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Clinical Investigation

Survey of Radiation Oncologists to Assess Interest and Potential Use of a Genetic Test Predicting Susceptibility for the Development of Toxicities After Prostate Cancer Radiation Therapy

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Abstract

Purpose: A genetic test predicting susceptibility for the development of toxicities after prostate cancer radiation therapy is in development. This test intends to help physicians with treatment decision making.

Methods and Materials: Radiation oncologists were surveyed using a web-based questionnaire to gauge their interest in using a genetic test predictive of increased risk of radiation therapy toxicities as an aid in determining therapy for men with prostate cancer. Responses were summarized using frequencies, and a χ^2 test compared responses among participants. Multivariable ordinal regression identified factors associated with anticipated adoption or nonadoption of such a genetic test by radiation oncologists.

Results: Among 204 radiation oncologists (64% from the United States, 36% from other countries), 86.3% would order a genetic test and 80.2% said the test would be useful for treatment discussions. There was wide acceptance (76.7%) to offer a genetic test to all patients considering radiation therapy for prostate cancer. Additionally, 98.1% indicated that patients would be receptive to the test information. There were no significant differences in the likelihood of ordering a genetic test based on practice setting, familiarity with scientific literature, time spent on research, or geographic location (all $P > .05$).

Conclusions: Radiation oncologists who treat prostate cancer are interested in and willing to order a genetic test predictive of susceptibility to radiation therapy toxicity to aid their treatment decision making.

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Introduction

Prostate cancer is the fourth most common cancer worldwide, with 1.28 million new cases in 2018.[1] Given the various treatment choices and risk to quality of life, treatment decisions for prostate cancer are challenging.[2,3] In recent years, decision making for prostate cancer treatment has shifted to account for its preference-sensitive nature,[4] which is informed by clinical parameters along with patient values and outcome goals.[3] Consequently, physicians and patients are encouraged to follow a shared decision-making paradigm.[5]

Regardless of treatment, prostate cancer has a high survival rate, and side effects are a primary decision-making factor for newly diagnosed men.[6] Recognizing this issue, the National Cancer Institute highlights adverse treatment effects as a critical survivorship issue that warrants increased research aimed at reducing burden of disease for cancer survivors.[7] It is crucial to prevent complications and make efforts to exclude patients at high-risk from particular treatment modalities.

Radiation therapy, used to treat over half of men diagnosed with prostate cancer, aims to destroy cancer cells while minimizing damage to nearby tissue. Individual variation exists for tissue responses after radiation therapy, and studies suggest that some of this variation is due to germline genetic variation.[8] Thus, to maximize the therapeutic ratio of radiation therapy, treatment should be tailored to characteristics of the cancer *and* the genetic makeup of each individual. Genetic testing is improving decision making in cancer management,[9] and efforts are underway to apply such tools in precision radiation oncology.[10] Decision aids for cancer treatment, including genetic tests, have already resulted in more patients wanting and assuming an active role in treatment decisions.[3] This is a positive trend, as passive decision making has been associated with later regret and negative evaluations of provider interactions. Furthermore, the National Comprehensive Cancer Network recommends patients and clinicians consider genetic tests for prostate cancer to help inform treatment decisions.[4]

Acknowledging the contribution of genetics to radiation sensitivity, the field of radiogenomics was established.[11] Germline genetic markers, primarily single nucleotide polymorphisms, have been identified and validated to correlate with adverse reactions to doses used in radiation therapy.[12] This work has been facilitated through the creation of the Radiogenomics Consortium, a National Cancer Institute cancer epidemiology consortium (https://epi.grants.cancer.gov/Consortia/) with over 200 investigators globally. Radiogenomics Consortium investigators are developing an assay to help estimate the likelihood of adverse reactions after radiation therapy and to help providers make personalized treatment decisions.[13] Recognizing that such a genetic test will likely become available within the near future, we developed and conducted a survey to assess the potential adoption of such a test among radiation oncologists who treat prostate cancer. Specifically, we were interested in the use of a genetic test predictive for susceptibility to the development of adverse effects after radiation therapy for prostate cancer, in addition to factors that would influence adoption of such a test.

Methods and Materials

Study design and participants

This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai and consisted of 2 phases. Phase 1 included survey development and pilot testing. Survey questions were designed after interviewing 15 radiation oncologists, who primarily treat prostate cancer, from the institutions where the co-authors of this paper are based. The interviews focused on 3 areas: professional profile, knowledge and perceived acceptability of genetic testing, and intentions to use a genetic test if available. An initial version of the survey was pilot tested with these same 15 radiation oncologists.

