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Novel Genomic-Based Strategies to Personalize Lymph Node Radiation Therapy

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Current standard radiotherapy doses have been derived from empiric methods rather than a scientific framework. Subclinical nodal dosing remains relatively uniform across most disease sites, despite heterogeneity in patient and tumor biology. It is now clear that there are subsets of patients who will benefit from genomically-informed radiotherapy planning, and there are increasing efforts toward prescribing radiation dose to match the radiosensitivity of the tumor. By using novel genomic biomarkers to personalize delivery of radiotherapy, there is an opportunity to improve loco-regional control and cure rates. We survey the current landscape of personalized radiation oncology across commonly treated disease sites.
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Introduction

Oncology potentially represents an ideal field for the use of personalized medicine. In fact, recent years have seen the identification of aberrant genes and targeted systemic therapies (eg, anaplastic lymphoma kinase (ALK) in lung cancer or microsatellite instability (MSI) in colorectal cancer). Genomic assays in breast cancer help inform the utility of additional chemotherapy. In contrast, the discipline of radiation oncology has historically lagged behind in the arena of precision medicine. Yet radiotherapy is the most frequently utilized anticancer modality, with more than half of all cancer patients receiving radiotherapy as part of their treatment; the general contribution toward cancer cure by radiotherapy has been cited at approximately 40%.[1] Technological advances such as intensity-modulated radiotherapy (IMRT) and stereotactic radiotherapy have improved delivery of radiotherapy through modifications in dose fractionation and treatment target volumes. However, radiation oncologists have traditionally delivered homogenous doses for any given disease and stage despite underlying biology following a Gaussian distribution. Given the presence of heterogeneous tumor biology within a particular disease population, it is reasonable to hypothesize that there are subpopulations of patients for whom the therapeutic index of radiotherapy is not sufficiently optimized.[2,3] This point likely explains the results of clinical trials in which uniform dose-escalation has not proven to be consistently effective across multiple disease sites and stages of disease.[4-6]

Adaptive planning techniques have largely depended on anatomic changes to maximize conformal radiation delivery using newer technologies such as image-guided radiotherapy and IMRT.[7,8] Yet adaptations in the delivery of radiotherapy based on differences in intrinsic tumor biology have not been fully explored. For example, unique aspects of the tumor habitat, radiosensitivity, and microenvironment may allow an even more sophisticated method of adaptive treatment planning.[9] Effective use of such data could allow radiation oncologists to prescribe an optimal personalized dose, potentially leading to improved cure rates.

A recent area of focus in the field of personalized oncology is the use of clinical-genomic biomarkers. These are generally classified as being either prognostic or predictive; the former relates to long-term patient outcome regardless of treatment, the latter depends on the specific treatment in question. Ease of application and validation of the biomarkers through clinical trial are necessary benchmarks prior to routine clinical implementation of such tools.[10]

Management of lymph nodes as it pertains to subclinical radiation dose has remained fairly consistent across disease sites, generally prescribed to a range of 45-54 Gy. The

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potential detriment of a one-size-fits-all approach has been previously discussed in the treatment of primary tumors[11]; however, this principle likely applies to lymph node dosing as well. While common modern biomarkers predominantly predict endpoints such as distant metastasis, few predict radiosensitivity, or loco-regional recurrence. Therefore, advances improving both regional control and therapeutic ratio carry significant implications. In this review, we report on clinically established genomic biomarker signatures across common disease sites regularly treated with radiotherapy.

Head and Neck Cancer

Radiotherapy has become the primary treatment modality for many head and neck squamous cell cancers (HNSCC) and is commonly employed in the definitive as well as post-operative setting. Despite improvements in the current standard of care, the 5-year overall survival (OS) remains ~50% for HNSCC in aggregate.[12] Aside from improvements related to technological advances (ie, IMRT and image-guided radiotherapy), the treatment paradigm for primary HNSCC and regional lymph nodes has largely remained unchanged with respect to prescribed dose and target coverage. Regional lymph nodes have historically been treated to 70 Gy for gross disease, 63 Gy for high-risk regions concerning for microscopic disease, and 56 Gy for low-risk regions—regardless of primary histology. However, a greater understanding of the underlying epidemiology of HNSCC has recently allowed for the introduction of personalized dosing to regional lymph nodes, most notably, through dose de-escalation for HPV-associated oropharyngeal disease.

Despite their anatomic proximity, there is a remarkable diversity of presentation, progression, and treatment response among HNSCC subsites. Studies evaluating the radiosensitivity values in the HNSCC population demonstrated a relative 3-fold difference between the most radiosensitive and the most radioresistant HNSCC cancers.[9] It is therefore reasonable to postulate that different patients would each require unique doses for optimal treatment. HNSCC tumor staging continues to be determined by the primary disease site and clinicopathologic factors. HPV status has been incorporated into the recent implementation of the American Joint Commission of Cancer staging system (eighth edition) for oropharyngeal cancers, but its final impact on the clinical decision-making process remains a topic of active investigation.[13] For a more detailed discussion please see the review article by Tam et al in this issue of Seminars in Radiation Oncology. The role and clinical utility of other biologic markers continue to be explored.

Early studies focused on the role of epidermal growth factor receptor (EGFR) in the setting of HNSCC. EGFR is found to be upregulated in a significant portion of HNSCC,[14] and overexpression is concerning for more aggressive disease due to its association with decreased loco-regional control (LRC),[15-17] disease-free survival (DFS),[17] and OS in HNSCC. For many years cetuximab, an anti-EGFR monoclonal antibody has been the only targeted biologic agent available toward EGFR. In a seminal paper by Bonner et al, the addition of cetuximab to radiotherapy improved both LRC and OS, compared to those patients who received radiation alone.[18] With minimal toxicity compared to cytotoxic chemotherapy, cetuximab was thought to potentially offer a de-escalated treatment by omitting cytotoxic chemotherapy. RTOG 1016 evaluated this question by comparing radiotherapy and cetuximab to radiotherapy and cisplatin for HPV-associated oropharyngeal disease. This study revealed an inferior outcome with cetuximab vs cisplatin.[19] This highlights the potential danger of deintensifying treatment in the absence of randomized data. However, radiation dose to the elective neck and involved lymph nodes per the RTOG protocol has not been altered from historical norms. Currently there are minimal data on the role of EGFR status in respect to personalized dose or volumes for primary or nodal disease.

In comparison, the role of HPV in guiding HNSCC treatment has illuminated the potential opportunities for personalized radiotherapy. HPV was the first prognostic marker in HNSCC that suggested the potential for the personalization of treatment to gross disease and the regional lymph nodes. As the rates of HPV-associated cancers have increased significantly over the past several decades,[20] it has become evident that HPV-positive HNSCC is a distinct entity with superior LRC, cause-specific survival (CSS), and OS when compared to its HPV-negative cohorts.[12,21,22]

The exact mechanism for increased radiosensitivity among HPV-associated cancers remains unclear, but is most likely due to multiple contributing factors. As viral DNA incorporates into the host genome, the overexpression of viral-associated oncoproteins E6 and E7 promotes the proteolysis of the tumor suppressor genes p53 and Rb, respectively.[23] With impaired DNA repair function, HPV-associated cancers have a reduced ability to withstand and overcome the double-stranded DNA damage from radiotherapy.[24,25] Furthermore, the relative radiosensitivity may also be a result of an immunologic response to virally associated cancers. It has been shown that exposure of viral antigens following radiotherapy augments the immune response.[26,27] This is supported clinically by evidence of an improved OS in patients with increased levels of circulating T cells following radiotherapy.[28] Additionally, presence of HPV16DNA has predicted improved rates of LRC following postoperative chemoradiation.[29]

An understanding of the inherent radiosensitivity of HPV-associated HNSCC when compared with HPV-negative HNSCC led to an array of de-escalation trials, with the common goal of maintaining comparable disease control while decreasing radiation-associated toxicities (Table 1).[30-35] All of these trials, while not exclusive to HPV-related disease, employed IMRT with varied regimens of dose reduction to the primary and/or nodal sites of disease. Importantly, de-escalation with elective dosing as low as 40 Gy.[34,35] and 36 Gy[32] was accomplished without compromising disease control. In addition to radiation de-escalation, the NRG trial HN-002 is evaluating the possible exclusion of concurrent chemotherapy. This prospective, multi-institutional,

