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Research Letter

Head and Neck Cancer Clinical Research on ClinicalTrials.gov: An Opportunity for Radiation Oncologists

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Abstract

Purpose: Many improvements in head and neck cancer (HNC) outcomes are related to optimization of radiation therapy (RT) dose, fractionation, normal-tissue sparing, and technology. However, prior work has shown that the literature of randomized controlled trials is dominated by industry-sponsored trials that have lower rates of incorporating RT. We characterized HNC clinical trials, hypothesizing that RT-specific research questions may be relatively underrepresented among HNC randomized controlled trials.

Methods and Materials: A web query of all open interventional trials on www.ClinicalTrials.gov was performed using search terms "head and neck cancer" and specific HNC subsites. Trial details were captured including the modality used, principal investigator (PI) specialty, funding, and whether the study tested a RT-modality specific hypothesis. Chi-square testing and logistic regression were used to compare groups.

Results: There were 841 open HNC trials, including definitive (47.6%) and recurrent/metastatic (41.9%) populations. Most trials (71.7%) were phase I or nonrandomized phase II studies, rather than phase III or randomized phase II (28.3%). Among single-arm studies, most (79.6%) incorporated systemic therapy (ST), and fewer (25.2%) incorporated RT. Even fewer phase III and randomized phase II trials tested an RT-specific hypothesis (11.1%), compared with ST-related hypotheses (77.1%; $P < .001$); trials were more likely to test an RT-hypothesis if the study PI was a radiation oncologist (20.9% vs 6.0%; $P < .001$). Among RT trials, most early-phase studies tested novel modalities (eg, stereotactic body radiation therapy, proton therapy), whereas most later-phase studies tested dose and fractionation. RT-focused trials had low rates of federal (10.4%) or industry (2.6%) funding.

Conclusions: RT-specific research hypotheses are a minority of phase II-III HNC trials, which mostly focus on incorporating ST in the definitive or recurrent/metastatic setting and have higher rates of industry funding. Radiation oncologist PI leadership and increased nonindustry funding access may ensure that RT-specific hypotheses are incorporated into trial design.

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Introduction

We aimed to characterize clinical trials in head and neck cancer (HNC) and the frequency of radiation therapy (RT)–related research questions, especially for phase III and randomized phase II trials, which have the greatest potential to change long-term practice patterns.

Methods and Materials

A search was performed on June 26, 2017, of www.ClinicalTrials.gov for open interventional clinical trials using search terms "head and neck cancer" and specific subsites: "salivary gland cancer," "paranasal sinus cancer," "nasal cavity cancer," "nasopharyngeal cancer," "oral cavity cancer," "larynx cancer," "hypopharynx cancer," "oropharynx cancer," "thyroid cancer." Studies were excluded if they did not include HNC or exclusively enrolled pediatric patients. Other details regarding data collection and classification were previously published.[1] For each study, the authors characterized the treatment modalities included, trial characteristics, and whether the study tested an RT-specific hypothesis (including comparing RT dose, fractionation, modality, use of RT, imaging, or other), an systemic therapy (ST)–specific hypothesis, or both. Chi-square testing and logistic regression were used to identify associations among trial characteristics, including study question, study principal investigator (PI) specialty, and study funding. A P value of $\leq$.05 was considered statistically significant.

Results

Trial characteristics

Table 1 demonstrates the clinical trial characteristics for the study cohort (n = 841). Most trials were phase I/nonrandomized phase II trials (71.7%), rather than phase III/randomized phase II (28.3%). Among single-arm trials, most (n = 363, 79.6%) incorporated ST, 241 (52.9%) were ST-only, 115 (25.2%) incorporated RT, 30 (6.6%) were RT-alone trials, and 34 (7.5%) included surgery.

Among phase III and randomized phase II trials (n = 253), 11.1% tested a RT-specific hypothesis, compared with 77.1% testing an ST-specific hypothesis ($P < .001$). Trials were more likely to test an RT-specific hypothesis if one of the study PIs was a radiation oncologist (RO) (20.9% vs 6.0%; $P < .001$). When the analysis was restricted to phase III and randomized phase II trials incorporating RT as a treatment modality, there was still a higher, but not statistically different, percentage of trials testing an RT-specific hypothesis if the PI was an RO (22.5% vs 13.2%; $P = .129$).

Characteristics of radiation trials

Among single-arm RT-alone trials (n = 33), most (63.6%) tested treatment modalities (eg, stereotactic treatment, proton therapy) or imaging modalities (eg, positron emission tomography), rather than radiation dose/fractionation (21.2%). Among phase III and randomized phase II RT trials (n = 28), 50% tested dose/fractionation (eg, dose de-escalation, hyperfractionation), 21.4% tested the need for any RT, and 17.9% evaluated RT treatment modalities.

Funding sources

Among all HNC trials, 14.4% had National Institutes of Health (NIH) or other federal funding, 31.8% had industry funding, and 79.6% had other sources of funding; 25.1% of trials had more than 1 source of funding. Funding rates among these sources were similar for phase I/nonrandomized phase II trials and for phase III/randomized phase II trials ($P > .05$).

Funding sources differed significantly by whether trials tested an RT-specific hypothesis. Rates of NIH funding were similar for RT and non-RT trials (10.4% vs 14.8%; $P = .294$), but trials testing an RT hypothesis were much less likely to have industry funding compared with other trials (2.6% vs 34.7%; $P < .001$) and were more likely to have "other" funding (100% vs 77.5%; $P < .001$).

