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Scientific Article

Evolution in the Presence and Evidence Category of Radiation Therapy Treatment Recommendations in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology

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Abstract

Purpose: The changes in the recommended use of radiation therapy (RT) in the presence of expanding systemic cancer therapies and technological advances are poorly characterized. We sought to understand the recommended utilization of RT across a broad range of malignancies by examining National Comprehensive Cancer Network (NCCN) Guidelines.

Methods and Materials: We conducted a comprehensive review and categorization of RT recommendations, with their subsequent supporting evidence categories, in 3 versions of NCCN Guidelines, specifically years 2000, 2009, and 2019. These NCCN Guidelines were individually examined for RT-specific recommendations among the 10 most common tumors. The presence of RT as a recommended modality was recorded for each tumor type in each guideline. Recommendation categories including Category 1, 2A, 2B, and 3 were tallied and compared with examine totals and percentage distributions in each tumor type.

Results: A total of 3858 NCCN recommendations were individually reviewed. The presence of a recommendation inclusive of RT increased from incidence of 205 in the year 2000 to 992 in the year 2019 (383%). In the 2019 NCCN Guidelines, the most Category 1 RT recommendations were found within small cell lung (13%), non-small cell lung (5%), breast (5%), bladder (2%), rectal (2%), and non-Hodgkin lymphoma (1%). Pancreatic, uterine, prostate, melanoma, kidney, and colon cancer guidelines had no Category 1 RT recommendations. Rectal cancer had 31 (27%) preferred recommendations. The majority (89%) of 2019 RT recommendations were for initial therapy, and 9% were specific to salvage therapy. Tumor sites

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with the highest proportion of RT Category 1 evidence were small cell lung (29%), non-small cell lung (24%), and breast cancer (24%).

Conclusions: The frequency of recommendations for using RT in NCCN Guidelines has increased by >300% in the past 20 years among the 10 most common malignancies. Consideration of the quality of evidence supporting these recommendations by tumor type is useful to identify specific malignancies in need of higher-level evidence supporting the role of RT.

Introduction

The role of radiation therapy (RT) is rapidly evolving in the management of cancer. Historically, certain malignancies, such as lymphomas, were routinely treated with RT, but with improvements in chemotherapy, the role of RT is now declining.[1] Although there has been a decline in the use of RT in some malignancies, other tumor types have seen significant increases in its use. For example, patients with metastatic disease were historically treated with chemotherapy alone, RT being reserved for palliation. Similarly, early-stage lung cancers were historically treated with surgery but are now often treated with focal RT often in place of surgery.[2] The field of immune-modulation has emerged and introduced RT as a novel potential immunomodulator.[3] These types of changes are just a few examples of the evolving role of RT in the management of cancer rapidly occurring across several tumor types.

There are numerous reasons it is vital to understand the evolving use of RT across the spectrum of all malignancies. First, this enables careful consideration of expertise needed across different tumor types and conditions. Second, such data could inform trainee experience, case log expectations, focus areas for board or recertification examinations and proportional allocation of physician workforce resources in practice settings.[4] Third, this can help all oncologists recognize the importance of RT across the continuum of oncologic care, affecting the funding of RT-focused research and technological development.[5,6] Finally, these data present an opportunity to investigate the use of RT broadly in oncology, showing tumors for which RT is either increasing or decreasing in use.[7-9]

The National Comprehensive Cancer Network (NCCN) creates well-respected clinical practice guidelines, which include treatment recommendations for more than 50 types of cancers. Examining these guidelines presents an excellent consensus platform to understand cancer management recommendations broadly, and such work has been done previously. For example, Poonacha and Go[10] have used the NCCN guidelines to describe the distribution in evidence and consensus (EC) of the 10 most common cancers in the United States and their relevant NCCN clinical guidelines. Noy et al evaluated the distribution of levels of evidence underlying RT recommendations for the 20 most prevalent cancers in the United States with at least 10 RT recommendations in the NCCN clinical guidelines for the year 2020. They found that the percentage of Category 1 recommendations for RT was approximately 10%.[11]

In the discipline of oncology broadly, limited data exist regarding changes in the utilization of RT with increasing systemic therapy options and effectiveness.[12] This concern continues to be reported by medical students when considering radiation oncology as a specialty.[13] Given the lack of data on this subject, we sought to understand the evolution in the recommended use of RT over the course of 2 decades. Specifically, we selected 2000 to 2019, during which there has been a substantial increase in the approval of novel oncologic systemic therapies.[14] To investigate this question further, we conducted a comprehensive review of recommendations for the use of RT in 3 versions of NCCN Clinical Practice Guidelines in Oncology from the years 2000, 2009, and 2019.