Table 1 Recent Studies Evaluating De-escalation of Dose for Oropharyngeal Cancer

Study Type	TN Stage	N	Dose (Gy)	Fractions	Endpoint(s)	Clinical Outcome	Chemotherapy	Reference	Comment
Phase II trial	T0-T3 N0-N2c	43	60, p 54, s	30	pCR	87%	CC	Chera 2015[31]	Patients had minimal smoking history
Phase II trial	T1-T4 N0-N3	45	60 vs 54, p 48 vs 43, s	30 vs 27 30 vs 27	LRR DM PFS (2 yr)	7% 2% 92%	Induction CP CC	Chen 2017[30]	55% received adaptive de-escalation based on response to induction chemotherapy
Prospective trials	TX-T4 NX-N3	233	70, p 40, s	35 20	LC (2 yr) RC (2 yr) DC (2 yr) DSS (2 yr) OS (2 yr)	84.1% 89.2% 83.2% 64.2% 71.2%	Mixed	Nevens 2017[34,35]	61% received concomitant chemotherapy, 2% received induction chemotherapy
Phase II trial	T1-T4 N0-N2b	54	70, p 36, s	35 18	ENF (3 yr) OS (3 yr)	0% 91%	CC	Maguire 2018[32]	Patients received sequential rather than simultaneous boost to macroscopic disease
Phase II trial	T1-T3 N0-N2b	80	69.3 vs 54, p 51.3, s	33 vs 27 27	cCR PFS (2 yr) OS (2 yr)	70% 80% 94%	Induction CP Cetuximab	Marur 2016[33]	Adaptive de-escalation with Cetuximab based on cCR

Abbreviations: CC, concomitant weekly cisplatinum; cCR, clinical complete response rate; CP, carboplatin/paclitaxel; DC, distant control; DSS, disease-specific survival; ENF, elective nodal failure; LC, local control; LRR, loco-regional recurrence; OS, overall survival; p, primary dose; pCR, pathologic complete response rate; PFS, progression-free survival; RC, regional control; s, subclinical dose.

randomized phase II trial compares conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) plus concomitant weekly cisplatin to accelerated radiotherapy alone (60 Gy in 30 fractions over 5 weeks) for patients with HPV-associated oropharyngeal disease and minimal smoking history. Per treatment protocol, involved lymph nodes are to receive 60 Gy, high-risk nodal regions 54 Gy, and low risk nodal regions 48 Gy. This trial has achieved its targeted patient accrual and is pending data maturation.

While HPV status has played a large role in the evolving management of oropharyngeal cancer, the exploration for biomarkers in other sites of HNSCC has been less fruitful. Compared to other carcinomas like prostate and breast cancer, there is currently no validated multigene assay available for widespread use to assist with HNSCC treatment decisions. Akervall et al proposed a panel of biomarkers to predict radioresistance of HNSCC. Originally identified in 38 patients and subsequently validated in another 86 patients, several markers were correlated with decreased relapse free survival (YAP1, BCL2) and CSS (YAP-1, VEGF, CLAUDIN-4) as well as synergistic radioresistance (YAP-1 and c-MET).[36]

The development and decreasing cost of next-generation sequencing, whole exome sequencing, and gene copy number analyses have allowed researchers to simultaneously evaluate several genetic mutations and understand their relationships within molecular systems gene networks that drive individual tumors.[37] To this point, the Cancer Genome Atlas is currently performing a multiplatform analysis with the goal of creating a comprehensive profile of 500 HNSCC patients. An interim report of the first 279 patients identified 6 frequently mutated genes that have been determined to key signal pathways for HNSCC carcinogenesis: TP53, NOTCH1, CDKN2A, PIK3CA, HRAS, and PTEN. On their subset analysis, HPV-positive tumors were associated with upregulation of PIK3CA, loss of TRAF3, and amplification of E2F1, while smoking associated HPV-negative disease was associated with loss of TP53 and CDKN2A.[38] The therapeutic implications of these results are unclear, yet the molecular distinctions provide avenues for future research. One early application of these data are being implemented in the third generation of a recent de-escalation trial.[31] Based on TP53 status, researchers are aiming to select the subset of HPV-positive patients with a smoking history $\leq$10 pack-years who would benefit from deintensification of primary dose to 60 Gy with concomitant weekly cisplatin.[39]

Last, many groups have evaluated the potential for circulating tumor cells (CTCs) to steer radiation therapy into precision medicine.[40,41] Perhaps the most specific evidence supporting the use of CTC for lymph node personalization comes from Hristozova et al, who found a significant correlation of N2b or greater nodal stage of HNSCC with CTCs frequency.[42] Interestingly, this observation was not significantly correlated with the primary tumor stage or volume suggesting a potential marker for greater elective lymph node coverage. Further studies are required to fully understand the clinical significance of these findings in order to incorporate them into clinical practice.

Prostate Cancer

In the management of prostate cancer, the decision−making process for determining whether to pursue active surveillance, watchful waiting, definitive treatment, or alternative management options is complicated by the balance between life expectancy, comorbidities, clinical benefits, and treatment side effects. Treatment recommendations for men with localized prostate cancer have become increasingly difficult owing to the availability of various treatment options. The current guidelines for patients with organ−confined prostate cancer include definitive modalities such as radical prostatectomy and radiation therapy, with either treatment modality providing equivalent disease−free outcomes in large randomized studies.[43] Furthermore, the role of treating the pelvic lymph nodes in prostate cancer has been debated for over 30 years.[44-49] The targets involved in elective nodal irradiation for this disease site generally include the obturator, internal and external iliac lymph nodes, with doses typically prescribed to 45 Gy in 25 fractions. An ongoing clinical trial (RTOG 0924, NCT01368588) is investigating the use of irradiation to the pelvic lymph nodes for unfavorable intermediate risk and favorable high risk disease; the results of this study are highly anticipated. In the definitive treatment setting, studies involving dose-escalation have shown mixed results, without a uniform benefit amongst disease risk subgroups.[50,51] As a result, further patient characterization was needed to guide appropriate patient selection for treatment modalities that can offer the most clinical benefit, leading to the development of innovative diagnostic, prognostic, and predictive biomarkers in the management of prostate cancer.

Combined with the use of established nomograms based on clinicopathologic factors,[52-54] novel genomic tools have refined decision-making for the individual patient. In an effort to decrease the number of patients undergoing biopsy, a diagnostic 4k score comprised of 4 kallikrein markers, digital rectal exam, and age was established to identify aggressive disease.[55] For patients with a PSA between 2.0 and 10.0 ng/mL who have not yet had a biopsy or have had a negative biopsy, the 4k score is suggested as a means of assessing the risk of distant metastases.[56,57] The OncotypeDx Genomic Prostate Score is a 17-gene assay for patients with either very-low risk or low risk disease and a life expectancy greater than 10 years who have undergone biopsy.[57] While this is suggested as a biomarker for selecting patients suitable for active surveillance, the Genomic Prostate Score has been slow to assimilate into routine clinical practice.[58,59]

The cell cycle progression score (Prolaris) is a prognostic biomarker based on 31 cell cycle genes, first described in a retrospective study evaluating biochemical recurrence or CSS in American and British patients with localized disease managed with either radical prostatectomy or watchful waiting following transurethral resection of the prostate.[60] Increase of the cell cycle progression score was independently associated with biochemical recurrence (hazard ratio [HR] 1.77, 95% confidence interval [CI] 1.40-2.22, $P < 0.0001$) after prostatectomy, as well as time to death from prostate cancer in the watchful waiting cohort HR 2.57, 95% CI 1.93-3.43, $P < 0.0001$). Similar findings were shown in a study of patients treated with definitive radiotherapy,[61] with subsequent studies demonstrating a potential role for this biomarker in selecting candidates with very low-risk or low-risk disease for active surveillance following initial biopsy.[62-66]

The use of genomic biomarkers as a predictor for the risk of recurrence following definitive treatment has also become an attractive tool for selecting patients who will derive the most benefit from additional therapy. As traditional risk group classifications are most useful for predicting biochemical recurrence in prostate cancer,[67-69] the Decipher 22-gene signature was established in an effort to better predict distant metastasis-free survival in patients with localized disease following definitive treatment.[70] Den et al reviewed Decipher scores from 2342 patients undergoing adjuvant or salvage radiotherapy and found that Decipher scores significantly correlated with pathologic features and predicted freedom from biochemical (area under curve (AUC) 0.75) and distant (AUC 0.78) recurrence.[71] The predictive utility was further improved in combination with a validated model predicting outcomes in the postoperative setting.[53] The Decipher score has since undergone validation in multiple studies,[70,72-75] demonstrating its clinical value for patients at high risk for recurrence based on known adverse features (positive margins, pT3, rising PSA above nadir).[76,77] Recently, a large multicenter study demonstrated both the improved risk classification and clinical facility provided by the Decipher score using multiple training and validation cohorts.[75]

The Postoperative Radiotherapy Outcome Score (PORTOS) is a 24-gene signature score which is inversely related to the 10-year rate of distant metastases in the postprostatectomy setting (high PORTOS = lower incidence of metastases).[78] For the 39 patients in the training cohort with a high PORTOS, there was a significant difference in the rate of distant metastases (5% vs 63%, respectively) between those receiving postoperative radiotherapy and those who did not (HR 0.12, 95% CI 0.03-0.41, $P < 0.0001$). This finding was subsequently validated and distinguished PORTOS as the first biomarker predictive of response to postoperative radiotherapy. Taken together, PORTOS and Decipher scores are valuable tools which can be used in combination with traditional risk stratifications for individualized selection to adjuvant rather than salvage radiotherapy. While the above clinical-genomic biomarkers were designed with distant failure as the primary endpoint, they should be viewed as surrogates of more aggressive disease and may provide further guidance when considering which individuals would be most apt to benefit from nodal irradiation.