Phase 2 consisted of an online survey. The survey was created and distributed via email using REDCap (Research Electronic Data Capture). Eligible survey participants were radiation oncologists who treat prostate cancer, as stated in the email invitation to participate. Possible participants were identified from a PubMed search as authors of publications that contained the words "prostate," "cancer," and "radiation therapy" in the title or abstract and from the American Society for Radiation Oncology member directory in which occupation was listed as *radiation oncologist* and disease site specialty as *genitourinary cancers*. Answers were anonymous, and a reminder email was sent a week later to anyone marked as incomplete. Internet access and the ability to read English were required for participation. Participants were not compensated for completing the survey.

Survey measures

The first section of the survey collected information on experience treating prostate cancer. Participants reported length of time in practice, whether they specialized in radiation treatment for prostate cancer, an approximate number of patients they treated for prostate cancer, and which radiation therapy modalities they used to treat prostate cancer. This section included questions on practice setting, primary affiliation, and time spent on research.

The second section assessed likelihood of using a genetic test to determine patient risk of developing

adverse treatment effects. Familiarity with scientific literature related to such a test was also assessed. Respondents reported the magnitude of predicted increased risk of adverse effects they considered acceptable before determining a patient is unsuitable for radiation therapy. This was followed with questions about the type and grade of complications relevant to answers regarding the magnitude of acceptable risk.

The final survey section pertained to interest in a genetic test. Respondents provided their thoughts on how useful such a test would be during treatment discussions, why they would order such a test, and whether such a test should be offered to *all* patients considering radiation therapy for prostate cancer. This section also asked about qualities that make the test more desirable and factors important in determining its use. Furthermore, this section asked about an acceptable turn-around time for results, when the test should be ordered, when the results should be provided to patients, and who should provide the results to the patient.

Statistical analysis

Survey responses were summarized using descriptive statistics. Percentages for each question were calculated using its specific number of respondents as the denominator. A 2-sided χ^2 test assessed differences in responses by location of practice (United States vs outside the United States), with $P \leq .05$ considered statistically significant. A multivariable ordinal regression model characterized associations of potential explanatory items with each of 2 preselected outcome items: interest in ordering a genetic test and the amount of predicted, acceptable increased risk before recommending a patient is unsuitable for radiation therapy. Bivariate associations between potential explanatory items and each of these 2 outcomes were first performed, and any association with a 2-sided χ^2 P value $<.1$ was considered for inclusion in the multivariable model. Items were retained in the final multivariable model if the 2-sided P value was $<.05$. All analyses used Statistical Package for the Social Sciences Statistics 23 (IBM Corp., Armonk, NY).

Results

The survey was sent to 3434 email addresses. Of these, 78.7% (n = 2703) practiced in the United States, and the remainder (n = 731) practiced outside of the United States (Table E1). Overall, 131 radiation oncologists in the United States and 73 from outside the United States completed the survey, for a total of 204 respondents (6% response rate). No statistically significant differences were identified between U.S. and non-U.S. respondents for our main outcome questions (Table E2). Thus, data from all respondents were combined for analysis of these outcomes. However, aside from the main outcomes, significant differences in the responses were obtained for several questions between the respondents from the United States and those whose practices were located outside of the United States. However, it would not be appropriate in this paper to draw any specific conclusions as to the basis of these variances because there were relatively small numbers of radiation oncologists based in each of the 22 different countries who responded to this survey, representing a diversity of health care systems. Nevertheless, it may be of interest for a future study to investigate possible variations in responses between radiation oncologists who treat prostate cancer across a range of countries.

Most survey respondents had been in practice for at least a decade (69.6%), specialized in radiation therapy for prostate cancer (77.5%), and worked in a multidisciplinary practice setting (83.3%) (Table 1). The majority spent less than 10% of their time in research (65.3%), and primary affiliation was closely split between academic (40.7%) and private practice (46.6%), with 12.7% primarily affiliated with other types of institutions (Table 1). The most common radiation therapy modalities used (Fig 1) were image guided radiation therapy (88.7%), intensity modulated radiation therapy (80.9%), and volumetric modulated arc therapy (70.1%).

