



Clinical Trials in Spinal Tumors: A Two-Decade Review

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■ **OBJECTIVE:** Clinical trials are essential for assessing the advancements in spine tumor therapeutics. The purpose of the present study was to characterize the trends in clinical trials for primary and metastatic tumor treatment during the past 2 decades.

■ **METHODS:** The ClinicalTrials.gov database was queried using the search term “spine” for all interventional studies from 1999 to 2020 with the categories of “cancer,” “neoplasm,” “tumor,” and/or “metastasis.” The tumor type, phase data, enrollment numbers, and home institution country were recorded. The sponsor was categorized as an academic institution, industry, government, or other and the intervention type as procedure, drug, device, radiation therapy, or other. The frequency of each category and the cumulative frequency during the 20-year period were calculated.

■ **RESULTS:** A total of 106 registered trials for spine tumors were listed. All, except for 2, that had begun before 2008 had been completed. An enrollment of 51–100 participants (29.8%) was the most common, and most were phase II studies (54.4%). Most of the studies had examined metastatic tumors (58.5%), and the number of new trials annually had increased 3.4-fold from 2009 to 2020. Most of the studies had been conducted in the United States (56.4%). The most common intervention strategy was radiation therapy (32.1%), although from 2010 to 2020, procedural studies had become the most frequent (2.4/year). Most of the studies had been sponsored by academic institutions (63.2%), which during the 20-year period had sponsored 3.2-fold more studies compared with the industry partners.

■ **CONCLUSIONS:** The number of clinical trials for spine tumor therapies has rapidly increased during the past 15 years, owing to studies at U.S. academic medical institutions investigating radiosurgery for the treatment of metastases. Targeted therapies for tumor subtypes and sequelae have updated international best practices.

INTRODUCTION

Tumors of the spine have been broadly categorized as either primary tumors, which arise from the spine and adjacent structures, or metastatic tumors, which originate from distant organs and spread to the spine.¹ The standard of care for metastatic tumors has been intralesional resection and decompressive surgery aimed at palliation and restoration of neurological function, in addition to corticosteroids and targeted radiation therapy.^{1,2} Primary spinal tumors have been much less common than have metastatic tumors to the spine.³ Their rarity has made their management more complex and less well-established. Although surgery has remained a critical component in the treatment of primary spine tumors, a comprehensive care strategy with a multidisciplinary approach will often be required.³

Surgical techniques, pharmacologic management, percutaneous intervention, radiation therapy, and molecular sequencing approaches are now part of the physician's armamentarium.⁴ However, the significant morbidity for both primary and metastatic tumor populations warrants further research to develop safe and efficacious treatment options.^{2,4} As the field continues to evolve, clinical trials are essential for assessing the utility of ongoing advancements in the management of spine tumor pathologies. In the present review, we analyzed the

Key words

- Clinical trial
- Metastasis
- Radiosurgery
- Spine
- Tumor

Abbreviations and Acronyms

NIH: National Institutes of Health

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historical and ongoing trends for spine tumor clinical trials to provide insight regarding the various stakeholders and advancements in the past 2 decades.

METHODS

The [ClinicalTrials.gov](https://www.clinicaltrials.gov) database was queried using the search term “spine” for all available studies.⁵ The search results were limited to interventional trials only and were broadly categorized as trials of procedures (e.g., spine fusion, cryoablation), drugs (e.g., tranexamic acid, zoledronic acid), devices (e.g., magnetic resonance imaging, balloon kyphoplasty), radiation therapy (e.g., stereotactic body radiation therapy, brachytherapy), and

“other” for miscellaneous interventions (e.g., comprehensive bone health assessment, physical rehabilitation). Next, studies with the condition category of “cancer,” “neoplasm,” “tumor,” “metastasis,” or “metastases” were selected. One study, for which spine tumor therapy was not a main outcome, was excluded.

The study data were analyzed using this final cohort. The trials were categorized as pertaining to primary tumors or metastatic tumors, or both. The available phase data and current enrollment numbers were also collected. The studies were classified according to the following progress status when such data were available: not yet recruiting, recruiting, active, completed, terminated, withdrawn, or suspended. A study’s home institution country was