Methods and Materials

The 2000, 2009, and 2019 versions of NCCN comprehensive practice guidelines were requested on September 23, 2019, from prior archives. We manually examined 36 practice guidelines. All management pathways were reviewed, and we focused on tallying RT-specific recommendations for the 10 most common cancers in the United States by incidence excluding nonmelanoma skin cancer (breast, non-small cell and small cell lung, colorectal, pancreas, kidney, prostate, urinary bladder, uterus, melanoma, and diffuse large B-cell non-Hodgkin lymphoma), as modeled previously.[15] The presence of RT, which included all forms of external beam RT and brachytherapy as a recommended modality, was individually recorded for each tumor type, along with the branch of management (staging, initial and salvage therapy, and surveillance). Specifically, when recommendations were broken down within a branch to reflect variability of a particular situation, such as in the case of RT after mastectomy in breast cancer, each stratification was tallied. In regard to staging and surveillance, RT was tallied when it influenced staging recommendations. For example, in the 2019 NCCN Breast Guidelines on axillary lymph node staging, "axillary staging may be considered optional in patients . . . for whom the selection of adjuvant systemic

and/or RT is unlikely to be affected"; therefore, this was tallied. In the 2019 NCCN Bladder Guidelines, surveillance is stratified based on observation, cystectomy, or bladder sparing treatment; therefore, each surveillance modality recommendation for chemoRT was tallied. Categories of EC (Category 1, 2A, 2B, 3, Preferred, Disagree) were also manually scored and compared descriptively to examine totals and percentage distributions.

Results

A total of 3858 recommendations were individually reviewed. RT as a recommended modality increased by 129% from 2000 (205) to 2009 (470), and by 111% from 2009 to 2019 (992), for a total increase of 383% increase over the course of 2 decades (Fig. 1). In 2019, EC percentage distribution was 2% for Category 1, 90% for Category 2A, 3% were Category 2B, and 1% for Category 3. In 2009, EC percentage distribution was 4% (Category 1), 83% (Category 2A), 10% (Category 2B) and 2% (Category 3). In 2000, EC percentage distribution was 7% (Category 1), 75% (Category 2A), 14% (Category 2B), and 3% (Category 3) (Fig. 2). By comparison, total NCCN recommendations across medical, surgical and radiation therapies for 2019 were Category 1 (7%,), 2A (87%), 2B (6%), and 3 (0%). This is shown in Table 1 and the trends over time for each tumor site can be seen in Table 2 and Fig. 3. In NCCN practice guidelines for the year 2019, RT-specific Category 1 EC recommendations were found in small cell lung (13%), non-small cell lung (5%), breast (5%), bladder (2%), and rectal (2%) cancers as well as non-Hodgkin lymphoma (1%). Pancreatic, uterine, prostate, melanoma, kidney, and colon cancer guidelines had no recommendations with Category 1 EC designation. Of note, rectal cancer had 31 (27%) "preferred" recommendations.