Breast Cancer

Elective treatment of lymph nodes in breast cancer has been an area of rigorous investigation and controversy. Comprehensive treatment involving the axillary, supraclavicular, infraclavicular, and internal mammary lymph nodes has been standard care in older studies and more recently, the MA-20 and EORTC

clinical trials.[79-82] Practice involving elective irradiation of levels I and II of the axilla varies but is generally considered following surgical staging when there is evidence of extracapsular extension, greater than 33% positivity of sampled lymph nodes, or no axillary lymph node dissection in the presence of a positive sentinel lymph node biopsy. Elective nodal dose has consistently been prescribed to a range of 45-50 Gy, with some studies suggesting that coverage of the internal mammary lymph nodes may not be necessary for some patients.[83,84] Robust integration of genomic, radiomic, clinicopathologic, and other biologic data into a predictive model are needed to further identify patients most likely to benefit from elective nodal radiotherapy.

Genomic tests have become useful tools in predicting clinical outcomes and for guiding treatment decisions in breast cancer. The Oncotype Dx Recurrence Score (RS) was shown to be an accurate predictor for the risk of distant recurrence and OS at 10 years independent of age and tumor size in patients with lymph node negative, ER+ tumors treated with tamoxifen.[85] In lymph node positive patients treated with tamoxifen, adjuvant chemotherapy provided little benefit in terms of 10-year distant recurrence in tumors with Oncotype Dx RS of less than 18, while patients with RS greater than 31 benefited from chemotherapy.[86,87] Furthermore, prospective studies revealed that patients with node-negative, ER+, HER2-negative tumors, and RS <11 had less than a 1% risk of distant recurrence at 5 years and that such patients may be safely spared chemotherapy even if they are at high risk of distant failure by traditional clinicopathologic risk estimation.[88,89] With growing acceptance of data supporting the use of tumor genomics in clinical practice, the newly-released AJCC eighth edition staging guidelines incorporate the Oncotype DX RS as staging modifiers.

The 21 gene RS has also been studied for its association between loco-regional recurrence (LRR) in both node-negative and node-positive ER+ breast cancer. Tissue samples from node-negative patients from the NSABP B-14 and NSABP B-20 studies were assessed for the ability of the 21 gene RS to predict LRR. The 21 gene RS was found to be a significant predictor of LRR regardless of whether women were treated with tamoxifen, placebo, or chemotherapy plus tamoxifen. The RS appeared to better stratify women treated with mastectomy regardless of age compared to those women treated with lumpectomy plus radiotherapy.[90] The Oncotype DX score was also used to assess outcomes in node-positive patients from the NSABP B-28 study of ER+ patients treated with doxorubicin and cyclophosphamide for 4 cycles with or without paclitaxel. The RS was a statistically significant predictor of LRR on univariate analyses (10-year cumulative incidence of LRR 3.3%, 7.2%, and 12.2% for low, intermediate, and high RS, respectively, $P < 0.001$). The score remained significant on multivariate analysis. However, when assessing the 21 gene RS by number of positive nodes, only patients with ≥4 positive nodes and not 1-3 positive nodes were significantly stratified.[91]

The Mammaprint 70-gene signature has also been shown to be a powerful predictor of distant metastasis in node-negative breast cancer, and there is evidence it is a more accurate predictor of OS and metastasis-free survival than standard clinicopathological risk assessment methods.[92,93] The MINDACT Trial found that 46% of women with early stage breast cancer who were at high clinical risk but low genomic risk may not require chemotherapy if they are placed in the low genomic risk category by the Mammaprint signature.[94] These women were found to gain no benefit in 5-year metastasis-free survival with adjuvant chemotherapy. Similar to the Oncotype DX Score, Mammaprint has been used to predict for LRR. Drukker et al reported on 1053 breast cancer patients with T1-3N0-1, margin negative tumors treated between 1984 and 2002 with breast conservation surgery with radiation therapy or mastectomy with or without radiation therapy at the NKI. The Mammaprint assay was found to be a significant predictor of LRR in patients treated with breast conservation surgery and mastectomy with radiation therapy.[95]

Various groups have developed gene signatures to predict the benefit of adjuvant breast cancer radiation therapy. In the context of the Danish 82b and 82c trials, the Danish Group published a gene signature, which predicted the benefit of postmastectomy RT in patients with high-risk breast cancer.[96] A 7-gene signature was identified from 191 patients and then validated in 112 patients ultimately identifying a group of patients with sufficiently low risk of LRR in whom there was no benefit from postmastectomy radiation therapy.[90,97] In addition, the University of Michigan developed the radiation sensitivity signature (RSS) to identify patients who would benefit from adjuvant radiotherapy.[98] The RSS was developed using clonogenic survival assays across breast cancer cell lines. The RSS was validated in 2 independent datasets outperforming all clinical and pathologic features. Further prospective validation of these signatures may reveal which cohorts of patients may derive the most benefit from adjuvant radiotherapy.

Last, biomarkers of normal tissue toxicity may play an important role in dose personalization. While there has been a long-standing interest in biomarkers predictive of tumor response to treatment, recent studies evaluating the role of single-nucleotide polymorphisms (SNPs) in predicting radiation-associated toxicity have provided insight relating to dose modulation based on these factors.[99-101] Formed in 2009, the Radiogenomics Consortium successfully genotyped 92 SNPs in 46 genes from a group of 1613 breast and prostate cancer patients receiving radiotherapy.[100] While this initial study did not show an association between SNPs and radiation toxicity, a subsequent meta-analysis ($N = 5456$) of breast and prostate cancer patients found a significant association between an *ATM* SNP and normal tissue toxicity.[101] This important work by the Radiogenomics Consortium is ongoing in these and other disease sites, and efforts towards optimizing treatment based on normal tissue toxicity may help us identify which patients would be most suitable for dose personalization.[102]

Lung Cancer

Target delineation of lymph nodes in lung cancer has been the subject of controversy over the past decade. Traditional

subclinical doses of 44-50 Gy were delivered as elective nodal irradiation (ENI) to account for microscopic disease to mediastinal nodal stations in non−small cell lung cancer (NSCLC). It has been posited that even when ENI is not intentionally undertaken, incidental irradiation of the regional nodes provides some degree of regional control for microscopic disease.[103] Furthermore, ENI may be more appropriate for residual microscopic disease following resection of gross tumor, whereas failure following definitive treatment of intact tumor is generally local or distant. Due to concerns for toxicity and marginal regional control benefit with ENI, image-guided selective nodal irradiation (SNI) of involved nodal fields was evaluated as an alternative.[104-107] By utilizing PET/CT to target only FDG-avid regions in the mediastinum, De Ruysscher et al were able to safely escalate dose to 60 Gy in 30 fractions.[107] In another study by the same group, isolated nodal recurrences were as low as 2% with SNI.[104] Recent phase III randomized studies recommend targeting involved nodal areas as designated by diagnostic CT or PET-CT with the prescription dose of radiotherapy,[4,108] generally 60-70 Gy.

Similar findings regarding involved nodal radiation fields have been made in limited-stage small cell lung cancer. Van Loon et al observed a low isolated nodal recurrence rate of 3% (95% CI, 1%-11%) with the delivery of PET/CT-guided SNI.[109] Rates of grade 3 esophageal toxicity were significantly lower (12% vs 30%) than those noted in the traditional fields involving ENI established by Turrisi et al for limited-stage small cell lung cancer.[110] Yet there was a lower OS in this study (median 19 months vs 23 months) than in the earlier study by Turrisi et al, which the authors attribute to differences in study design such as chemotherapy regimen, time interval between chemotherapy and radiotherapy, and inclusion of contralateral hilum and supraclavicular lymph nodes in the treatment fields.[109]

Efforts toward personalizing treatment for advanced NSCLC have manifested in predictive models for patients treated with chemoradiation,[111] as well as targeted biologic agents toward *EGFR* mutation and *ALK* gene rearrangement.[112-114] These therapies have now become integrated into clinical practice. Additional molecular targets including ROS1, BRAF, MEK, Trk1/2/3, and others have available targeted therapies which can be utilized for delivery of personalized, biologically targeted therapy.[115] As molecular profiling improves, increasing numbers of patients with NSCLC will be eligible for biologically targeted therapies. For patients with stage I lung cancer treated with surgery or stereotactic body radiotherapy, there is a need for prognostic data that could inform decisions on adjuvant treatment.

While many attempts to define a high-risk patient population have been undertaken, there has been an overall paucity of validated genomic biomarkers for NSCLC relative to the previously mentioned disease sites. Several recent studies have shown promise for novel genomic biomarkers in early-stage NSCLC. The malignancy-risk gene signature, originally derived from a cell-proliferation signature in breast cancer, was shown to be a potential predictive tool for response to adjuvant chemotherapy.[116] In a recent meta-analysis by Tang et al, 20 of 42 published prognostic gene signatures performed better than random signatures with respect to predicting survival outcomes in early-stage NSCLC, adjusting for known adverse tumor and patient characteristics.[117] While these advances may provide useful information to guide decision-making about adjuvant systemic therapy, they are not routinely utilized and there remains a clear need for novel biomarkers predicting risk of LRR, which could help inform decision-making about adjuvant radiotherapy.