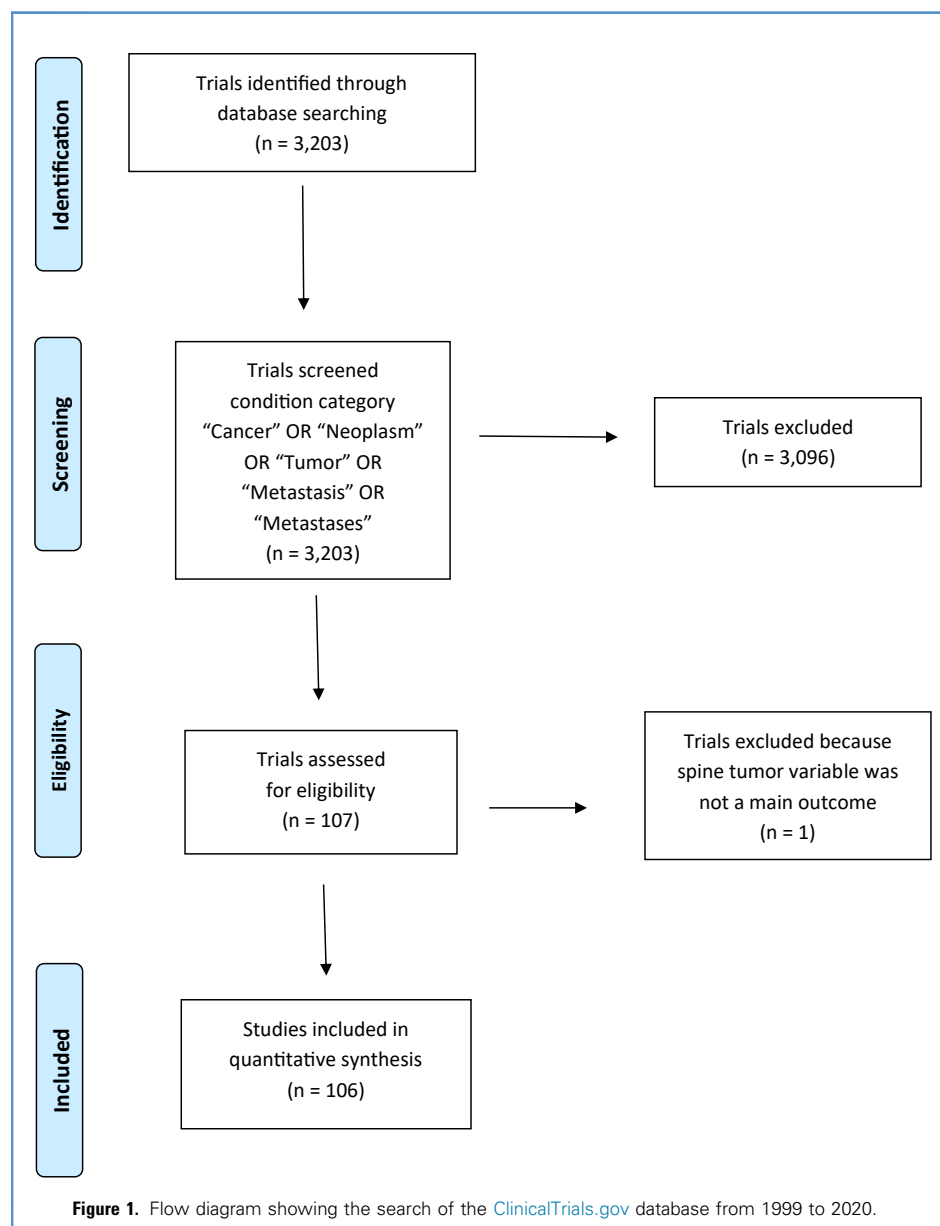


Table 1. Clinical Trials Directory

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Funder	
NCT01308489	Minimally invasive surgery in treating patients with spinal tumors	Terminated	Spinal neoplasm and metastases	City of Hope Medical Center, National Cancer Institute	NA	7	NIH
NCT01407341	Beta-tricalcium phosphate bone graft in treating patients undergoing surgery for metastatic spine cancer	Terminated	Spinal neoplasm and metastases	University of Southern California, National Cancer Institute	I	1	NIH
NCT01345903	Robotic-assisted surgery in treating patients with spine tumors	Withdrawn	Spinal neoplasms and metastases	City of Hope Medical Center, National Cancer Institute	NA	0	NIH
NCT04119037	Cordotomy in reducing pain in patients with advanced cancer	Recruiting	Spinal neoplasms and metastases	MD Anderson Cancer Center, National Cancer Institute, National Institute of Nursing Research	NA	42	NIH
NCT03658070	A study of XY0206 in subjects with advanced or metastatic solid tumours	Not yet recruiting	Spinal neoplasms and metastases	Shijiazhuang Yiling Pharmaceutical Co., Ltd.	I	34	Industry
NCT03204942	Dorsal root ganglion thermal radiofrequency versus pulsed radiofrequency for metastatic pain in thoracic vertebral body	Completed	Spinal metastases	National Cancer Institute, Egypt	NA	69	Academic
NCT00819832	Anderson circulating tumor cell burden (CTCB) study	Terminated	Spinal neoplasms and metastases	MD Anderson Cancer Center, Arthro Care Corp.	IV	3	Academic
NCT00211237	CAFE study - cancer patient fracture evaluation	Completed	Spinal neoplasms and metastases	Medtronic Spine LLC	NA	134	Industry
NCT02856048	Co-treatment with GnRH analogs on the ovarian reserve in young women treated with alkylating agents for cancer	Active, not recruiting	Spinal neoplasms and metastases	Assistance Publique — Hopitaux de Paris	II, III	11	Academic
NCT01651182	Tranexamic acid versus placebo for blood to reduce perioperative bleeding post-liver resection	Completed	Spinal neoplasms and metastases	Sunnybrook Health Sciences Centre, University of Toronto	III	24	Other
NCT01346124	High dose intensity modulated proton radiation treatment +/- surgical resection of sarcomas of the spine, sacrum and base of skull	Active, not recruiting	Spinal neoplasms	Massachusetts General Hospital, MD Anderson Cancer Center, National Cancer Institute	NA	64	NIH
NCT00592748	Charged particle RT for chordomas and chondrosarcomas of the base of skull or cervical spine	Completed	Spinal neoplasms	Massachusetts General Hospital	I, II	381	Academic

ID, identification; NA, not applicable; NIH, National Institutes of Health; GnRH, gonadotropin-releasing hormone; RT, radiation therapy; iGame, digital intervention for the modification of lifestyles; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; t-RFA, targeted radiofrequency ablation; RF-TVA, radiofrequency targeted vertebral augmentation; SRS, stereotactic radiosurgery; TPS, treatment planning system; NHS, National Health Services Trust; NR, not reported; PAD, bortezomib, doxorubicin, dexamethasone; Mgmt, management; MRI, magnetic resonance imaging; RF, radiofrequency; MR, magnetic resonance; SSRS, spine stereotactic radiosurgery; IMRT, intensity-modulated radiation therapy; NCRI, National Cancer Research Institute; SBRT, stereotactic body radiation therapy; PEEK, polyether ether ketone; IDF, Israel Defense Forces.

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Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Funder
NCT00394888	Hemangioma associated with high rates of morbidity	Completed	Spinal neoplasms	Medical College of Wisconsin, University of California, San Francisco, Columbia University, Baylor College of Medicine	NA	433 Academic
NCT04343573	Proton craniospinal radiation therapy vs. partial photon radiation therapy for leptomeningeal metastasis from solid tumors	Recruiting	Spinal neoplasms	Memorial Sloan Kettering Cancer Center	II	100 Academic
NCT04019119	iGame randomized control trial protocol	Not yet recruiting	Spinal neoplasms and metastases	University of Malaga, Horizon 2020-European Commission	NA	400 Academic
NCT00802659	A phase I/II dose escalation study using extracranial stereotactic radiosurgery to control pain	Terminated	Spinal metastases	Washington University School of Medicine	NA	2 Academic
NCT03249584	OsteoCool tumor ablation post-market study	Recruiting	Spinal metastases	Medtronic Neuro	NA	250 Industry
NCT00525590	Exploratory study, evaluating the treatment effect of surgery plus GLIADEL® wafer in patients with metastatic brain cancer	Completed	Spinal metastases	Eisai Inc.	II	69 Industry
NCT02966574	Magnetic resonance imaging of the whole body, including diffusion, in the medical evaluation of breast cancers at high risk for metastasis and the follow-up of metastatic cancers	Recruiting	Spinal metastases	Brugmann University Hospital	NA	50 Academic
NCT00853528	Stereotactic radiosurgery in treating patients with spinal metastases	Completed	Spinal metastases	Boston Medical Center, U.S. Department of Defense	I	18 U.S. federal government
NCT00030628	Radiosurgery with or without whole-brain radiation therapy in treating patients with brain metastases	Completed	Spinal metastases	Alliance for Clinical Trials in Oncology, National Cancer Institute	III	480 NIH
NCT00922974	Image-guided radiosurgery or stereotactic body radiation therapy in treating patients with localized spine metastasis	Completed	Spinal metastases	Radiation Therapy Oncology Group, National Cancer Institute, NRG Oncology	II, III	399 NIH
NCT00080912	Single vs. multiple-fraction therapy in treating patients with previously irradiated painful bone metastases	Completed	Spinal metastases	National Cancer Institute of Canada Clinical Trials Group, National Cancer Institute, Radiation Therapy Oncology Group, Trans-Tasman Radiation Oncology Group, Cancer Research UK	NA	850 NIH
NCT00855803	Stereotactic body radiation therapy and vertebroplasty in treating patients with localized spinal metastasis	Recruiting	Spinal metastases	University of Texas Southwestern Medical Center	II	42 Academic
NCT02376933	Vertebral augmentation and radiotherapy of collapse spinal metastatic cancer	Terminated	Spinal metastases	University of Arizona	NA	11 Academic
NCT00678158	Study using high-dose single fraction image-guided radiotherapy for metastatic lesions to soft tissue masses, lymph node, or bone	Completed	Spinal metastases	Memorial Sloan Kettering Cancer Center	I	68 Academic