Respondents had a positive attitude toward a genetic test predicting risk of radiotoxicity from prostate cancer treatment. Most radiation oncologists would probably (44%), very likely (29.7%), or definitely (12.6%) order such a test (Fig 2). Most respondents described the usefulness of the test as moderately (30.2%), very (37.4%), or extremely (12.6%) useful (Fig 3). Lastly, 51.0% responded that the results would definitely or very likely, and 37.1% probably, help patients decide among radiation therapy, surgery, or active surveillance (Fig 2). Overall, these responses indicated that radiation oncologists are favorably inclined to use a genetic test. However, it is anticipated that they would have responded more enthusiastically if a genetic test were actually already available and if published data demonstrated that it was capable of predicting risk for development of toxicities on an individual patient basis with a high level of sensitivity and specificity. The survey asked participants about the magnitude of increased risk of side effects predicted by the genetic test that would be allowable before recommending a patient would be unsuitable for radiation therapy (Fig 4). Over half (52.1%) would only allow up to a 50% increase in predicted risk before considering a patient unsuitable for radiation therapy, whereas 19.8% would allow a 51% to 100% increase, and 16.1% would allow 100% or greater increase. Among those who would consider a patient unsuitable for radiation therapy, responses mainly applied to risk of genitourinary and gastrointestinal symptoms and risk of severe symptoms (Fig 5). Only 12.0% of the respondents indicated they

Table 1 Medical background characteristics of study population (N = 204)

Question	Possible answers	n	%
How long have you been in practice as an independent physician?			
	Less than 1 y	0	0%
	1-4 y	24	11.8%
	4-10 y	38	18.6%
	10-15 y	33	16.2%
	Over 15 y	109	53.4%
Do you specialize in radiation treatment for prostate cancer?			
	Yes	158	77.5%
	No	46	22.5%
Number of your patients treated for prostate cancer annually?			
	0	0	0%
	1-25	21	10.3%
	26-50	65	31.9%
	51-100	58	28.4%
	101-200	40	19.6%
	Over 200	20	9.8%
Percentage of your patients treated for prostate cancer?*			
	0%	0	0%
	1%-10%	26	12.8%
	11%-25%	70	34.5%
	26%-50%	42	20.7%
	51%-100%	65	32.0%
Do you work in a multidisciplinary practice setting?			
	Yes	170	83.3%
	No	34	16.7%
What is your primary affiliation?			
	Academic	83	40.7%
	Private practice	95	46.6%
	Other§	26	12.7%
Percent of your time spent in research?†			
	Less than 10%	132	65.3%
	10-25%	54	26.7%
	26-50%	8	4.0%
	51-100%	8	4.0%
Familiarity with literature identifying genetic markers indicative of susceptibility to side effects to radiation therapy?‡			
	Extremely	6	3.1%
	Very	21	11.0%
	Moderately	57	29.8%
	Slightly	71	37.2%
	Not at all	36	18.9%

(*continued on next column*)

Table 1 (*continued*)

Written-in responses include: Veterans Affairs (VA) hospital, community-based hospital, a non-VA government facility.

* One response missing

† Two responses missing

‡ Thirteen responses missing

§ Other = any affiliation not already listed as a choice.

would *not* consider a patient unsuitable for radiation treatment regardless of the level of increased risk for complications predicted by a genetic test (Fig 4).

When asked whether patients would be receptive to the information from such a test, only 3 respondents (1.5%) said patients would probably not or definitely not be receptive. Additionally, there was wide acceptance (76.7% probably, very likely, or definitely) to offer a genetic test to all patients considering radiation therapy for prostate cancer (Fig 2). Respondents said that results should be provided while giving the patient an overall treatment recommendation based on both genetic information and other clinical considerations (56.3%), instead of providing test results after giving a treatment recommendation (15.8%), without giving a treatment recommendation (26.6%), or another combination (1.3%). However, there were a few fundamental concerns. Most respondents chose cost (76.3%) and inaccuracy (83.3%) as important in determining the test's use. Nevertheless, apprehension over the potential for substantial harm resulting from erroneous predictions by the genetic test was low, with concern for severe harm indicated by 17.1% and 13.9% of respondents resulting from a false positive or false negative result, respectively.