Biomarkers may be useful to guide personalized radiation dose prescription. In past years, dose-escalation for NSCLC has been a strategy to improve local control in a number of studies; however this technique is limited by toxicity to lung parenchyma and neighboring structures.[4,118-120] Based on their prior work, Vinogradskiy et al conducted a retrospective analysis of SNPs as biomarkers predicting for radiation pneumonitis.[121,122] The goal of their study was to create a model using both genetic and dosimetric elements to allow safe personalization of dose. Using their model, they found that an individualized mean lung dose based on SNPs data led to a prescription change >5 Gy in 59% of patients. The model also would have predicted a lower prescribed dose in nearly all (96%) patients who developed pneumonitis. Other promising biomarkers in NSCLC include single-gene mutations characteristic of more radioresistant tumors, such as *KEAP1* and *NRF2*.[123,124]

As immunotherapy becomes increasingly utilized for patients with NSCLC, novel biomarkers to guide treatment decision-making are required. Increased PD-L1 expression as measured by immunohistochemistry has been consistently shown to enrich for selection of responders to anti-PD-1 therapy.[125] Tumor mutational burden has been found to predict response to anti-PD1 therapy in NSCLC[126]; however, there remains a further need for validated biomarkers predicting response to frequently prescribed immunotherapies. Results from the recent PACIFIC trial have led to FDA approval of PD-L1 blockade following definitive chemoradiation for stage III NSCLC.[108] The benefits of this therapy were irrespective of the baseline expression of PD-L1, which suggests there may be a synergistic effect with radiotherapy to account for low PD-L1 levels.

Novel biomarkers to detect and predict for synergistic effects with radiotherapy and systemic immunotherapy are required. Additionally, radiation oncologists may need to consider tailoring primary and lymph node radiotherapy doses to enhance immune effects. There are a number of ongoing clinical trials evaluating the combination of immunotherapy and hypofractionated radiotherapy regimens in patients with NSCLC.[127] Based on results from these trials, a potential technique may be to design smaller radiation fields targeting the primary tumor site with precise treatment setup and steep radiation dose gradients allowing for improved mobilization of an immunogenic antitumor response. The use of PET/CT has shown promise in guiding radiation target volume delineation based on response to systemic therapy in addition to identifying potential regions of radioresistance.[128-130] A strategy aimed at combining image-based and molecular biomarkers in conjunction with novel systemic

therapies aimed at activating immune response may offer potential for improved outcomes with personalized radiation dose prescription.

Gastrointestinal Cancers

The role of radiotherapy in the treatment of gastrointestinal (GI) malignancies is critical, yet biomarker-driven personalization of treatment has been lacking. In an attempt to improve this situation, several groups have correlated multiple gene expression signatures across a variety of microarray platforms with patient outcomes.[131-133] As the use of IMRT has allowed for more selective dose distribution in sites such as esophageal, gastric, and anal cancer, there is a growing interest in the role of biologically-guided personalized radiotherapy.

Historic fields for esophageal cancer were based on bony landmarks using 2D technology, with field borders extending 5 cm craniocaudally to account for nodal and subclinical disease.[134,135] With the advent of newer technologies (3DCRT, IMRT, and 4D-CT) allowing for the ability to spare normal tissue, it became imperative to define specific nodal targets, and expert consensus guidelines were subsequently published to meet this need.[136] Even so, there is considerable variation in elective nodal coverage among radiation oncologists. Regarding coverage of the para-esophageal, supraclavicular, lesser curvature, splenic, and celiac nodes, NCCN guidelines recommend to "consider treatment" of these areas based on the anatomic location of disease.[137] In particular, the inclusion of mediastinal nodal stations, as well as lymph nodes of the greater curvature and splenic hilum (based on Siewert type), are areas of current controversy.[136,138] Perioperative doses consistently range from 45 Gy to 50.4 Gy, while dose-escalation >50.4 Gy for primary squamous cell histology in the setting of definitive chemoradiation has been suggested due to reports of superior pathologic complete response (pCR) rates.[139,140]

Studies in esophageal cancer have also suggested the presence of genetic biomarkers that could be used to alter therapy. In the neoadjuvant chemoradiotherapy setting, McLaren et al have shown over-expression of the CCL28 and under-expression of the DKK3 genes to be independently associated with a pCR.[141] In the same clinical setting, Wadhwa et al have associated high nuclear levels of Gli-1 found via pCR with a lower probability of achieving a pCR (odds ratio = 0.84, $P < 0.0001$).[142] Tsou et al have found the GALNT14 "GG" genotype to be associated with a lower response rate and longer time to complete/partial response when treated with chemoradiation for stage IV esophageal squamous cell carcinoma.[143] By predicting the likelihood of pCR, such markers could provide future indications for dose personalization in treatment-resistant tumors.

The same advances in conformal radiotherapy have allowed excellent target coverage with sparing of neighboring tissue in gastric cancer, and contouring guidelines have been authored to assist with detailed guidance of nodal targets.[136,144,145] Current outcomes for gastric cancer remain poor and optimal treatment regimens are unclear.[137,146,147] The role for preoperative chemoradiation is being investigated, and a shift toward this practice would further call for dose optimization, given the large treatment volumes.[148,149] While the above-mentioned consensus guidelines have been an important resource for practicing radiation oncologists, they are based on the collective experience of physicians, and to an extent, clinical and pathologic factors. The previously described assays offer possible pathways for dose alteration based on pretreatment gene expression. By modeling patients with gastroesophageal and gastric cancers using genomic markers preoperatively, one could potentially correlate pathologic response at the time of surgery with the dose distributions delivered. This could provide important feedback for radiation oncologists that may lead to optimizing both radiation dose and selection of nodal targets.

Total mesorectal excision preceded by chemoradiation has been the standard of care for locally advanced rectal cancer, established by the German Rectal Cancer Study.[150] The traditional elective radiation field covering the mesorectal, presacral and internal iliac (adding external iliac for T4 disease) nodal stations, prescribed to 45 Gy, has remained unchanged. However, it has been noted that there is a wide range of pathologic response following neoadjuvant treatment, and recent studies have suggested that selective nonoperative management with a watch-and-wait approach may be preferable for a select subgroup of patients.[151-153] Genomic signatures identifying such patients would be of great importance and would allow further dose personalization in the definitive treatment of both primary and regional disease. In consideration of personalized dose, preliminary studies have associated specific genetic biomarkers, gene expression profiles, and protein expression with worse colorectal outcomes or response to treatment.[154-157] In a recent study, the median level of circulating tumor DNA was significantly correlated with nodal involvement, more advanced disease and recurrence in rectal cancer.[158] Thus, standardization of circulating tumor DNA detection levels could indicate the presence of occult nodal disease and dictate further elective nodal coverage. In looking at patients with all forms of GI cancers, a meta-analysis demonstrated that an overexpression of the long noncoding RNA PVT1 (LncRNA PVT1) was associated with worse OS (HR = 1.86, $P < 0.0001$), DFS, CSS, and relapse-free survival.[159]

The current standard treatment of lymph nodes in anal cancer involves dose-escalation using a simultaneous integrated boost technique based on size of involved lymph nodes.[160] While biomarker prognostication is not commonly explored in anal cancer, one group has isolated a number of prognostic tumor related biomarkers via immunohistochemistry. In their pretreatment multivariate analysis, Ajani et al associated the presence of Ki67 ($P = 0.005$), NF-κB ($P = 0.002$), SHH ($P = 0.02$), and Gli-1 ($P = 0.02$) with improved DFS in patients treated with definitive chemoradiation.[161] Just as dose-reduction efforts are being made in other sites of HPV-related cancers, novel predictive biomarkers in anal cancer may supplement the standard anatomic criteria in selection of nodal dose. Overall, the evidence in support of personalizing radiotherapy dose in GI malignancies is still in

its infancy. Tailoring abdominal dose is particularly challenging given the potential for small bowel, mucosal, and biliary radiation-induced toxicity.[162] Therefore, given the restrictive dose constraints of these disease sites, there is a clear need for suitable markers capable of identifying patients for individualized dose modification.

Melanoma

Melanoma distinguishes itself among cutaneous malignancies by demonstrating a propensity for regional and distant metastasis compared with other common skin cancers. While regional radiotherapy is often recommended postoperatively for high-risk features (eg, extranodal extension, number of nodes involved, location) in melanoma, it remains a category 2B recommendation in the NCCN guidelines due to concern for toxicity.[163-165] This is a result of predictive outcomes based on clinicopathologic features being less reliable for melanoma than in other prevalent malignancies. Immunotherapy plays an increasingly prominent role in advanced stages of disease, yet only a subset of patients will experience a significant benefit. Response rates with traditional and more recent immunotherapies have generally ranged from 25% to 45%.[166-169] In the postoperative setting, anti-CTLA4 and anti-PD1 agents have shown improved recurrence-free survival,[166,170] with the latter demonstrating a superior toxicity profile.[171,172] As these new immunotherapies lead to improvements in survival outcomes, there will likely be an increased role for radiotherapy in LRC. It has been reported that aggregating immune tumor-infiltrating cells are independently prognostic of outcomes in solid tumors.[173] Based on this work, Messina et al were able to predict ectopic lymphoid structures within primary and metastatic melanoma tumor samples through use of a 12-chemokine gene expression signature.[174] The presence of these node-like structures was correlated with improved OS in patients with stage IV melanoma, potentially identifying a subgroup better selected for immunotherapy.