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Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase	Enrollment	Funder
NCT03632005	Negative pressure wound therapy vs. sterile dressing for patients undergoing thoracolumbar spine surgery	Recruiting	Spinal metastases	John Street, KCI USA, Inc., University of British Columbia Orthopaedics Research Excellence Fund, University of British Columbia	NA	550	Industry
NCT01254903	Phase I study of feasibility of single session spine stereotactic radiosurgery (SSRS) in the primary management in patients with inoperable, previously unirradiated metastatic epidural spinal cord compression (MESCC)	Active, not recruiting	Spinal metastases	MD Anderson Cancer Center	I	43	Academic
NCT01256554	Single session spine stereotactic radiosurgery in metastatic epidural spinal cord compression	Active, not recruiting	Spinal metastases	MD Anderson Cancer Center	I	11	Academic
NCT03575949	Dual-time point (DTP) FDG PET CT for the post-treatment assessment of head and neck tumors following definitive chemoradiation therapy	Recruiting	Spinal metastases	MD Anderson Cancer Center, National Cancer Institute	NA	50	NIH
NCT02081053	Evaluating clinical outcomes of targeted radiofrequency ablation and kyphoplasty (also known as vertebral augmentation) to treat painful metastatic vertebral body tumors	Terminated	Spinal metastases	DFINE Inc., Merit Medical Systems, Inc.	NA	30	Industry
NCT02225223	Evaluation of t-RFA and RF-TVA prior to/following radiation therapy to treat painful metastatic vertebral body tumor(s)	Terminated	Spinal metastases	Merit Medical Systems, Inc., DFINE, Inc.	NA	36	Industry
NCT02716948	SRS and nivolumab in treating patients with newly diagnosed melanoma metastases in the brain or spine	Active, not recruiting	Spinal metastases	Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University, Accuray Inc.	I	90	Industry
NCT02387905	Cement augmentation in preventing vertebral body compression fracture following spine stereotactic radiosurgery in patients with solid tumors and spinal metastases	Recruiting	Spinal metastases	MD Anderson Cancer Center, National Cancer Institute	II	80	NIH
NCT01542736	Concurrent carboplatin and reduced dose craniospinal radiation for medulloblastoma and primitive neuroectodermal tumor (PNET)	Completed	Spinal metastases	University of Colorado, Denver	II	8	Academic
NCT01757717	Image-guided navigation for high dose rate temporary interstitial brachytherapy in the palliative management of previously treated tumors of the spine and pelvis	Completed	Spinal metastases	Memorial Sloan Kettering Cancer Center	NA	3	Academic
NCT00216060	Risedronate to prevent skeletal related events in patients with metastatic prostate cancer commencing hormonal therapy	Terminated	Spinal metastases	Christopher Sweeney, MBBS, Sanofi, Walther Cancer Institute, Hoosier Cancer Research Network	III	63	Industry

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Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Funder	
NCT03523351	Study of palliative radiation therapy vs. no palliative radiation therapy for patients with high risk bone metastases that are not causing significant pain	Recruiting	Spinal metastases	Memorial Sloan Kettering Cancer Center	I, II	74	Academic
NCT02284945	Randomized controlled trial of open stabilisation versus TPS	Completed	Spinal metastases	The Leeds Teaching Hospitals NHS Trust	NA	NR	Other
NCT02278744	Trial for salvage re-irradiation of metastatic spine lesions using single-fraction stereotactic radiosurgery	Recruiting	Spinal metastases	Memorial Sloan Kettering Cancer Center	I	18	Academic
NCT00747123	A safety, tolerability and efficacy study of ACE-011 in patients with osteolytic lesions of multiple myeloma	Completed	Multiple myeloma	Celgene	II	30	Industry
NCT03804424	64 Cu-LLP2A for imaging multiple myeloma	Recruiting	Multiple myeloma	Washington University School of Medicine	I	32	Academic
NCT01286077	Velcade consolidation bone study	Completed	Multiple myeloma	Janssen-Cilag International NV	II	106	Industry
NCT00972959	Effect of combination of bortezomib/dexamethasone/zoledronic acid on bone disease in patients with multiple myeloma relapsed after 1–3 prior lines of therapy	Completed	Multiple myeloma	University of Athens	II	17	Academic
NCT03475628	Effects of daratumumab monotherapy on bone parameters in patients with relapsed and/or refractory multiple myeloma	Unknown status	Multiple myeloma	Hellenic Society of Hematology, Janssen Pharmaceuticals	II	57	Industry
NCT01852799	A study of PAD followed by autologous stem cell transplantation (ASCT) to treat newly diagnosed multiple myeloma	Completed	Multiple myeloma	Shanghai Changzheng Hospital	II	18	Academic
NCT02230917	A phase IIa study of sotatercept on bone mass and turnover in patients with multiple myeloma	Withdrawn	Multiple myeloma	Rebecca Silbermann, Celgene, Indiana University	II	0	Industry
NCT00216151	Zoledronic acid in the management of patients with asymptomatic/early stage multiple myeloma	Terminated	Multiple myeloma	Hoosier Cancer Research Network, Novartis Pharmaceuticals, Walther Cancer Institute	II	3	Industry
NCT01829412	Whole body diffusion weighted magnetic resonance imaging (DW-MRI) in multiple myeloma	Completed	Multiple myeloma	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan	NA	50	Academic
NCT01175278	Vertebral augmentation with kyphoplasty vs nonsurgical Mgmt for vertebral body compression fractures	Withdrawn	Multiple myeloma	H. Lee Moffitt Cancer Center and Research Institute, Medtronic, Inc.	NA	0	Industry
NCT00166855	Clinical implication of bone marrow perfusion patterns imaged by dynamic MRI in multiple myeloma	Unknown status	Multiple myeloma	National Taiwan University Hospital	NA	40	Academic
NCT01410929	Evaluation of vertebral compression fracture fixation with RF kyphoplasty in patients with multiple myeloma	Withdrawn	Multiple myeloma	DFINE Inc., Merit Medical Systems, Inc.	IV	0	Industry
NCT04303091	The feasibility of a physical activity intervention for advanced multiple myeloma patients	Completed	Multiple myeloma	Dr. Nicole Culos-Reed, University of Calgary	NA	19	Academic