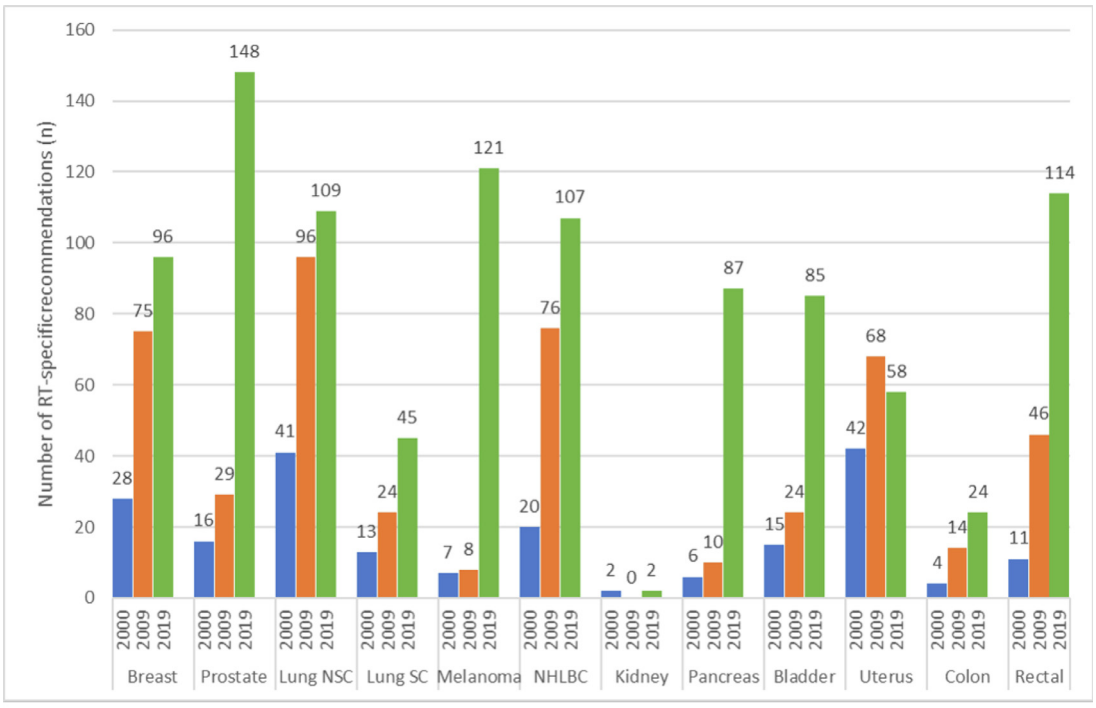
The majority (89%) of 2019 therapeutic recommendations pertained to initial therapy, and 9% were specific to salvage therapy. An increase in the recommended use of RT was also observed in 2000 and 2009 without much change over time: 84% initial, 15% salvage, and 89% initial, 11% salvage, respectively. Guidelines with the highest proportion of therapeutic Category 1 EC were small cell lung (29%), non-small cell lung (24%), and breast (24%). Of the 12 Category 3 EC, 6 were found in initial therapy for melanoma, 4 in salvage therapy for uterine cancer, and 2 in initial therapy for rectal cancer.