A recent study by Strom et al investigated the role of regional radiotherapy in node-positive cutaneous melanoma.[175] As the association between regional control and OS in melanoma has been a subject of debate, the study aimed to identify a subset of patients in which regional radiotherapy might provide a survival benefit. They evaluated the radiosensitivity index (RSI, discussed in further detail below) gene expression scores in available tumor samples for 42 patients in the study. While regional radiotherapy improved regional control in patients with extranodal extension and clinically apparent lymphadenopathy, they also showed worse OS in patients with a high RSI (high RSI = more radioresistant) receiving postoperative regional radiotherapy (HR, 10.68; 95% CI, 1.24-92.14; Table 2). These data indicate there might be a subset of melanoma patients who would derive a survival benefit from regional radiotherapy. Future validation of RSI and the 12-chemokine gene expression signature as it relates to regional control would be of great value in the present debate surrounding the value of regional radiotherapy for melanoma.

RSI and GARD

Radiotherapy has traditionally been prescribed to a uniform dose for a given disease and stage. In response to a need for a more personalized treatment approach in radiotherapy, the RSI was established and validated over the past 10 years. Using a systems biology approach, this 10-gene molecular signature was trained to predict the inherent radiosensitivity of a tumor based on the cellular survival at 2 Gy (SF2) after radiotherapy in 48 human cancer cell lines.[176,177] The 10 genes identified were selected from the top 500 genes predicting radiosensitivity in various primary tumors, including melanoma, breast, prostate, renal, colon, NSCLC, pancreas, glioblastoma, and leukemia.[178-184] In addition to predicting radiosensitivity in vitro, RSI has been further validated in patient cohorts in rectal, esophageal, prostate, glioblastoma, pancreas, lung, head and neck, and breast cancer primaries.[180,182,185-189] RSI has predicted outcomes (LRC, distant

Table 2 Predicted Clinical Outcomes Using RSI in Patients treated with Radiotherapy Across Disease Sites (*N* = 1373)

Disease Site	*N*	Endpoint	Clinical Outcome RS vs RR	*P* Value	Reference
Breast	77	RFS	95% vs 75% (5 yr)	0.02	Eschrich 2012[186]
Breast	288	DMFS	77% vs 64% (5 yr)	0.04	Eschrich 2012
Breast	343	LRFS	–	0.0006	Torres-Roca 2015[190]
Lung	53	DFS	63% vs 22% (5 yr)	0.02	Creelan 2014[188]
Lung	27	DFS	–	0.09	Creelan 2014
Lung	16	DFS	75% vs 25% (5 yr)	0.18	Creelan 2014
GBM	214	OS	84% vs 54% high MGMT (1 yr)	0.005	Ahmed 2015[182]
Pancreas	49	OS	78% vs 42% vs 8% (3 yr)	0.003	Strom 2015[189]
Prostate	82	DMFS	94% vs 72% (10 yr)	0.03	Torres-Roca 2014[180]
Prostate	132	BFFS	80% vs 60% (5 yr)	0.026	Torres-Roca 2014
Head and neck	92	LRFS	86% vs 61% (2 yr)	0.05	Eschrich 2009[185]
Melanoma	42	OS	75% vs 0% (5 yr)	SS	Strom 2017[175]

Abbreviations: BFFS, biochemical failure-free survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; GBM, glioblastoma; LRFS, local recurrence-free survival; OS, overall survival; RFS, relapse-free survival; RS, radiosensitive; RR, radioresistant; SS, statistically significant.

metastasis-free survival, relapse-free survival, OS, response rate) in a number of patient cohorts for the aforementioned disease sites following radiotherapy but not in tumors not treated with radiotherapy (Table 2). It is postulated from these data that there is a heterogeneous benefit of radiotherapy, which is dependent on cell biology and independent of tissue type. Combining RSI with other genomic, clinical, and image-based prognostic markers offers important prospects for optimizing treatment through biologic guidance of both treatment fields and dose fractionation. Future studies investigating the evolution of RSI during the course of treatment or in response to chemotherapy will provide valuable information about this genomic signature.

Steps toward clinical integration of the RSI signature were taken in the recent study by Scott et al. Since RSI is based on SF2, it was hypothesized that RSI could be integrated into the biologically effective dose to develop a clinically actionable metric based on the intrinsic genomic radiosensitivity/radioresistance of tumors. Use of the genomic adjusted radiation dose (GARD) represents an application through which radiotherapy can be employed as a component of precision medicine. In the above study, GARD values from 8271 tumor samples (independently validated in 5 cohorts comprised of breast, lung, pancreas, and glioblastoma patients) were calculated by combining RSI with the traditional linear quadratic radiobiologic model to predict the effect of radiotherapy. Higher GARD values corresponded to a greater benefit from radiotherapy and were associated with tumors traditionally believed to be more radiosensitive, such as HPV-associated cervical and oropharyngeal cancers. Tumor types considered to be more radioresistant, such as sarcoma or glioma, were found to have lower GARD scores. In 2 independent datasets of patients, GARD was predictive of distant metastasis-free survival in patients receiving adjuvant therapy for breast cancer. In light of the current high rates of local control in breast cancer, it is reasonable to hypothesize from this data that there is a substantial population of patients who may be candidates for dose personalization.

In addition to treatment of primary tumors, RSI and GARD may provide valuable guidance for escalating treatment in patients at higher risk for nodal and distant recurrence based on their predicted response to radiotherapy. Two studies specifically looking at LRC as an endpoint found RSI to be predictive in head and neck and breast cancers[185,190] (Table 2). A third study by Ahmed et al evaluated the differences in RSI values in colorectal primary and metastatic disease sites.[183] RSI analyses for 1362 primary colon and 704 metastatic sites of disease were performed, revealing a higher incidence of radioresistant samples in metastatic (64%) compared to primary tumors (54%, $P = 0.01$). They were able to categorize disease sites in descending order of radioresistance as follows: ovary (0.48), abdomen (0.47), liver (0.43), brain (0.42), lung (0.32), and lymph nodes (0.31), $P < 0.0001$, where an RSI score of <0.375 was considered radiosensitive (Fig. 1). It has been suggested based on this study that combining RSI with other genomic biomarkers such as telomeres to predict individual radiosensitivity and patterns of failures could lead to cures in well-selected patients with oligometastatic colon cancer.[191-193]

It is noteworthy that among the sites of colorectal metastasis, lymph nodes were shown to have the lowest RSI values (low RSI, more radiosensitive). This evidence allows us to consider differential lymph node radiotherapy doses to personalize treatments.[183] Furthermore, the study by Scott et al

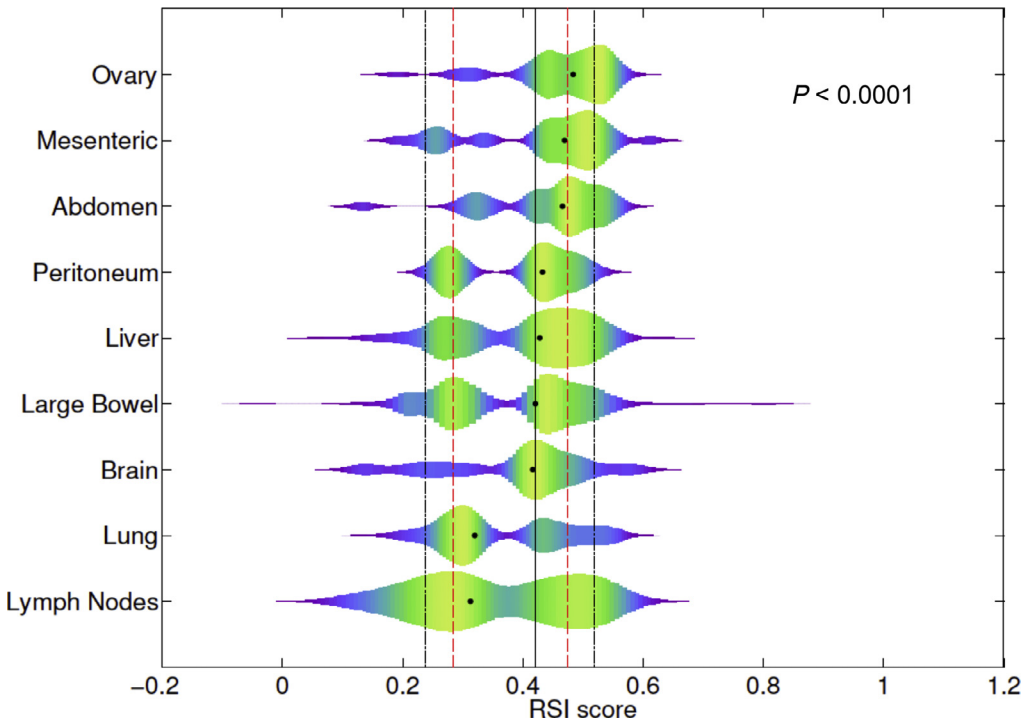

Figure 1 Differences in radiation sensitivity indexes (RSI) of colon cancer metastases based on anatomical location.

showed that GARD score distribution was widely variable in disease sites where regularly prescribed subclinical (perioperative) doses are approximately 45 Gy. Taken together, these data warrant further investigation into radiation dose personalization to lymph nodes across most, if not all, sites of disease.