Continues

Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Funder	
NCT02622841	Stereotactic body radiotherapy followed by surgical stabilization for patients with unstable spinal metastases	Completed	Spinal neoplasms and metastases	University Medical Center, Utrecht	I, II	13	Academic
NCT00512460	RTA744 injection in patients with leptomeningeal disease	Terminated	Spinal neoplasm	MD Anderson Cancer Center, Reata Pharmaceuticals, Inc.	I	7	Industry
NCT01950195	SRS (stereotactic radiosurgery) plus ipilimumab	Terminated	Spinal metastases	Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University	I	4	Academic
NCT03878485	Pilot study of same-session MR-only simulation and treatment with stereotactic MRI-guided adaptive radiotherapy (SMART) for oligometastases of the spine	Recruiting	Spinal metastases	Washington University School of Medicine	NA	10	Academic
NCT04375891	Radiation therapy alone versus radiation therapy plus radiofrequency ablation (RAF)/vertebral augmentation	Not yet recruiting	Spinal metastases	Baptist Health South Florida, Medtronic	NA	80	Industry
NCT00267033	Evaluation of vertebroplasty associated with radiotherapy for spine metastases (EVAR)	Completed	Spinal metastases	Assistance Publique — Hopitaux de Paris	III	186	Academic
NCT00211211	FREE study — fracture reduction evaluation	Completed	Multiple myeloma	Medtronic Spine LLC, Medtronic Spinal and Biologics	IV	300	Industry
NCT02632903	Intravenous zoledronic acid for the treatment of osteoporosis and osteonecrosis in children with leukemia: a pilot study	Withdrawn	Spinal metastases	Children's Hospital of Eastern Ontario	II	0	Academic
NCT01986829	Cryoablation, radiofrequency ablation, or microwave ablation in treating patients with metastatic sarcoma stable on chemotherapy	Terminated	Osteosarcoma	Washington University School of Medicine	II	9	Academic
NCT01525745	Randomized study of stereotactic body radiotherapy vs. conventional radiation for spine metastasis	Terminated	Spinal neoplasm	Beth Israel Deaconess Medical Center	II	6	Academic
NCT04033536	Involved versus elective target SSRS for spinal metastases	Recruiting	Spinal metastases	National Taiwan University Hospital	NA	114	Academic
NCT02608866	Single versus multiple fractionated SSRS for spinal metastases	Active, not recruiting	Spinal Metastases	National Taiwan University Hospital	NA	68	Academic
NCT02802969	Improvement of local control in skull base, spine and sacral chordomas treated by surgery and proton therapy targeting hypoxic cells revealed by [18F]FAZA PET/CT tracers	Recruiting	Spinal neoplasms	Institut Curie	II	64	Academic
NCT02520128	A study of IMRT in primary bone and soft tissue sarcoma	Recruiting	Spinal neoplasm	University College, London, Cancer Research UK, NCRI Radiotherapy Trials Quality Assurance Group	NA	200	Academic
NCT01752036	Radiotherapy for solid tumor spine metastases	Active, not recruiting	Spinal metastases	Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University	II	35	Academic

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Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Funder
NCT02700308	A study of kyphoplasty and vertebroplasty in the treatment of spine metastases	Recruiting	Spinal metastases	Centre Leon Berard	II	60 Academic
NCT00185666	Cyberknife precision radiation delivery system for tumors of the spine	Completed	Spinal neoplasm	Stanford University	I, II	200 Academic
NCT03660540	Spine and tumor screening and supplementation	Not yet recruiting	Spinal neoplasm	Nathan Hendrickson, Orthopaedic Trauma Association, University of Iowa	NA	100 Academic
NCT04248543	Quantitative MRI for functional assessment following SBRT for spinal metastases	Suspended	Spinal metastases	Duke University	NA	20 Academic
NCT01365715	Preoperative embolization in surgical treatment of spinal metastases	Completed	Spinal metastases	Rigshospitalet, Denmark	NA	48 Academic
NCT01865942	Surgical spinal decompression of metastatic spinal cord compression, minimal access versus open surgery	Completed	Spinal metastases	Rigshospitalet, Denmark	NA	50 Academic
NCT03768167	Corpectomy with pyramesh titanium cage reconstruction in dorsolumbar metastatic lesions	Completed	Spinal metastases	Sohag University	NA	26 Academic
NCT02512965	Study comparing stereotactic body radiotherapy vs conventional palliative radiotherapy (CRT) for spinal metastases	Active, not recruiting	Spinal metastases	Canadian Cancer Trials Group, Trans-Tasman Radiation Oncology Group	NA	229 Other
NCT02987153	Kypho-intra operative radiation therapy (IORT) for localized spine metastasis, phase I/II study	Recruiting	Spinal metastases	Northwell Health	NA	22 Academic
NCT04242589	Trial of combined radiotherapy and vertebroplasty for patients with painful metastatic spinal lesions	Not yet recruiting	Spinal metastases	AHS Cancer Control Alberta, Cross Cancer Institute	II	64 Other
NCT02320825	Randomized study comparing local tumor control after post-operative single-fraction or hypofractionated stereotactic radiosurgery in the treatment of spinal metastases	Completed	Spinal metastases	Memorial Sloan Kettering Cancer Center, The Johns Hopkins University, Massachusetts General Hospital, Stanford University	III	16 Academic
NCT01290562	Stereotactic body radiotherapy (SBRT) for spinal/para-spinal metastases (Spine SBRT)	Completed	Spinal metastases	University Health Network, Toronto, Canada	II	90 Academic
NCT00593320	Stereotactic radiosurgery (SRS) for spine metastases	Terminated	Spinal metastases	Washington University School of Medicine	NA	2 Academic
NCT01347307	Stereotactic body radiotherapy for spine tumors	Unknown status	Spinal metastases	Mercy Research	NA	50 Academic
NCT02480036	Combining intraoperative radiotherapy with kyphoplasty for treatment of spinal metastases	Recruiting	Spinal metastasis	Loyola University	I	10 Academic
NCT00706485	Intra-operative dural brachytherapy with yttrium-90 plaque applicators	Terminated	Spinal neoplasms	Massachusetts General Hospital, National Institutes of Health, Implant Sciences	NA	5 NIH
NCT00492817	Evaluation of single session stereotactic body radiotherapy	Active, not recruiting	Spinal neoplasms	MD Anderson Cancer Center	I, II	71 Academic
NCT02777398	Surgical treatment of intra-spinal canal tumors via trans-quadrant channel	Unknown status	Spinal neoplasms	First Affiliated Hospital Xi'an Jiaotong University	NA	58 Academic