Discussion

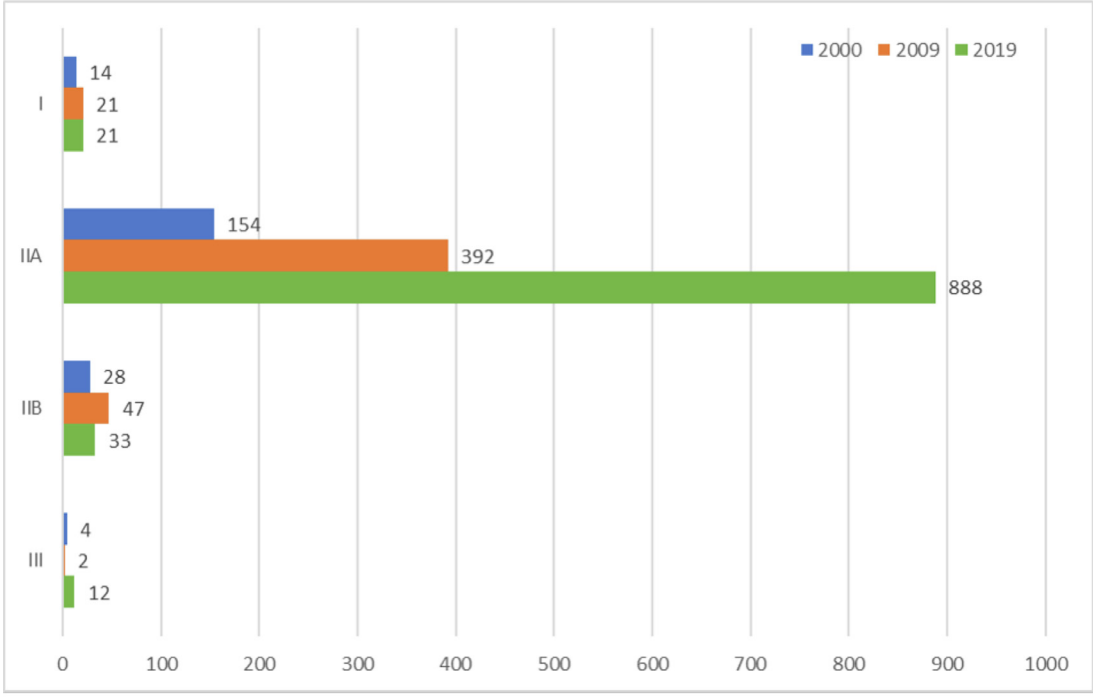
We have presented an analysis of the NCCN practice guideline recommendations that examined RT proportionally compared with total recommendations, for the 10 most common cancers in the United States. The results of this study demonstrate that the number of recommendations inclusive of RT has substantially increased between the years of 2000 to 2019 (from 205 to 992). Prior studies have demonstrated the trends in all NCCN recommendations over time, as well as one which defined the differences between EC for radiation and systemic therapies.[10,11,16] However, to our knowledge, our study is the first of its kind to combine these concepts and offer a longitudinal perspective.

We found that, overall, the number of pathway recommendations inclusive of radiation has increased by 383% between the years 2000 and 2019. This has coincided with a simultaneous significant increase in availability and type of systemic therapy.[6] Additionally, RT had a proportionally greater increase compared with total pathway recommendations between 2010 and 2019 (111% compared with 77%,[3] respectively). Not only is the use of RT increasing across the 10 most common cancers, it is also increasing at a rate greater than that of the combined oncologic therapies. These findings are critical and suggest that alongside the growth of systemic therapy options, the role of RT continues to expand; they may additionally counter-inform the beliefs which have led to decreased numbers of US medical students who apply and match into radiation oncology.[17] There are important components of our data that warrant careful consideration. Although combined NCCN recommendations with Category 1 EC increased from 6% to 7% from 2010 to 2019,[3] Category 1 RT-specific recommendations decreased from 4% to 2% during this same timeframe. This decline suggests that there is a need for RT studies with increased quality, quantity, and consistency of data. Furthermore, it is known that there is low representation of radiation oncologists among NCCN committees, which may limit "the discussion during guideline development and negatively impact[s] the diversity of perspectives in management recommendations."[5] Therefore, a potential solution to resolve a discrepancy between the proportion of Category 1 EC for RT compared with overall recommendations is increased representation of radiation oncologists on NCCN guideline committees. Moreover, NCI-funded oncology cooperative groups need to collectively focus the generation of level I evidence supporting the use of RT.

The limitations for this study include analysis of only the 10 most common cancers in the United States and use of overall NCCN data from prior studies as the point of comparison, which closely, but not exactly, match analyzed practice guidelines. To best make comparisons between RT recommendations and total recommendations as described by Poonacha and Go, we limited our analysis of recommendations to the same 10 most common cancers included in these studies.[10] This prevents the study from making conclusions regarding RT recommendations for all cancer types included in the NCCN guidelines. Additionally, these selection criteria resulted in the inclusion of disease sites, such as kidney, in which



(a)



(b)

Figure 1 (a) Number of National Comprehensive Cancer Network radiation therapy recommendations for the 10 most common cancers in the United States across years 2000 to 2019. (b) Number of National Comprehensive Cancer Network radiation therapy recommendations for the 10 most common cancers in the United States by main evidence and consensus categories across years 2000 to 2019. *Abbreviations*: NHLBC = non-Hodgkin lymphoma, B cell; NSC = non-small cell; RT = radiation therapy; SC = small cell.

