and stereotactic radiosurgery for melanoma and non-small cell lung cancer brain metastases (NCT02858869). *J Clin Oncol*. 2021;39:2022.
8. Reynolds JV, Preston SR, O'Neill B, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). *J Clin Oncol*. 2021;39:4004.
9. Cunningham D, Allum WH, Stenning SP, et al. perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
10. Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial. *Lancet*. 2019;393:1948–1957.
11. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–2084.
12. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577. *J Clin Oncol*. 2021;39:4003.
13. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med*. 2021;384:1191–1203.
14. Shah MA, Almhanna K, Iqbal S, et al. Multicenter, randomized phase II study of neoadjuvant pembrolizumab plus chemotherapy and chemoradiotherapy in esophageal adenocarcinoma (EAC). *J Clin Oncol*. 2021;39:4005.
15. Thompson H, Kim JK, Yuval JB, et al. Survival and organ preservation according to clinical response after total neoadjuvant therapy in locally advanced rectal cancer patients: A secondary analysis from the organ preservation in rectal adenocarcinoma (OPRA) trial. *J Clin Oncol*. 2021;39:3509.
16. Morris MJ, Bono JSD, Chi KN, et al. Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). *J Clin Oncol*. 2021;39. LBA4-LBA4.
17. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385:1091–1103.
18. Gillessen S, Choudhury A, Rodriguez-Vida A, et al. Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: An updated safety analysis. *J Clin Oncol*. 2021;39:5002.
19. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:408–419.
20. McBride SM, Spratt DE, Kollmeier M, et al. Interim results of AASUR: A single arm, multi-center phase 2 trial of apalutamide (A) + abiraterone acetate + prednisone (AA+*P*) + leuprolide with stereotactic ultra-hypofractionated radiation (UHRT) in very high risk (VHR), node negative (N0) prostate cancer (PCa). *J Clin Oncol*. 2021;39:5012.
21. D'Amico AV, Xie W, McMahon E, et al. Radiation and androgen deprivation therapy with or without docetaxel in the management of nonmetastatic unfavorable-risk prostate cancer: A prospective randomized trial. *J Clin Oncol*. 2021. 0:JCO.21.00596.
22. D'Amico AV, Xie W, McMahon E, et al. Radiation and androgen deprivation therapy with or without docetaxel in the management of non-metastatic unfavorable-risk prostate cancer: A prospective randomized trial. *Journal of Clinical Oncology*. 2021;39:5011.
23. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415–1424.
24. Balar AV, Milowsky MI, O'Donnell PH, et al. Pembrolizumab (pembro) in combination with gemcitabine (Gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIBC): A multicenter phase 2 trial. *J Clin Oncol*. 2021;39:4504.
25. Choudhury A, Porta N, Hall E, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: An individual patient data meta-analysis of the BC2001 and BCON trials. *Lancet Oncol*. 2021;22:246–255.
26. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol*. 2014;32:3801–3809.
27. XGd Muro, Valderrama BP, Medina A, et al. Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy (RT) in patients (pts) with localized muscle invasive bladder cancer (MIBC) treated with a selective bladder preservation approach: IMMUNOPRESERVE-SOGUG trial. *J Clin Oncol*. 2021;39:4505.
28. Masini C, Carlinfante G, Iotti C, et al. Programmed death ligand-1 (PD-L1) expression in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with nivolumab (NIVO) in combination with stereotactic body radiotherapy (SBRT) in NIVES study. *J Clin Oncol*. 2021;39:4558.
29. Hannan R, Christensen M, Garant A, et al. Phase II trial of stereotactic ablative radiation (SAbR) for oligoprogressive kidney cancer. *J Clin Oncol*. 2021;39:4564.
30. Mileshkin LR, Moore KN, Barnes E, et al. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). *J Clin Oncol*. 2021;39. LBA3-LBA3.
31. Liu F, Fu S, Chen Y, et al. A randomized phase II trial of diffusion-weighted MR imaging-guided radiotherapy plus chemotherapy versus standard chemoradiotherapy in locoregional advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2021;39:6018.
32. LaCasce AS, Dockter T, Ruppert AS, et al. CALGB 50801 (Alliance): PET adapted therapy in bulky stage I/II classic Hodgkin lymphoma (cHL). *J Clin Oncol*. 2021;39:7507.