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Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Funder	
NCT00508443	Evaluation of a novel CT-on-rails or trilogy stereotactic spine radiotherapy system (SSRS)	Active, not recruiting	Spinal neoplasms	MD Anderson Cancer Center	I, II	150	Academic
NCT02790294	Optimal timing of postoperative magnetic resonance imaging (MRI) in patients with extradural spinal	Recruiting	Spinal neoplasms and metastases	Case comprehensive cancer center	NA	8	Academic
NCT02613390	Safety evaluation of intra-operative MRI-based guidance for laser ablation of epidural metastasis	Completed	Spinal neoplasms and metastases	MD Anderson Cancer Center	NA	11	Academic
NCT03893110	Carbon PEEK versus titanium pedicle screws in the treatment of spinal tumors	Withdrawn	Spinal neoplasms and metastases	Balgrist University Hospital	NA	0	Academic
NCT01624220	A prospective study using implanted fiducial markers to assess treatment accuracy and esophageal toxicity in spinal stereotactic body radiation therapy	Active, not recruiting	Spinal neoplasms and metastases	MD Anderson Cancer Center	NA	41	Academic
NCT01813240	Prevention of imminent paralysis following spinal cord trauma or ischemia by minocycline: a multi-center study in Israel with IDF primary care involvement	Unknown status	Spinal neoplasms and metastases	Hadassah Medical Organization	II, III	444	Academic
NCT02174107	Health economics evaluation of percutaneous vertebroplasty compared to radiation therapy in patients with painful spine metastases	Terminated	Spine metastases	Centre Leon Berard	NA	7	Academic
NCT04218617	Single- vs. two-fraction spine stereotactic radiosurgery for the treatment of vertebral metastases	Recruiting	Spine metastases	Case Comprehensive Cancer Center	II	130	Academic
NCT01231061	Spinal met_radiosurgery/SBRT study	Completed	Spine metastases	Chinese University of Hong Kong	II	1	Academic
NCT03853434	Efficacy of angiographic embolization vs. non-embolization of moderate/poor vascularized vertebral metastases on intraoperative bleeding during surgery decompression and vertebral stabilization	Recruiting	Spine metastases	Istituto Ortopedico Rizzoli	NA	100	Academic
NCT03585699	Percutaneous fluoroscopic vs CT guided core needle biopsy for spinal infection and tumor	Completed	Spinal neoplasms and metastases	University of Malaya	NA	60	Academic
NCT03593330	Neurosurgical transitional care programme	Unknown status	Spinal neoplasms and metastases	Barts & The London NHS Trust, Brigham and Women's Hospital, Harvard Medical School	NA	400	Other

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Table 1. Continued

ClinicalTrials.gov ID	Title	Status	Conditions	Sponsor and Collaborators	Phase Enrollment	Enrollment	Funder
NCT02304367	Study of KRN23 in adult subjects with tumor-induced osteomalacia (TIO) or epidermal nevus syndrome (ENS)	Active, not recruiting	Spinal neoplasms and metastases	Ultragenyx Pharmaceutical Inc.	II	17	Industry
NCT00179764	Immunoablative mini transplant (hematopoietic peripheral blood stem cell transplant [HPBSC])	Completed	Spinal neoplasms and metastases	Ann & Robert H. Lurie Children's Hospital of Chicago	NA	68	Academic
NCT01409720	Isometric muscle training in patients with spinal bony metastases under radiation therapy	Completed	Spine metastases	Heidelberg University	II	60	Academic
NCT02847754	Differentiated resistance training of the paravertebral muscles in patients with unstable spinal bone metastasis under concomitant radiotherapy	Unknown status	Spine metastases	Heidelberg University	II	60	Academic
NCT02832765	Intensity-modulated radiotherapy with integrated-boost in patients with spinal bone metastases	Unknown status	Spine metastases	Heidelberg University	II	120	Academic
NCT02832830	Image-guided and intensity-modulated radiotherapy versus external beam radiotherapy for patients with spine metastases	Unknown status	Spine metastases	Heidelberg University	II	60	Academic
NCT02464761	Photodynamic therapy for the treatment of vertebral metastases	Completed	Spine metastases	Sunnybrook Health Sciences Centre	I	30	Academic
NCT01654068	Conformal high dose intensity modulated radiation therapy for disease to thoracic and lumbar spine	Terminated	Spine metastases	Ronald McGarry, University of Kentucky	NA	14	Academic
NCT03028337	Single versus multifraction salvage spine stereotactic radiosurgery for previously irradiated spinal metastases	Recruiting	Spinal neoplasms and metastases	MD Anderson Cancer Center	II	80	Academic

ID, identification; NA, not applicable; NIH, National Institutes of Health; GnRH, gonadotropin-releasing hormone; RT, radiation therapy; iGame, digital intervention for the modification of lifestyles; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; t-RFA, targeted radiofrequency ablation; RF-TVA, radiofrequency targeted vertebral augmentation; SRS, stereotactic radiosurgery; TPS, treatment planning system; NHS, National Health Services Trust; NR, not reported; PAD, bortezomib, doxorubicin, dexamethasone; Mgmt, management; MRI, magnetic resonance imaging; RF, radiofrequency; MR, magnetic resonance; SSRS, spine stereotactic radiosurgery; IMRT, intensity-modulated radiation therapy; NCRI, National Cancer Research Institute; SBRT, stereotactic body radiation therapy; PEEK, polyether ether ketone; IDF, Israel Defense Forces.

recorded as the United States, Canada, Germany, other European country, or other non-European country. Finally, the sponsor for each study was categorized as an academic institution, industry, U.S. federal government, or other, and the intervention type was categorized as procedure, drug, device, radiation therapy, or other.