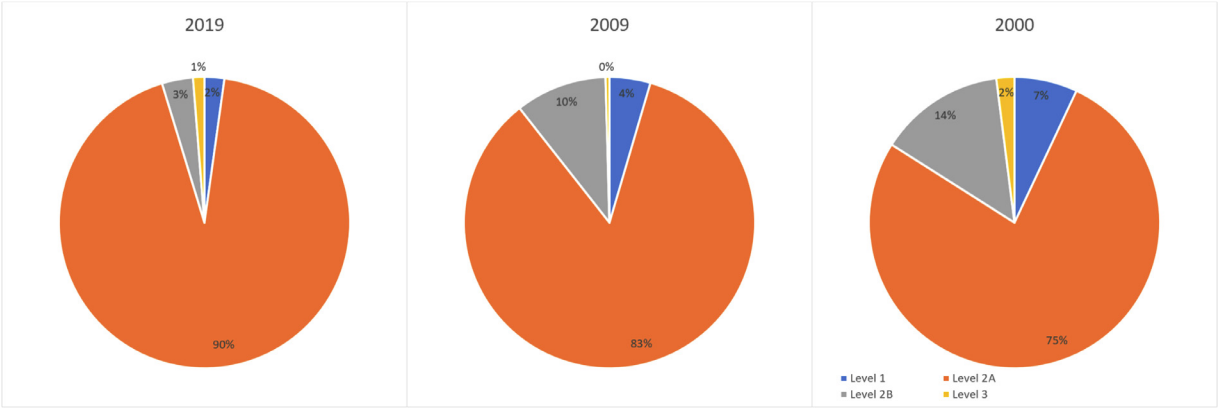


Figure 2 Percentage distribution of National Comprehensive Cancer Network radiation therapy recommendations for the 10 most common cancers in the Unites States by main evidence and consensus categories across years 2000 to 2019.

the presence of RT recommendations in the NCCN guidelines are quite limited. By comparison, in the analysis by Noy et al, they included the 20 most prevalent primary cancer disease sites in the United States with at least 10 RT-specific recommendations in the NCCN Guidelines.[11] This strategy also presents a potential limitation in that by comparing our RT data to total data published by another group (Poonacha and Go), we lacked this raw information.[10] Another limitation of the study is that it does not, and cannot, consider the potential evolution of the methods by which the NCCN makes its recommendations. For example, although there is known low representation of radiation oncologists as mentioned previously, disease site committees may have become more intentionally diverse and inclusive of radiation oncologists over the previous 20 years, possibly explaining the increase in RT evidence-based recommendations. Ultimately, in drawing conclusions about the use of RT in oncology with data collected from the NCCN, we are constrained to the consensus of a