Conclusion

Current standard radiotherapy doses have been derived from trial and error, and subclinical nodal dosing remains relatively uniform across most disease sites. These have traditionally been based on the maximum tolerated dose rather than a scientific or molecular framework. Generally speaking, regional control with subclinical doses of 45-50 Gy has been excellent (above 90% in the majority of clinical situations). Therefore it is reasonable to suggest that such good outcomes are indicative of overtreatment, particularly in patients who are without disease in the nodal basin at outset. It is now clear that there are subsets of patients who will benefit from genomically-informed radiotherapy planning, and there are increasingly more opportunities to prescribe radiation dose to match the radiosensitivity of the tumor. While the majority of currently validated biomarkers relate to distant control and OS, assays predictive of regional control are needed. As these methods are further refined, a paradigm toward biology-driven prescription of radiotherapies will aid in optimizing LRC and cure rates while minimizing toxicity. Future clinical trials aimed at incorporating genomic guidance and interventions into individualized dose determination will be of fundamental importance in ushering our field into the era of precision medicine.

References

1. Lievens Y, Grau C. Health economics in radiation oncology: Introducing the ESTRO HERO project. Radiother Oncol 103:109-112, 2012
2. Ramaswamy S, Tamayo P, Rifkin R, et al: Multiclass cancer diagnosis using tumor gene expression signatures. Proc Natl Acad Sci 98:15149-15154, 2001
3. Lawrence MS, Stojanov P, Polak P, et al: Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 499:214-218, 2013
4. Bradley JD, Paulus R, Komaki R, et al: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. Lancet Oncol 16:187-199, 2015
5. Minsky BD, Pajak TF, Ginsberg RJ, et al: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167-1174, 2002
6. Chan JL, Lee SW, Fraass BA, et al: Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. J Clin Oncol 20:1635-1642, 2002
7. Brown E, Owen R, Harden F, et al: Predicting the need for adaptive radiotherapy in head and neck cancer. Radiother Oncol 116:57-63, 2015
8. Castadot P, Lee JA, Geets X, et al: Adaptive radiotherapy of head and neck cancer. Semin Radiat Oncol 20:84-93, 2010
9. Scott JG, Berglund A, Schell MJ, et al: A genome-based model for adjusting radiotherapy dose (GARD): A retrospective, cohort-based study. Lancet Oncol 18:202-211, 2017
10. Bibault JE, Fumagalli I, Ferte C, et al: Personalized radiation therapy and biomarker-driven treatment strategies: A systematic review. Cancer Metastasis Rev 32:479-492, 2013
11. Torres-Roca JF. A molecular assay of tumor radiosensitivity: A roadmap towards biology-based personalized radiation therapy. Per Med 9:547-557, 2012
12. Ang KK, Harris J, Wheeler R, et al: Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24-35, 2010
13. Liu J, Ebrahimi A, Low TH, et al: Predictive value of the 8th edition American Joint Commission Cancer (AJCC) nodal staging system for patients with cutaneous squamous cell carcinoma of the head and neck. J Surg Oncol 117:765-772, 2018
14. Sheikh Ali MA, Gunduz M, Nagatsuka H, et al: Expression and mutation analysis of epidermal growth factor receptor in head and neck squamous cell carcinoma. Cancer Sci 99:1589-1594, 2008
15. Chung CH, Zhang Q, Hammond EM, et al: Integrating epidermal growth factor receptor assay with clinical parameters improves risk classification for relapse and survival in head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 81:331-338, 2011
16. Demiral AN, Sarioglu S, Birlik B, et al: Prognostic significance of EGF receptor expression in early glottic cancer. Auris Nasus Larynx 31:417-424, 2004
17. Chua DT, Nicholls JM, Sham JS, et al: Prognostic value of epidermal growth factor receptor expression in patients with advanced stage nasopharyngeal carcinoma treated with induction chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 59:11-20, 2004
18. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567-578, 2006
19. Gillison ML, Trotti AM, Harris J, et al: Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): A randomized, multicenter, non-inferiority trial. Lancet, 2018. In Press. PMID: 30449625
20. Blitzer GC, Smith MA, Harris SL, et al: Review of the clinical and biologic aspects of human papillomavirus-positive squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys 88:761-770, 2014
21. Fakhry C, Westra WH, Li S, et al: Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 100:261-269, 2008
22. Kumar B, Cordell KG, Lee JS, et al: Response to therapy and outcomes in oropharyngeal cancer are associated with biomarkers including human papillomavirus, epidermal growth factor receptor, gender, and smoking. Int J Radiat Oncol Biol Phys 69:S109-S111, 2007
23. Dok R, Kalev P, Van Limbergen EJ, et al: p16INK4a impairs homologous recombination-mediated DNA repair in human papillomavirus-positive head and neck tumors. Cancer Res 74:1739-1751, 2014
24. Rieckmann T, Tribius S, Grob TJ, et al: HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity. Radiother Oncol 107:242-246, 2013
25. Kimple RJ, Smith MA, Blitzer GC, et al: Enhanced radiation sensitivity in HPV-positive head and neck cancer. Cancer Res 73:4791-4800, 2013
26. Lassen P, Eriksen JG, Hamilton-Dutoit S, et al: Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. J Clin Oncol 27:1992-1998, 2009
27. Wansom D, Light E, Worden F, et al: Correlation of cellular immunity with human papillomavirus 16 status and outcome in patients with advanced oropharyngeal cancer. Arch Otolaryngol Head Neck Surg 136:1267-1273, 2010
28. Ward MJ, Thirdborough SM, Mellows T, et al: Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. Br J Cancer 110:489-500, 2014
29. Lohaus F, Linge A, Tinhofer I, et al: HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: Results from a multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). Radiother Oncol 113:317-323, 2014