33. Dixon SB, Liu Q, Ehrhardt MJ, et al. Mortality among five-year survivors of childhood cancer: Results over five decades of follow-up in the Childhood Cancer Survivor Study. *J Clin Oncol*. 2021;39:10013.
34. Bates JE, Shrestha S, Liu Q, et al. Low-dose radiation to cardiac substructures and late-onset cardiac disease: A report from the Childhood Cancer Survivor Study (CCSS). *J Clin Oncol*. 2021;39:10027.
35. Haas RLM, Stelmes J-J, Zaffaroni F, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the 62092-22092 STRASS trial. *J Clin Oncol*. 2021;39:11566.
36. Bonvalot S, Gronchi A, Le Péchoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1366–1377.

37. Chowdhary M, Spraker MB. Preoperative radiotherapy for retroperitoneal sarcoma. *Lancet Oncol*. 2021;22:e2.
38. DeLaney T, Mullen JT, Wang D, et al. Preoperative radiotherapy for retroperitoneal sarcoma. *Lancet Oncol*. 2021;22:e1.
39. Izzuddeen Y, Sharma DN. Preoperative radiotherapy for retroperitoneal sarcoma. *Lancet Oncol*. 2021;22:e3.
40. Abrams RA, Winter KA, Regine WF, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704—: A phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys*. 2012;82:809–816.
41. Ohri N, Shen X, Dicker AP, et al. Radiotherapy protocol deviations and clinical outcomes: A meta-analysis of cooperative group clinical trials. *J Natl Cancer Inst*. 2013;105:387–393.
42. Glynne-Jones R, Meadows HM, Lopes A, et al. Impact of compliance to chemoradiation on long-term outcomes in squamous cell carcinoma of the anus: Results of a post hoc analysis from the randomised phase III ACT II trial☆. *Ann Oncol*. 2020;31:1376–1385.
43. Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: Results from TROG 02.02. *J Clin Oncol*. 2010;28:2996–3001.
44. DeLaney TF, Mullen JT, Chen Y-L, et al. Preliminary results of phase 2 trial of preoperative image guided intensity modulated proton radiation therapy (IMPT) with simultaneously integrated boost (SIB) to the high-risk margin for retroperitoneal sarcomas (RPS). *J Clin Oncol*. 2021;39:11550.
45. Bogart JA, Wang XF, Masters GA, et al. Phase 3 comparison of high-dose once-daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. *J Clin Oncol*. 2021;39:8505.
46. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340:265–271.
47. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): An open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18:1116–1125.
48. Grønberg BH, Killingberg KT, Fløtten Ø, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: An open-label, randomised, phase 2 trial. *Lancet Oncol*. 2021;22:321–331.
49. Qiu B, Li Q, Liu J, et al. Moderately hypofractionated once-daily compared with twice-daily thoracic radiation therapy concurrently with etoposide and cisplatin in limited-stage small cell lung cancer: A multicenter, phase II, randomized trial. *Int J Radiat Oncol Biol Phys*. 2021;111:424–435.
50. Ross HJ, Hu C, Higgins KA, et al. NRG Oncology/Alliance LU005: A phase II/III randomized clinical trial of chemoradiation versus chemoradiation plus atezolizumab in limited stage small cell lung cancer. *J Clin Oncol*. 2020;38:TPS9082.
51. Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy in operable stage I NSCLC patients: Long-term results of the expanded STARS clinical trial. *J Clin Oncol*. 2021;39:8506.
52. Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy for operable stage 1 non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol*. 2021;22 (10):1448–1457. https://doi.org/10.1016/S1470-2045(21)00401-0.
53. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: A pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16:630–637.
54. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. *J Clin Oncol*. 2021;39:8511.
55. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.
56. Kong F-MS, Hu C, Haken RT, et al. NRG-RTOG 1106/ACRIN 6697: A phase IIR trial of standard versus adaptive (mid-treatment PET-based) chemoradiotherapy for stage III NSCLC—Results and comparison to NRG-RTOG 0617 (non-personalized RT dose escalation). *J Clin Oncol*. 2021;39:8548.
57. Natesan D, Thomas SM, Eisenstein E, et al. Impact of machine learning-directed on-treatment evaluations on cost of acute care visits: Economic analysis of SHIELD-RT. *J Clin Oncol*. 2021;39:1509.
58. Odei B, Agabalogun T, Bello-Pardo E, et al. Specialty representation on National Comprehensive Cancer Network guideline committees. *J Clin Oncol*. 2021;39:11041.