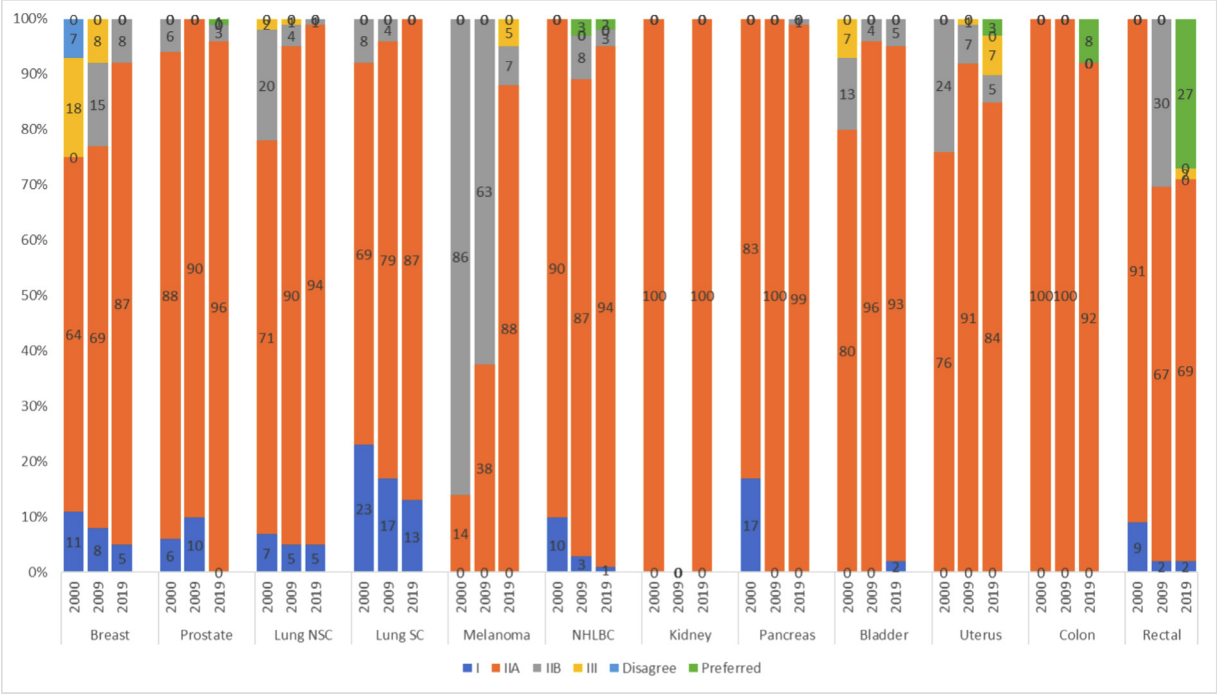


Figure 3 Distribution of National Comprehensive Cancer Network evidence and consensus categories of radiation therapy recommendations by the 10 most common cancers in the United States across years 2000 to 2019. *Abbreviations*: NHLBC = non-Hodgkin lymphoma, B cell; NSC = non-small cell; SC = small cell.

Table 1 Number and percentage distribution of NCCN radiation therapy recommendations for the 10 most common cancers in the United States by main EC categories across years 2000 to 2019

Category	2000	2009	2019
1	14 (7%)	21 (4%)	21 (2%)
2A	154 (75%)	392 (83%)	888 (90%)
2B	28 (14%)	47 (10%)	33 (3%)
3	4 (2%)	2 (<1%)	12 (1%)

Abbreviations: EC = evidence and consensus; NCCN = National Comprehensive Cancer Network.

Table 2 Number of NCCN radiation therapy recommendations for the 10 most common cancers in the United States across years 2000 to 2019

Cancer	2000	2009	2019
Breast	28	75	96
Prostate	16	29	148
NSCLC	41	96	109
SCLC	13	24	45
Melanoma	7	8	121
NHLBC	20	76	107
Kidney	2	0	2
Pancreas	6	10	87
Bladder	15	24	85
Uterus	42	68	58
Colon	4	14	24
Rectal	11	46	114

Abbreviations: NCCN = National Comprehensive Cancer Network; NHLBC = non-Hodgkin lymphoma, B cell; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

leading, but singular, cancer care entity. More research into specific types of RT used and modality was felt to be beyond the scope of this project, but may be an important future initiative. Finally, these data and results make no claims regarding radiation oncology workforce planning needs, which is beyond the scope of this work.

Conclusion

The frequency of RT recommendations in NCCN Guidelines has increased during the past 20 years among the 10 most common solid tumors. Most recommendations remain Category 2A, of which the number and proportion has increased over the years. Consideration of evidence categories by tumor type is highly relevant to identify areas in need of expanded prospective, randomized evidence regarding the use of RT.

Acknowledgments

Referenced with permission from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Uterine Neoplasms V.2009 and V.2000, Cutaneous Melanoma V.2009 and V.2000, B-Cell Lymphomas V.2009 and V.2000, Pancreatic Adenocarcinoma V.2009 and V.2000, Prostate Cancer V.2009 and V.2000, Rectal Cancer V.2009 and V.2000, Kidney Cancer V.2009 and V.2000, Non-Small Cell Lung Cancer V.2009 and V.2000, Small Cell Lung Cancer V.2009 and V.2000, Breast Cancer V.2009 and V.2000, Colon Cancer V.2009 and V.2000, Bladder Cancer V.2009 and V.2000. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 23, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

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