30. Chen AM, Felix C, Wang PC, et al: Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: A single-arm, phase 2 study. Lancet Oncol 18:803-811, 2017
31. Chera BS, Amdur RJ, Tepper J, et al: Phase 2 trial of de-intensified chemoradiation therapy for favorable-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 93:976-985, 2015
32. Maguire PD, Neal CR, Hardy SM, et al: Single-arm phase 2 trial of elective nodal dose reduction for patients with locoregionally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 100:1210-1216, 2018
33. Marur S, Li S, Cmelak AJ, et al: E1308: Phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx—ECOG-ACRIN cancer research group. *J Clin Oncol* 35:490-497, 2017
34. Nevens D, Duprez F, Daisne JF, et al: Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma: A randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol 122:171-177, 2017
35. Nevens D, Duprez F, Daisne JF, et al: Recurrence patterns after a decreased dose of 40 Gy to the elective treated neck in head and neck cancer. Radiother Oncol 123:419-423, 2017
36. Akervall J, Nandalur S, Zhang J, et al: A novel panel of biomarkers predicts radioresistance in patients with squamous cell carcinoma of the head and neck. *Eur J Cancer* 50:570-581, 2014
37. Bibault JE, Tinhofer I. The role of next-generation sequencing in tumoral radiosensitivity prediction. Clin Transl Radiat Oncol 3:16-20, 2017
38. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* 517:576-582, 2015
39. Chera BS, Amdur RJ. Current status and future directions of treatment deintensification in human papilloma virus-associated oropharyngeal squamous cell carcinoma. Semin Radiat Oncol 28:27-34, 2018
40. De Ruysscher D, Jin J, Lautenschlaeger T, et al: Blood-based biomarkers for precision medicine in lung cancer: Precision radiation therapy. Transl Lung Cancer Res 6:661-669, 2017
41. Merker JD, Oxnard GR, Compton C, et al: Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol 36:1631-1641, 2018
42. Hristozova T, Konschak R, Stromberger C, et al: The presence of circulating tumor cells (CTCs) correlates with lymph node metastasis in nonresectable squamous cell carcinoma of the head and neck region (SCCHN). Ann Oncol 22:1878-1885, 2011
43. Hamdy FC, Donovan JL, Lane JA, et al: 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 375:1415-1424, 2016
44. McGowan DG. The value of extended field radiation therapy in carcinoma of the prostate. Int J Radiat Oncol Biol Phys 7:1333-1339, 1981
45. Asbell SO, Krall JM, Pilepich MV, et al: Elective pelvic irradiation in stage A2, B carcinoma of the prostate: Analysis of RTOG 77-06. Int J Radiat Oncol Biol Phys 15:1307-1316, 1988
46. Perez CA, Michalski J, Brown KC, et al: Nonrandomized evaluation of pelvic lymph node irradiation in localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 36:573-584, 1996
47. Morikawa LK, Roach 3rd M. Pelvic nodal radiotherapy in patients with unfavorable intermediate and high-risk prostate cancer: Evidence, rationale, and future directions. Int J Radiat Oncol Biol Phys 80:6-16, 2011
48. Roach M, 3rd DM, Valicenti R, et al: Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the radiation therapy oncology group 9413 trial. Int J Radiat Oncol Biol Phys 66:647-653, 2006
49. Pommier P, Chabaud S, Lagrange JL, et al: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. Int J Radiat Oncol Biol Phys 96:759-769, 2016
50. Pollack A, Zagars GK, Smith LG, et al: Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 18:3904-3911, 2000
51. Kuban DA, Tucker SL, Dong L, et al: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 70:67-74, 2008
52. Zelefsky MJ, Kattan MW, Fearn P, et al: Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. *Urology* 70:283-287, 2007
53. Stephenson AJ, Kattan MW, Eastham JA, et al: Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 27:4300-4305, 2009
54. Roach 3rd M, Waldman F, Pollack A. Predictive models in external beam radiotherapy for clinically localized prostate cancer. *Cancer* 115:3112-3120, 2009
55. Vickers A, Cronin A, Roobol M, et al: Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. J Clin Oncol 28:2493-2498, 2010
56. Mottet N, Bellmunt J, Bolla M, et al: EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 71:618-629, 2017
57. Carroll PH, Mohler JL. NCCN guidelines updates: Prostate cancer and prostate cancer early detection. *J Natl Compr Cancer Netw* 16:620-623, 2018
58. Ross AE, D'Amico AV, Freedland SJ. Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. Prostate Cancer Prostatic Dis 19:1-6, 2016
59. Sanda MG, Cadeddu JA, Kirkby E, et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: Risk stratification, shared decision making, and care options. J Urol 2017
60. Cuzick J, Swanson GP, Fisher G, et al: Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: A retrospective study. *Lancet Oncol* 12:245-255, 2011
61. Freedland SJ, Gerber L, Reid J, et al: Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys 86:848-853, 2013
62. Bishoff JT, Freedland SJ, Gerber L, et al: Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 192:409-414, 2014
63. Shore N, Concepcion R, Saltzstein D, et al: Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. Curr Med Res Opin 30:547-553, 2014
64. Crawford ED, Scholz MC, Kar AJ, et al: Cell cycle progression score and treatment decisions in prostate cancer: Results from an ongoing registry. Curr Med Res Opin 30:1025-1031, 2014
65. Karnes RJ, Choeurng V, Ross AE, et al: Validation of a genomic risk classifier to predict prostate cancer-specific mortality in men with adverse pathologic features. Eur Urol 73:168-175, 2018
66. Nguyen PL, Haddad Z, Ross AE, et al: Ability of a genomic classifier to predict metastasis and prostate cancer-specific mortality after radiation or surgery based on needle biopsy specimens. Eur Urol 72:845-852, 2017
67. Amin MB, Greene FL, Edge SB, et al: The eighth edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67:93-99, 2017
68. D'Amico AV, Whittington R, Malkowicz SB, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 280:969-974, 1998
69. Mohler JL, Armstrong AJ, Bahnson RR, et al: Prostate Cancer, Version 1.2016. *J Natl Compr Cancer Netw* 14:19-30, 2016
70. Erho N, Crisan A, Vergara IA, et al: Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One* 8:e66855, 2013

71. Den RB, Santiago-Jimenez M, Alter J, et al: Decipher correlation patterns post prostatectomy: Initial experience from 2 342 prospective patients. Prostate Cancer Prostatic Dis 19:374-379, 2016
72. Badani KK, Thompson DJ, Brown G, et al: Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. BJU Int 115:419-429, 2015
73. Klein EA, Haddad Z, Yousefi K, et al: Decipher genomic classifier measured on prostate biopsy predicts metastasis risk. *Urology* 90:148-152, 2016
74. Ross AE, Feng FY, Ghadessi M, et al: A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate Cancer Prostatic Dis 17:64-69, 2014
75. Spratt DE, Zhang J, Santiago-Jimenez M, et al: Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. J Clin Oncol 36:581-590, 2018
76. Bolla M, van Poppel H, Tombal B, et al: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 380:2018-2027, 2012
77. Wiegel T, Bartkowiak D, Bottke D, et al: Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 66:243-250, 2014
78. Zhao SG, Chang SL, Spratt DE, et al: Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: A matched, retrospective analysis. Lancet Oncol 17:1612-1620, 2016
79. Fisher B, Jeong JH, Anderson S, et al: Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 347:567-575, 2002
80. Donker M, van Tienhoven G, Straver ME, et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 15:1303-1310, 2014
81. Whelan TJ, Olivotto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 373:1878-1879, 2015
82. Poortmans PM, Collette S, Kirkove C, et al: Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 373:317-327, 2015
83. Chen RC, Lin NU, Golshan M, et al: Internal mammary nodes in breast cancer: diagnosis and implications for patient management—A systematic review. J Clin Oncol 26:4981-4989, 2008
84. Thorsen LB, Offersen BV, Dano H, et al: DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 34:314-320, 2016
85. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817-2826, 2004
86. Albain KS, Barlow WE, Shak S, et al: Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial. Lancet Oncol 11:55-65, 2010
87. Paik S, Tang G, Shak S, et al: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24:3726-3734, 2006
88. Sparano JA, Gray RJ, Makower DF, et al: Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 373:2005-2014, 2015
89. Gluz O, Nitz UA, Christgen M, et al: West German study group phase III planB trial: First prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. J Clin Oncol 34:2341-2349, 2016
90. Mamounas EP, Tang G, Fisher B, et al: Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: Results from NSABP B-14 and NSABP B-20. J Clin Oncol 28:1677-1683, 2010
91. Mamounas EP, Liu Q, Paik S, et al: 21-gene recurrence score and locoregional recurrence in node-positive/er-positive breast cancer treated with chemo-endocrine therapy. J Natl Cancer Inst 109
92. Buyse M, Loi S, van't Veer L, et al: Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst 98:1183-1192, 2006
93. van de Vijver MJ, He YD, van't Veer LJ, et al: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347:1999-2009, 2002
94. Cardoso F, van't Veer LJ, Bogaerts J, et al: 70-Gene Signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375:717-729, 2016
95. Drukker CA, Elias SG, Nijenhuis MV, et al: Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: A pooled analysis. Breast Cancer Res Treat 148:599-613, 2014
96. Tramm T, Mohammed H, Myhre S, et al: Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: A study of gene expression in the DBCG82bc cohort. Clin Cancer Res 20:5272-5280, 2014
97. Jegadeesh NK, Kim S, Prabhu RS, et al: The 21-gene recurrence score and locoregional recurrence in breast cancer patients. Ann Surg Oncol 22:1088-1094, 2015
98. Speers C, Zhao S, Liu M, et al: Development and validation of a novel radiosensitivity signature in human breast cancer. Clin Cancer Res 21:3667-3677, 2015
99. Azria D, Lapierre A, Gourgou S, et al: Data-based radiation oncology: Design of clinical trials in the toxicity biomarkers era. *Front Oncol* 7
100. Barnett GC, Coles CE, Elliott RM, et al: Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: A prospective analysis study. Lancet Oncol 13:65-77, 2012
101. Andreassen CN, Rosenstein BS, Kerns SL, et al: Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. Radiother Oncol 121:431-439, 2016
102. Rosenstein BS. Radiogenomics: Identification of genomic predictors for radiation toxicity. Semin Radiat Oncol 27:300-309, 2017
103. Kepka L, Maciejewski B, Withers RH. Does incidental irradiation with doses below 50 gy effectively reduce isolated nodal failures in non-small-cell lung cancer: Dose-response relationship. Int J Radiat Oncol Biol Phys 73:1391-1396, 2009
104. De Ruysscher D, Wanders S, van Haren E, et al: Selective mediastinal node irradiation based on FDG-PET scan data in patients with non-small-cell lung cancer: A prospective clinical study. Int J Radiat Oncol Biol Phys 62:988-994, 2005
105. Senan S, Burgers S, Samson MJ, et al: Can elective nodal irradiation be omitted in stage III non-small-cell lung cancer? Analysis of recurrences in a phase II study of induction chemotherapy and involved-field radiotherapy. Int J Radiat Oncol Biol Phys 54:999-1006, 2002
106. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, et al: The impact of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. Radiother Oncol 55:317-324, 2000
107. De Ruysscher D, Wanders S, Minken A, et al: Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: A planning study. Radiother Oncol 77:5-10, 2005
108. Antonia SJ, Villegas A, Daniel D, et al: Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *N Engl J Med* 377:1919-1929, 2017
109. van Loon J, De Ruysscher D, Wanders R, et al: Selective nodal irradiation on basis of 18FDG-PET scans in limited-disease small-cell lung cancer: A prospective study. *Int J Radiat Oncol Biol Phys* 77:329-336, 2010
110. Turrisi 3rd AT, Kim K, Blum R, et al: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 340:265-271, 1999