Bivariate analysis of factors potentially associated with interest in ordering a genetic test is provided in Table E3. On multivariable analysis (Table E4), radiation oncologists who thought a genetic test predicting radiotoxicity susceptibility would be helpful for patient decision making were more interested in ordering a genetic test (odds ratio [OR] = 18.6 definitely helpful vs probably not/definitely not helpful; $P < .001$). Radiation oncologists who would determine a patient is unsuitable for radiation therapy due to increased risk were also more likely to

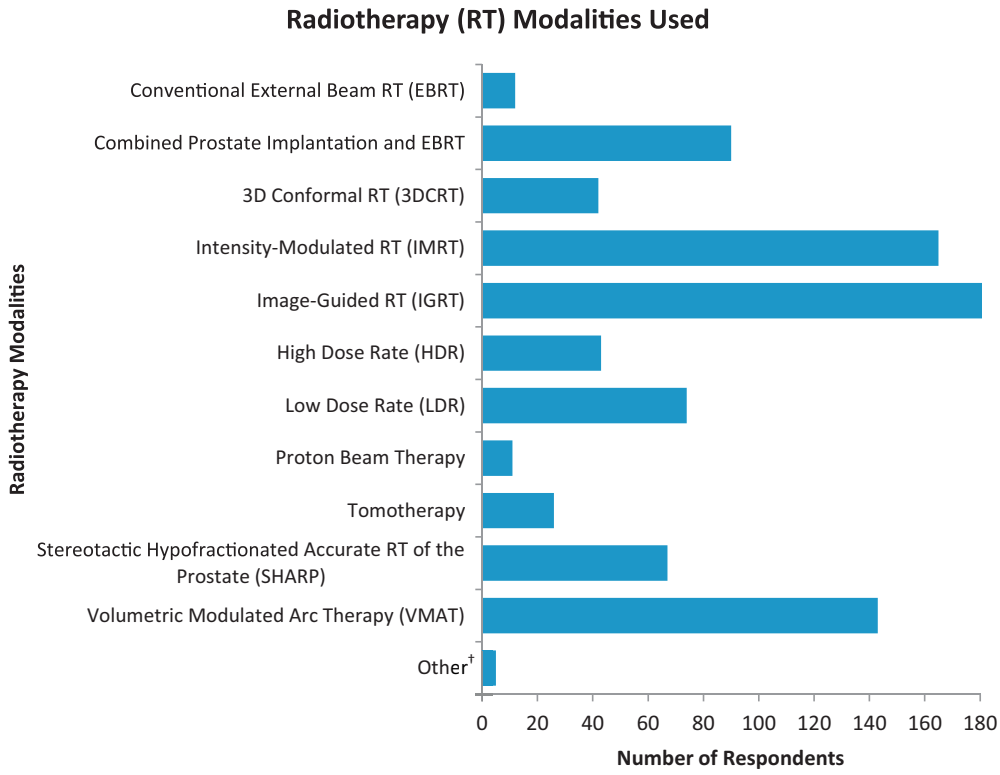

Figure 1 Types of radiation therapy modalities used by respondents to treat prostate cancer (N = 204). *This was a "select all that apply" question. Respondents were allowed to select more than one answer. †Other = any radiotherapy modality not already listed as a choice. Written-in responses included: IMRT + SBRT boost, cyberknife, endocrine therapy, hypofractionated IMRT, moderate external beam hypofractionation, radium 223.

select a higher category of interest in ordering a genetic test (OR = 5.22 for any predicted increased risk vs would not consider a patient unsuitable no matter the increased risk; $P = .04$).

Bivariate analysis of factors potentially associated with the predicted increased risk allowed by a radiation oncologist before recommending a patient is unsuitable for radiation therapy is provided in Table E5. The 2 factors associated with this outcome on multivariable analysis were the level of severity of predicted increased risk and the level of potential harm to a patient resulting from a false positive test result (Table E6). Radiation oncologists who receive test results