Survivorship and quality of life

Of the 385 multiarm trials in the cohort, 72 (18.7%) tested a survivorship or quality-of-life question, such as interventions to reduce side effects from treatment. These trials were less likely to have industry funding compared with other multiarm trials (6.9% vs 30.4%; $P < .001$) and more likely to have federal funding (19.4% vs 10.5%; $P = .038$) or other funding (97.2% vs 80.5%; $P = .001$). Most quality-of-life or survivorship studies (56.9%) were led by PIs who were not ROs, medical oncologists, or surgeons (eg, speech-language pathologists, dentists, nurses).

Discussion

This analysis of HNC clinical trials on www.ClinicalTrials.gov shows that approximately half of all studies (47.6%) were focused on the definitive/curative patient population and the rest were mostly focused on the recurrent/metastatic population (41.9%). Only 11.1% of phase III/randomized phase II trials, which are the most likely studies to influence long-term practice patterns, tested a radiation-specific hypothesis such as dose, fractionation, or other radiation-specific question. Trials were

Table 1 Clinical trial characteristics for the study cohort (n = 841)

Trial characteristic	n	%
Trial enrollment location		
US only	404	48.0%
International only	365	43.4%
US and international	66	7.8%
Unknown	6	0.7%
Funding source		
Any NIH/US federal government	121	14.4%
Any industry	264	31.4%
Other	669	79.5%
Phase		
I	181	21.5%
II	382	45.4%
III	115	13.7%
IV	15	1.8%
Unknown	148	17.6%
Patient population		
Definitive	400	47.6%
Recurrent/metastatic	352	41.9%
Definitive or recurrent/metastatic	47	5.6%
Other	42	5.0%
PI specialty		
Radiation oncology	197	23.4%
Medical oncology	287	34.1%
Surgery	134	15.9%
Other	239	28.4%
Modality used in clinical trial		
Any drug	639	76.0%
Any radiation	414	49.2%
Any surgery	100	11.9%
Single arm trials (n = 456)		
Incorporating RT	115	25.2%
Incorporating drug	363	79.6%
Incorporating surgery	34	7.5%
Other	46	10.1%
Multiarm trials (n = 385)		
Drug only studies	78	20.3%
RT and drug	113	29.4%
RT alone	16	4.2%
Surgery alone	14	3.6%
Surgery, drug, and RT	15	3.9%
Quality of life/survivorship study	72	18.7%
Mucositis or dermatitis prevention	36	9.4%
Other	41	10.6%
Disease site (definitive trials only)		
Larynx/hypopharynx	12	3.1%
Nasopharynx	60	15.3%
Oral cavity	23	5.9%
Oropharynx	33	8.4%
Multiple (>1 site included)	235	59.9%
Thyroid	21	5.4%
Other	8	2.0%

Abbreviations: NIH = National Institutes of Health; PI = principle investigator; RT = radiation therapy; US = United States.

more likely to test an RT hypothesis if 1 of the study PIs was an RO (20.9% vs 6.0%; $P < .001$). Most (77.1%) phase III/randomized phase II clinical trials tested ST-related hypotheses, often in conjunction with standard RT or surgical treatment.

These findings suggest that RO leadership is important to design large phase III/randomized phase II trials that evaluate the full potential of RT innovation—whether using novel treatment modalities, determining the optimal way to combine RT with ST, or pushing the envelope in adaptive replanning, dose, fractionation, and modification of standard treatment volumes. This is particularly important in HNC given the potential value of dose intensification in high-risk disease such as larynx/hypopharynx HNC or for deintensification of RT in p16-positive oropharyngeal cancer.[2]

Funding source significantly differed by the type of study question, with industry rarely funding radiation trials or survivorship-related questions, which may not be surprising because improvements in radiation that do not involve new technological innovation do not always offer a patentable innovation. Prior work also demonstrated that both radiation and surgery, standard-of-care modalities for HNC treatment, have low rates of industry and NIH funding.[3] Furthermore, head-to-head randomized trials were previously shown to be dominated by industry-sponsored comparisons, with results that tend to favor industry particularly when noninferiority designs were used.[4] Further restrictions on federal funding availability may shrink funding sources for trials of radiation-specific hypotheses. The relative availability of industry-funding may end up driving trial design and the future of HNC research rather than preclinical data-driven hypotheses that do not necessarily incorporate novel ST.

Limitations of our work include incomplete capture of all ongoing trials since www.ClinicalTrials.gov represents just 1 registry of trials (albeit capturing approximately 80% of all ongoing trials worldwide) and the time-dependent nature of this cross-sectional study. There is also limited information on variables such as "other" funding sources, due to limitations in the amount of specific detail provided by the database. Yet, each trial was individually queried with additional web-searching performed to determine as much detail as possible.

Most HNC trials, both in the recurrent/metastatic and definitive setting, focus on ST. This represents an opportunity for ROs to increase efforts to study radiation-specific questions and to explore how RT can synergize with ST.[5-7] Maximizing the potential for investigating RT-specific research questions will depend on increasing federal funding and other nonindustry funding sources, especially for research that seeks to

deintensify therapy by omitting ST altogether. Examples of ways to increase federal and foundation funding for RT-specific research include increased RO representation on federal grant review committees, increased financial support of RT-focused funding organizations (eg, Radiation Oncology Institute), and advocacy at the federal level to specifically increase funding for RT-related research to fill the gap caused by preferential funding of ST-related research by industry sources. Lastly, and perhaps most importantly, our field can nurture future clinician-scientists and clinician-trialists at the residency level. Opportunities for basic science research, such as the Holman Pathway, give residents the tools to identify preclinical and translational study questions. Coursework in clinical trial design and mentorship in industry collaboration are all early-career ways to provide ROs with the skills needed to cultivate the future of our field. This relies on subsequent departmental support and investment in such clinician-scientists and clinician-trialists as junior faculty and beyond.

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