All data were analyzed in Microsoft Excel (Microsoft, Corp., Redmond, Washington, USA) to determine the frequency in the cohort. In addition, the cumulative frequency was plotted from 1999 to 2020, from the beginning of the [ClinicalTrials.gov](https://clinicaltrials.gov) online registry to the end of the search period.⁵

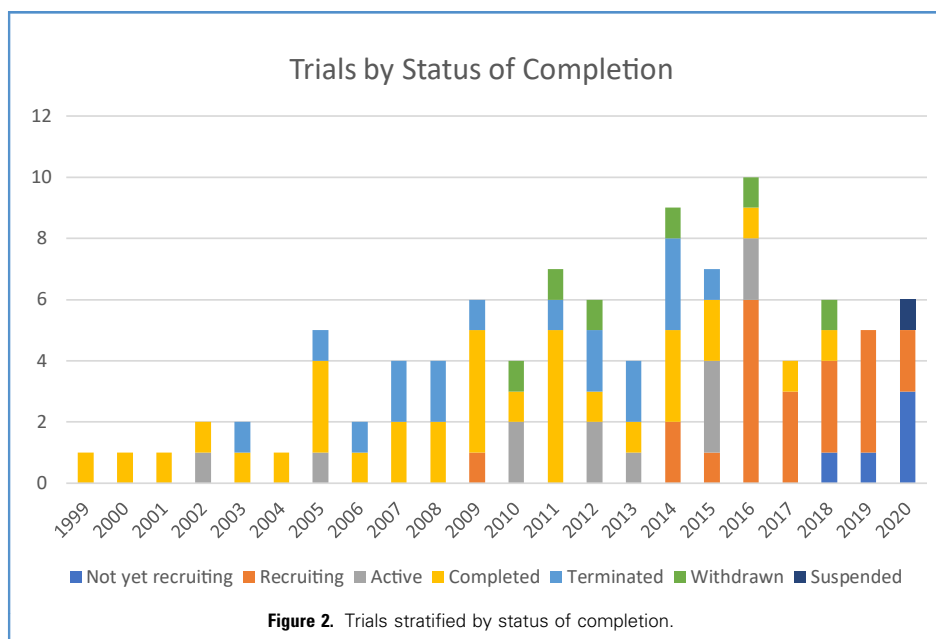
RESULTS

Our initial query of the [ClinicalTrials.gov](https://clinicaltrials.gov) database for interventional spine studies yielded 3203 clinical trials.⁵ Our subsequent

screening for studies with tumor therapeutic efficacy as the main outcome yielded a final list of 106 studies ([Figure 1](#) and [Table 1](#)). The inception of these trials ranged from 1999 to 2020—the year the online registry became publicly available to the end of our search period.

Trials Stratified by Completion Status

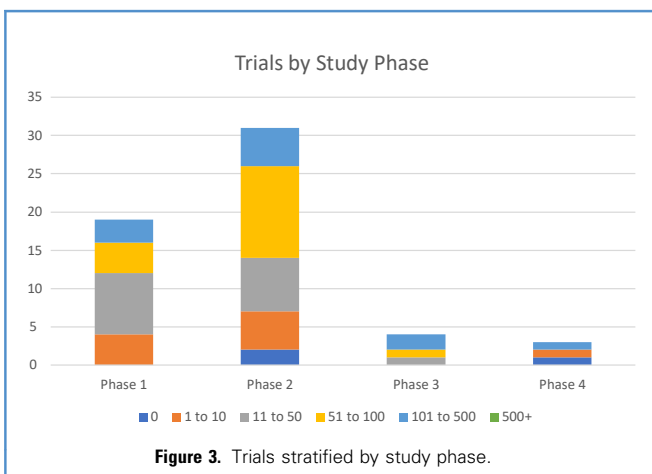
Of the 106 trials, 97 (91.5%) had reported the current trial status. Among the trials that had begun before 2008, all, except for 2, had been completed or terminated ([Figure 2](#)). The oldest active trial, a phase I trial of intraoperative computed tomography for stereotactic radiosurgery,⁶ had begun in 2002, and the oldest trial still recruiting, a phase II trial of radiation therapy and vertebroplasty for local metastasis,⁷ had begun in 2009. Of the



trials that reported the study status, the largest proportion had been completed (35.1%) or were continuing to recruit patients (22.7%). The remaining studies were categorized terminated (17.5%) or still active (12.4%). Only 1 study, which had begun in 2020, had been suspended.

Trials Stratified by Enrollment and Phase

Only 57 trials (53.8%) had reported information regarding the study phase (Table 1). For these 57 studies, the projected trial enrollment ranged from 0 participants (5.3%) to 101–500 participants (19.3%; Figure 3). The enrollment of 51–100 participants (29.8%) was the most common number. Of the trials, 17.5% and 28.1% had enrolled 1–10 and 11–50



participants, respectively. Most trials were phase II studies (54.4%), followed in frequency by phase I (33.3%), phase III (7.0%), and phase IV (5.3%) studies.

Trials Stratified by Clinical Category

Most of the retrieved trials (58.5%) had examined metastatic tumors, a smaller portion had studied primary tumors (36.8%), and a few trials (4.7%) had investigated both primary and metastatic spinal tumors (Table 2 and Figure 4A). The earliest trials (1999–2000) of spinal tumors had included both primary and metastatic tumors. It was not until 2005 that the first trial investigating primary tumors had begun. The rate of trials registered annually for metastatic spinal tumors had increased 3.4-fold from 2009 to 2020 relative to 1999 to 2008. In contrast, the number of studies devoted to primary tumors or both primary and metastatic tumors had increased only 1.5- and 1.6-fold, respectively, per year during the same period (Figure 4B).

Trials Stratified by Country of Origin

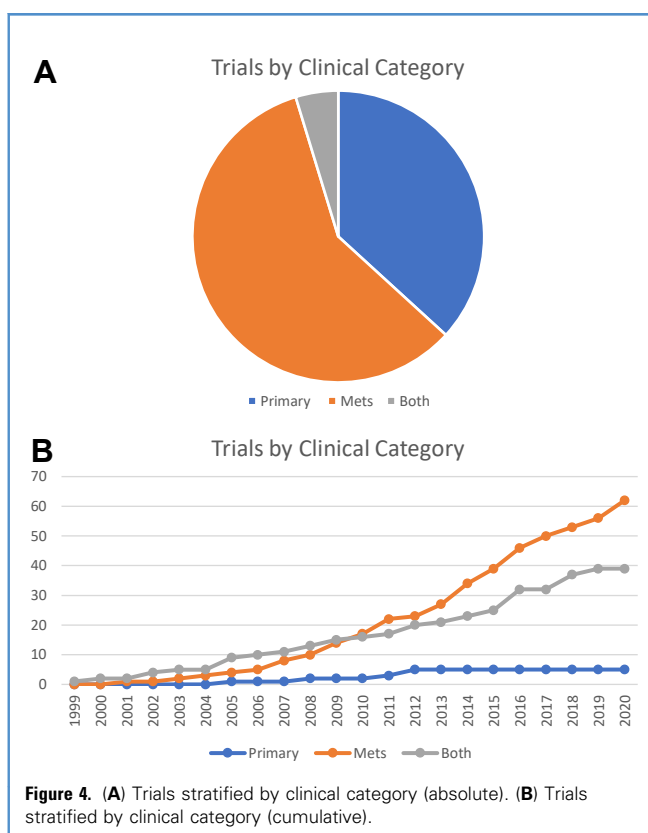
A total of 101 trials (95.3%) had reported information regarding the country of origin (Table 1). The 3 countries that had accounted for the greatest proportion of trials were the United States (56.4%), Canada (7.9%), and Germany (5.0%; Table 2 and Figure 5A). From 1999 to 2009, the United States had accounted for ~2.1 studies annually, followed by Canada (0.2/year), Germany (0.1/year), all other European countries (0.3/year), and the rest of the world (0.1/year; Figure 5B). However, from 2010 to 2020, the number of trials originating in the United States had increased only 1.5-fold. In contrast, those from Canada, Germany, all other European countries, and the rest of the world had increased by 3.0-, 4.0-, 5.0-, and 12.0-fold, respectively.