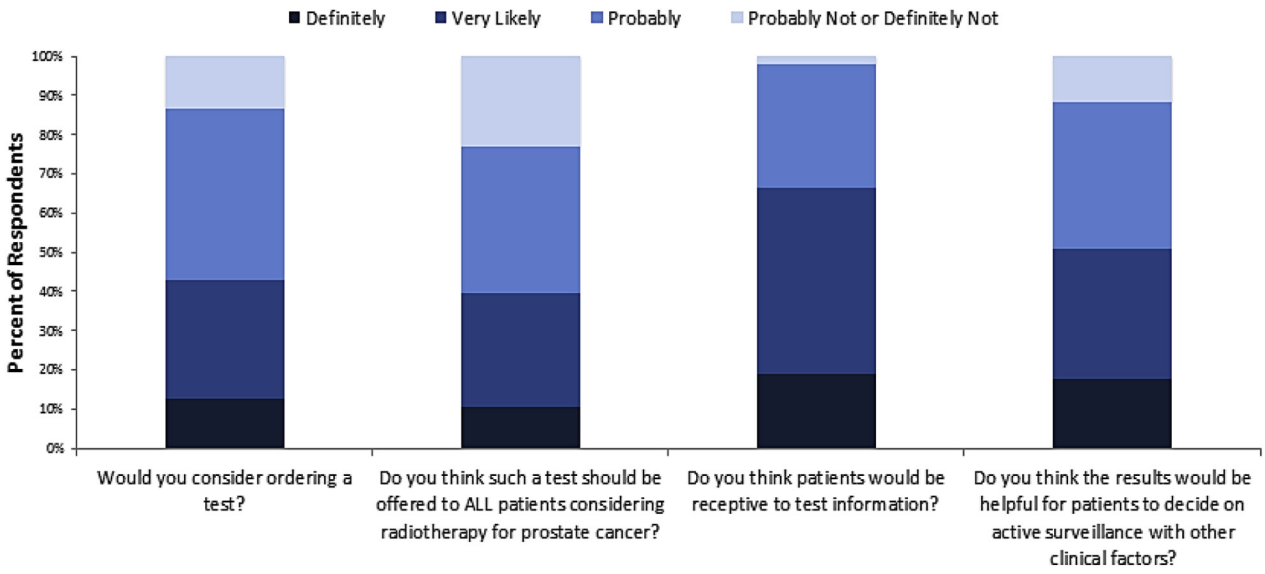

Figure 2 Attitudes toward genetic testing for prostate cancer patients.

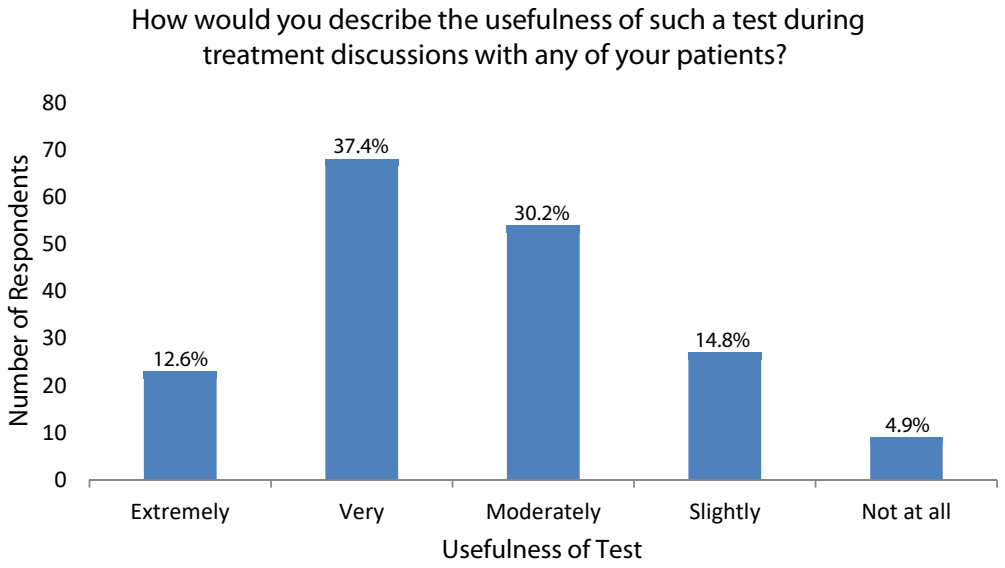

Figure 3 Perception of genetic test usefulness in treatment discussions with prostate cancer patients (N = 180).

predicting increased risk of severe radiotoxicity compared with mild or moderate radiotoxicity are more likely to require a higher magnitude of predicted increased risk before recommending a patient is unsuitable for radiation therapy (OR = 5.22 severe vs nonsevere; $P = .003$). Similarly, radiation oncologists who think a false positive result on the genetic test would result in severe harm to the patient are more likely to require a higher magnitude of predicted increased risk of toxicity before recommending a patient is unsuitable for radiation therapy (OR = 5.31 severe vs none; $P = .03$).

Discussion

This study examined the level of knowledge, interest, and possible use by radiation oncologists of a genetic test that can predict increased risk for radiation therapy toxicity to help guide treatment decision making. Among the key findings is that a majority of radiation oncologists who treat prostate cancer would order a genetic test if available, and a majority also indicated that such a test would be useful for treatment

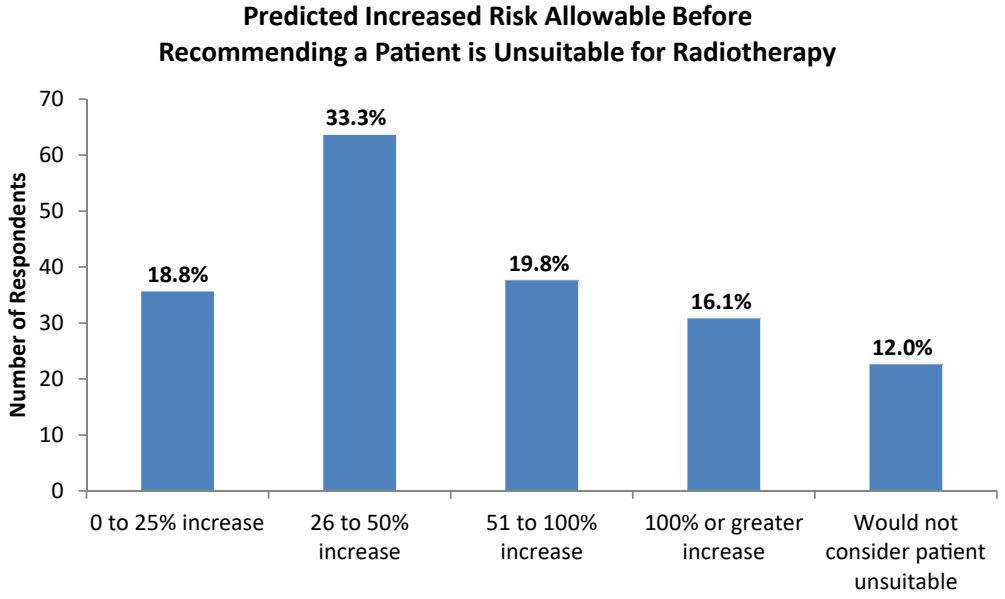

Figure 4 Magnitude of predicted increased risk of side effects by genetic test allowable before recommending a patient is unsuitable for radiation therapy and should consider other treatment options (N = 192). The exact question was stated as follows: "Putting clinical considerations aside and based solely on the results of the genetic test, in your practice what magnitude of predicted increased risk for development of an adverse effect specifically following treatment with radiation would you consider acceptable before recommending to a patient that he is not a suitable candidate for radiotherapy and should consider other treatment options?"