Trials Stratified by Intervention Strategy

One of 5 types of interventions was examined by each trial: device, drug, procedure, radiation therapy, or other (Table 2). The most common intervention strategy was radiation therapy (32.1%), followed by surgical or biopsy procedure (26.4%), drug (15.1%), device (15.1%), and other (11.3%; Table 2 and Figure 6A). From 1999 to 2009, ~1 radiation therapy study was conducted per year, followed by procedure (0.6/year), drug (0.6/year), device (0.4/year), and other (0.3/year) study types (Figure 6B). However, from 2010 to 2020, procedural studies had become the most frequent (2.4/year), followed in frequency by device (3.0/year), other (3.0/year), radiation therapy (2.1/year), and drug (1.3/year) studies.

Table 2. Number of Trials Stratified by Category	
Factor	n (%)
Study phase	57 (100)
I	19 (33.30)
II	31 (54.40)
III	4 (7.01)
IV	3 (5.26)
Clinical category	106 (100)
Primary	39 (36.80)
Metastasis	62 (58.50)
Both	5 (4.72)
Country of origin	101 (100)
United States	57 (56.40)
Canada	8 (7.92)
Germany	5 (4.95)
Other European	18 (16.82)
Other non-European	13 (12.15)
Intervention type	106 (100)
Procedure	28 (26.40)
Drug	16 (15.10)
Device	16 (15.10)
Radiotherapy	34 (32.10)
Other	12 (11.30)
Sponsor	106 (100)
NIH	14 (13.21)
Industry	20 (18.87)
Academic	67 (63.21)
Federal	1 (0.94)
Other	4 (3.77)

NIH, National Institutes of Health.

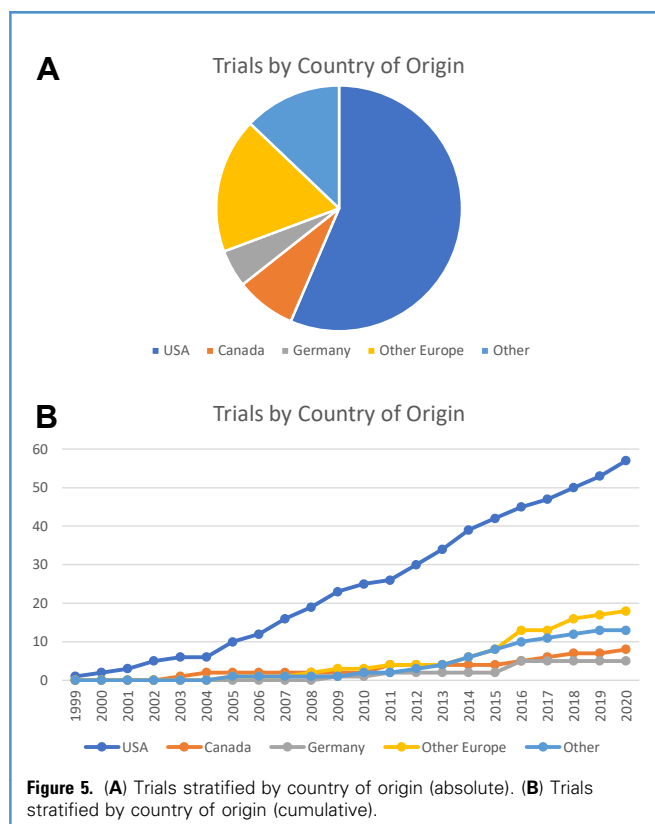


Trials Stratified by Sponsor

Most of the studies had been sponsored by academic institutions (63.2%), followed by industry partners (18.9%), the National Institutes of Health (NIH; 13.2%), non-NIH federal agencies (0.9%), and other agencies (3.8%; Table 2 and Figure 7A). From 1999 to 2009, academic institutions had sponsored 1.5 trials/year followed by industry (0.7/year), the NIH (0.5/year), and the federal government (0.1/year; Figure 7B). In the subsequent years, academic institutions had sponsored 3.2-fold more studies and industry partners and the NIH had funded only 1.5- and 1.3-fold more studies, respectively. The federal government has not sponsored trials pertaining to spine tumors since 2009, and other funding agencies have become more prevalent sponsors in recent years (0.4/year from 2011 to 2020).

DISCUSSION

The results from our descriptive study of clinical trials of spinal tumor treatments during the past 2 decades have highlighted a proliferation of trials from 2005 to 2020. A closer look at this increased rate, which had begun ~15 years earlier, demonstrated that most trials of radiation therapy and other procedures for metastatic spinal tumors had been conducted by academic institutions in the United States. The stark increase of this specific trial profile was reflected by the increasing frequency of these subtypes across 2 decades (Table 2).

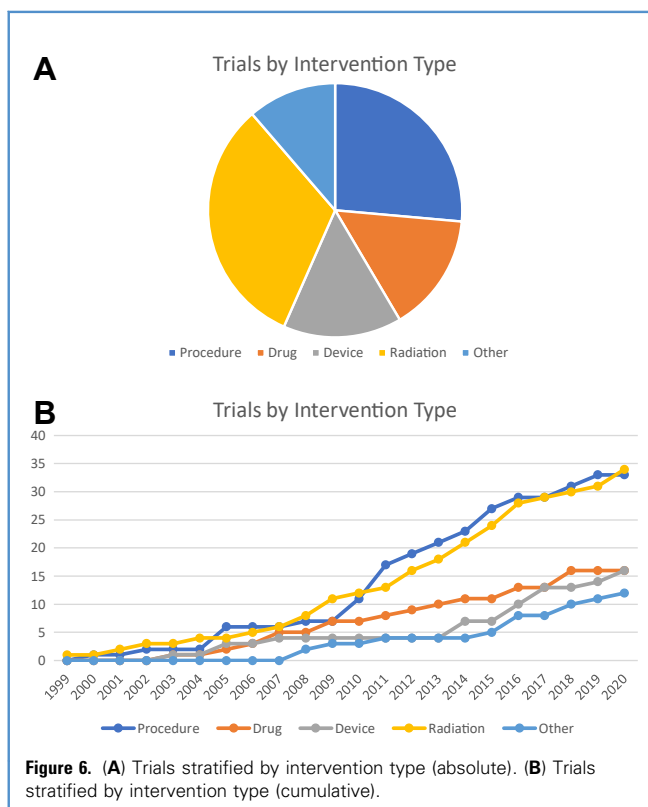


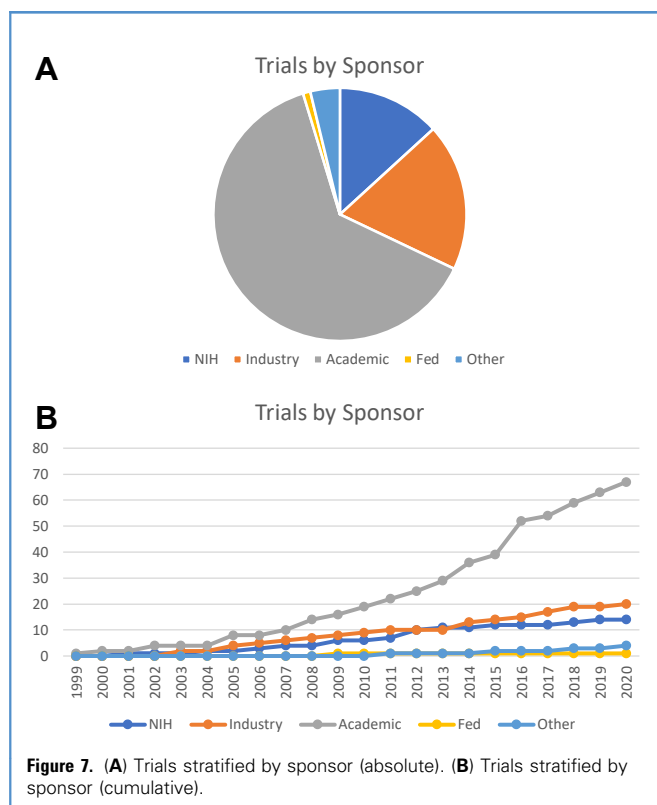
The increase in metastatic tumor trials was also found in the literature, with studies of the treatment of spinal cord compression, in particular, the most cited reports in the spine tumor literature.⁸ Early investigations of the surgical technique had studied the challenge of noncontiguous lesions, comparing modalities such as circumferential posterior decompression and combined anteroposterior approaches to minimize the intraoperative complications from single-stage procedures and demonstrating comparable survival times.⁹ A landmark trial in the early 21st century compared surgical resection and conventional radiation therapy and reported higher ambulation rates with decompressive surgery.² Nevertheless, the lesions in that study had been relatively localized. Subsequent trials explored radiosurgical modalities for metastases affecting multiple vertebrae, including intensity-modulated radiation therapy.¹⁰ In addition, with advancements in metastatic pathology, several trials have explored therapies that target subtypes, such as minimally invasive balloon kyphoplasty versus vertebral body implants for osteolytic lesions.¹⁴ Recent innovations have used tissue-engineered drugs to both induce bone growth and locally deliver chemotherapy to avoid systemic effects.¹² In the present review, a trial of cement augmentation for compression fractures was one such example of an innovation tailored to a specific indication.¹³

The exploration and refinement of novel therapeutics for metastatic lesions has been an international effort. Nevertheless,

many trials of spinal metastases conducted in the past decade were spearheaded by institutions in the United States. In the 1990s, research groups had focused predominantly on pain management for patients both during and after spine surgery, regardless of the clinical indication.^{14,15} At the turn of the century, however, new intraoperative imaging modalities to update stereotactic navigation systems in real time were used to more accurately target the lesions.¹⁶ More recent trials have focused predominantly on radiation therapy and stereotactic radiosurgery, in particular, at academic medical centers.^{7,17,18}

Whether the trials had been conducted solely within U.S. institutions or in collaboration with international partners, academic medical centers have led the charge in the past 15 years to explore spinal tumor therapeutics. Industry players, including pharmaceutical and device companies, have also sponsored several trials.^{19,20} However, most have been performed by academic institutions. These research groups have often studied cases that had accumulated during a long period, especially to test treatments of rare spinal tumor types.²¹ Collaborations between academic medical institutions at both international and national levels has also ensured large sample sizes for prospective studies comparing the outcomes for different indications, such as oligometastatic versus polymetastatic lesions or to assess the prognosis with different surgical margins.^{22,23} Collaborations between several different academic medical institutions is critical when performing a clinical trial because these groups often later become stakeholders in the drafting and





dissemination of therapeutic guidelines updated with trial data.²⁴ Thus, clinical trial findings can be translated directly into treatment optimization.

To the best of our knowledge, the present study is the first descriptive analysis of clinical trials of spine tumor therapies during the past 2 decades, quantifying the increase in trials of metastatic lesions led by academic institutions in the United States. Nevertheless, the present study had limitations in its data collection. The [ClinicalTrials.gov](https://clinicaltrials.gov) database does not include every clinical trial at every institution, only has records for studies with a

start date of 1999 or later, and might be biased toward the inclusion of trials from the United States owing to its sponsorship by the National Library of Medicine. Nevertheless, this government-maintained database is considered one of the most comprehensive registries in the world. Finally, the search terms, although systematic, might have excluded certain trials.

By describing the trends in trial modalities, clinical targets, and other characteristics over time, the results from the present study offer insights into the evolution of innovations in spine surgery, contributing to the ongoing discussion of the most efficacious methods for treating complex lesions and, ultimately, improve patient outcomes.

CONCLUSIONS

The number of clinical trials for spine tumor therapies has increased rapidly during the past 15 years, resulting largely from studies performed at academic medical institutions in the United States investigating radiosurgery and surgical procedures for the treatment of metastases. These largescale trials relied on collaboration among multiple institutions to ensure that enough patients will be recruited to follow up closely in a prospective manner. As trial treatments have become increasingly targeted, addressing, not only specific tumor subtypes, but also specific sequelae, working groups have been empowered to implement international best practices using the data afforded by these clinical trials.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Emily K. Chapman: Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Aly A. Valliani:** Writing – original draft. **William H. Shuman:** Writing – review & editing. **Michael L. Martini:** Writing – review & editing. **Sean N. Neifert:** Conceptualization, Writing – review & editing. **Jeffrey T. Gilligan:** Writing – review & editing. **Frank J. Yuk:** Writing – review & editing. **Alexander J. Schupper:** Writing – review & editing. **Jonathan S. Gal:** Conceptualization, Writing – review & editing. **John M. Caridi:** Conceptualization, Writing – review & editing, Supervision.

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