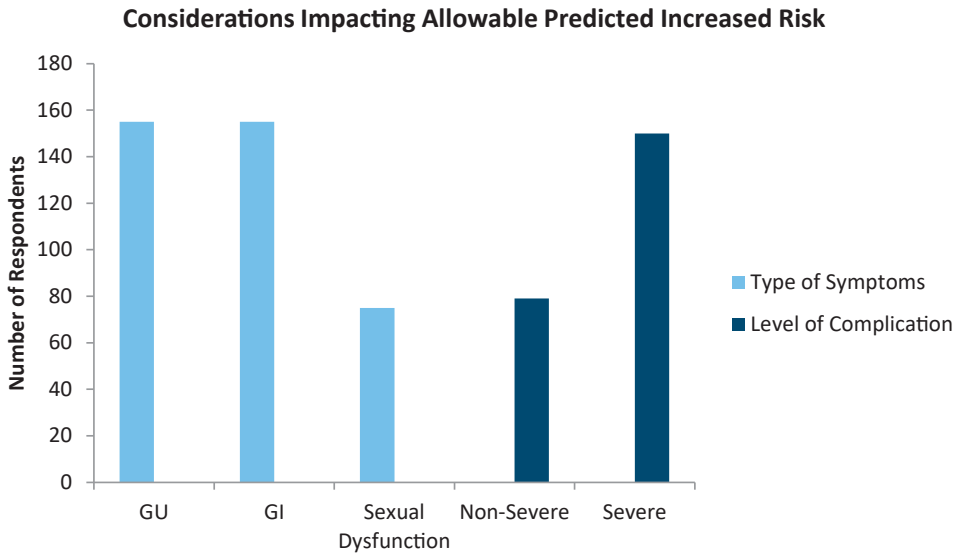

Figure 5 Considerations that affected respondents' allowable levels for predicted increased risk of adverse effects. Respondents were asked to choose the categories affecting his or her answer to the following question (Question 3): "Putting clinical considerations aside and based solely on the results of the genetic test, in your practice what magnitude of predicted increased risk for development of an adverse effect specifically following treatment with radiation would you consider acceptable before recommending to a patient that he is not a suitable candidate for radiotherapy and should consider other treatment options?" (Answers shown in Figure 4). "Type of Symptoms" question was asked as follows: "For which areas or categories of radiation symptoms would your answer to Question 3 apply? (Select all that apply)." "Level of Complications" question was asked as follows: "Would your response for Question 3 be applicable to mild (grade 1), moderate (grade 2) or severe (grade 3 and higher) complications following radiotherapy? (Select all that apply)."

discussions and reaching treatment decisions with patients.

Our international study complements recent national surveys investigating the views of radiation oncologists in regard to their use and interest in prostate cancer prediction tools and is, to our knowledge, the first such survey to focus on a prediction tool for treatment toxicity.[4,14] The recent studies report that radiation oncologists and urologists who have high confidence in genetic testing and view them as important use genetic testing more frequently, and if they do not use prediction tools, these specialties are less likely to recommend active surveillance for prostate cancer. We build on this with further comprehension of the factors that influence radiation oncologists' decisions to use such tests. Previous research in this area focused on patients' interest in genetic testing, and insight into the views of radiation oncologists is relatively sparse, especially in an international population.[4] Also, our findings build on genetic testing research as it relates to risk for development of prostate cancer[15] by extending this line of inquiry to the use of a genetic test to estimate risk for development of toxicities after prostate cancer radiation therapy.

The results of this study are consistent with previous research on physician perception of genetic testing, which found that although many physicians lack some confidence in their knowledge of genomics, they believe testing increases satisfaction of patients with cancer and the information available to them.[16,17] Over 50% of our participants indicated they were slightly or not at all familiar with scientific literature about genetic markers indicating adverse effects from radiation therapy for prostate cancer, although 50.3% responded that a genetic test would be very or extremely useful in provider-patient conversations. This is further evidence that increased effort to disseminate information about genomic testing is necessary, especially because genomics confidence is a strong predictor of physician attitude toward and anticipated use of genetic testing for cancer susceptibility.[17]

Surprisingly, over half (52.1%) of respondents would consider a patient unsuitable for radiation therapy with a modest ($\leq$50%) increase in risk of complications. A genetic test predicting increased risk of radiotoxicity would likely influence treatment decision making if radiation oncologists overall were similarly stringent. This is possibly most important regarding tumor aggressiveness. For patients with a modest predicted increased risk of toxicity, such information might only change treatment plans if the patient's tumor is low risk. A physician may require a higher predicted increased risk of toxicity before changing treatment plans for a patient with a very aggressive tumor where local control is of primary concern. The level of acceptable increased toxicity risk may also depend on how the treatment plan would be altered. However, our study found that accuracy is a concern for a genetic test predicting risk of radiotoxicity

for prostate cancer. This is in agreement with previous research where only about one-third of surveyed radiation oncologists expressed high confidence in a number of genetic risk prediction tools, although many such tools have been widely studied and validated.[4]

It should be noted that the survey response rate for radiation oncologists who primarily treat prostate cancer was likely greater than 6% because the selection of individuals for email invitations to the survey was broad and likely included a large percentage who were not eligible survey participants. It is also probable that some emails did not reach the intended recipients owing to changed or incorrect email addresses. Nonetheless, our rate of 6% is comparable to other physician specialty surveys.[18] Furthermore, this survey was not explicitly designed to obtain a representative cross-section of radiation oncologists. A particular concern was that most respondents would be radiation oncologists in academic centers with strong interest and knowledge of genetic testing; however, this was not the case.

Conclusions

This study evaluated radiation oncologists' responses to an online survey intended to gauge the level of interest and possible use of a genetic test predicting susceptibility to radiotoxicity. Our data suggest that a large percentage of radiation oncologists would order a genetic test and use the results to help guide their treatment consultations with patients with prostate cancer. Educational efforts are needed to ensure that radiation oncologists, and physicians in general, have a solid knowledge of genomics. This will increase physician interest in genetic testing, as well as patient understanding and acceptance of the results of predictive genomic/genetic assays that are increasingly being used to enhance precision medicine.

Supplementary Data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.03.019.

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