111. Oberije C, De Ruysscher D, Houben R, et al: A validated prediction model for overall survival from stage III non-small cell lung cancer: Toward survival prediction for individual patients. *Int J Radiat Oncol Biol Phys* 92:935-944, 2015
112. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 362:2380-2388, 2010
113. Shaw AT, Yeap BY, Solomon BJ, et al: Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: A retrospective analysis. Lancet Oncol 12:1004-1012, 2011
114. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010
115. Garinet S, Laurent-Puig P, Blons H, et al: Current and future molecular testing in NSCLC, what can we expect from new sequencing technologies? J Clin Med 7:pii:E144, 2018
116. Chen DT, Hsu YL, Fulp WJ, et al: Prognostic and predictive value of a malignancy-risk gene signature in early-stage non-small cell lung cancer. J Natl Cancer Inst 103:1859-1870, 2011
117. Tang H, Wang S, Xiao G, et al: Comprehensive evaluation of published gene expression prognostic signatures for biomarker-based lung cancer clinical studies. Ann Oncol 28:733-740, 2017
118. Kong FM, Ten Haken RK, Schipper MJ, et al: High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 63:324-333, 2005
119. Saunders M, Dische S, Barrett A, et al: Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: A randomised multicentre trial. CHART Steering Committee. *Lancet* 350:161-165, 1997
120. Timmerman R, McGarry R, Yiannoutsos C, et al: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 24:4833-4839, 2006
121. Vinogradskiy Y, Tucker SL, Bluett JB, et al: Prescribing radiation dose to lung cancer patients based on personalized toxicity estimates. J Thorac Oncol 7:1676-1682, 2012
122. Tucker SL, Li M, Xu T, et al: Incorporating single-nucleotide polymorphisms into the Lyman model to improve prediction of radiation pneumonitis. Int J Radiat Oncol Biol Phys 85:251-257, 2013
123. Abazeed ME, Adams DJ, Hurov KE, et al: Integrative radiogenomic profiling of squamous cell lung cancer. Cancer Res 73:6289-6298, 2013
124. Jeong Y, Hoang NT, Lovejoy A, et al: Role of KEAP1/NRF2 and TP53 mutations in lung squamous cell carcinoma development and radiation resistance. Cancer Discov 7:86-101, 2017
125. Yu H, Boyle TA, Zhou C, et al: PD-L1 expression in lung cancer. J Thorac Oncol 11:964-975, 2016
126. Rizvi NA, Hellmann MD, Snyder A, et al: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 348:124-128, 2015
127. Campbell AM, Decker RH. Mini-review of conventional and hypofractionated radiation therapy combined with immunotherapy for non-small cell lung cancer. Transl Lung Cancer Res 6:220-229, 2017
128. Aerts HJ, Bussink J, Oyen WJ, et al: Identification of residual metabolic-active areas within NSCLC tumours using a pre-radiotherapy FDG-PET-CT scan: A prospective validation. *Lung Cancer* 75:73-76, 2012
129. Aerts HJ, Grossmann P, Tan Y, et al: Defining a radiomic response phenotype: A pilot study using targeted therapy in NSCLC. Sci Rep 6:33860, 2016
130. van Elmpt W, Ollers M, Dingemans AM, et al: Response assessment using 18F-FDG PET early in the course of radiotherapy correlates with survival in advanced-stage non-small cell lung cancer. J Nucl Med 53:1514-1520, 2012
131. Ghadimi BM, Grade M, Difilippantonio MJ, et al: Effectiveness of gene expression profiling for response prediction of rectal adenocarcinomas to preoperative chemoradiotherapy. J Clin Oncol 23:1826-1838, 2005
132. Lin YH, Friederichs J, Black MA, et al: Multiple gene expression classifiers from different array platforms predict poor prognosis of colorectal cancer. Clin Cancer Res 13(2 Pt 1):498-507, 2007
133. Van Laar RK. An online gene expression assay for determining adjuvant therapy eligibility in patients with stage 2 or 3 colon cancer. Br J Cancer 103:1852-1857, 2010
134. Herskovic A, Martz K, al-Sarraf M, et al: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 326:1593-1598, 1992
135. Tepper J, Krasna MJ, Niedzwiecki D, et al: Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26:1086-1092, 2008
136. Wu AJ, Bosch WR, Chang DT, et al: Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. Int J Radiat Oncol Biol Phys 92:911-920, 2015
137. Ajani JA, D'Amico TA, Almhanna K, et al: Esophageal and esophagogastric junction cancers, version 1.2015. *J Natl Compr Cancer Netw* 13:194-227, 2015
138. Matzinger O, Gerber E, Bernstein Z, et al: EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. Radiother Oncol 92:164-175, 2009
139. van Hagen P, Hulshof MC, van Lanschot JJ, et al: Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 366:2074-2084, 2012
140. He L, Allen PK, Potter A, et al: Re-evaluating the optimal radiation dose for definitive chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Oncol* 9:1398-1405, 2014
141. McLaren PJ, Barnes AP, Terrell WZ, et al: Specific gene expression profiles are associated with a pathologic complete response to neoadjuvant therapy in esophageal adenocarcinoma. Am J Surg 213:915-920, 2017
142. Wadhwa R, Wang X, Baladandayuthapani V, et al: Nuclear expression of Gli-1 is predictive of pathologic complete response to chemoradiation in trimodality treated oesophageal cancer patients. Br J Cancer 117:648-655, 2017
143. Tsou YK, Liang KH, Lin WR, et al: GALNT14 genotype as a response predictor for concurrent chemoradiotherapy in advanced esophageal squamous cell carcinoma. Oncotarget 8:29151-29160, 2017
144. Tepper JE, Gunderson LL. Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Radiat Oncol 12:187-195, 2002
145. Wo JY, Yoon SS, Guimaraes AR, et al: Gastric lymph node contouring atlas: A tool to aid in clinical target volume definition in 3-dimensional treatment planning for gastric cancer. Pract Radiat Oncol 3:e11-e19, 2013
146. Cunningham D, Allum WH, Stenning SP, et al: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 355:11-20, 2006
147. Park SH, Sohn TS, Lee J, et al: Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol 33:3130-3136, 2015
148. Leong T, Smithers BM, Haustermans K, et al: TOPGEAR: A randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: Interim results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol 24:2252-2258, 2017
149. Ajani JA, Winter K, Okawara GS, et al: Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. J Clin Oncol 24:3953-3958, 2006

150. Sauer R, Becker H, Hohenberger W, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731-1740, 2004
151. Appelt AL, Ploen J, Harling H, et al: High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study. Lancet Oncol 16:919-927, 2015
152. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al: Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: Impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 88:822-828, 2014
153. Renehan AG, Malcomson L, Emsley R, et al: Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): A propensity-score matched cohort analysis. Lancet Oncol 17:174-183, 2016
154. Garcia-Aguilar J, Chen Z, Smith DD, et al: Identification of a biomarker profile associated with resistance to neoadjuvant chemoradiation therapy in rectal cancer. Ann Surg 254:486-492, 2011. discussion 492-483
155. Pathak S, Meng WJ, Zhang H, et al: Tafazzin protein expression is associated with tumorigenesis and radiation response in rectal cancer: A study of Swedish clinical trial on preoperative radiotherapy. PLoS One 9:e98317, 2014
156. Qin CJ, Song XM, Chen ZH, et al: XRCC2 as a predictive biomarker for radioresistance in locally advanced rectal cancer patients undergoing preoperative radiotherapy. Oncotarget 6:32193-32204, 2015
157. Smith JJ, Deane NG, Wu F, et al: Experimentally derived metastasis gene expression profile predicts recurrence and death in patients with colon cancer. Gastroenterology 138:958-968, 2010
158. Boysen AK, Wettergren Y, Sorensen BS, et al: Cell-free DNA levels and correlation to stage and outcome following treatment of locally advanced rectal cancer. Tumour Biol 39:1010428317730976
159. Liu F, Dong Q, Huang J. Overexpression of LncRNA PVT1 predicts advanced clinicopathological features and serves as an unfavorable risk factor for survival of patients with gastrointestinal cancers. Cell Physiol Biochem 43:1077-1089, 2017
160. Kachnic LA, Winter K, Myerson RJ, et al: RTOG 0529: A phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 86:27-33, 2013
161. Ajani JA, Wang X, Izzo JG, et al: Molecular biomarkers correlate with disease-free survival in patients with anal canal carcinoma treated with chemoradiation. Dig Dis Sci 55:1098-1105, 2010
162. Osmundson EC, Wu Y, Luxton G, et al: Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. Int J Radiat Oncol Biol Phys 91:986-994, 2015
163. Henderson MA, Burmeister BH, Ainslie J, et al: Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. Lancet Oncol 16:1049-1060, 2015
164. Agrawal S, Kane 3rd JM, Guadagnolo BA, et al: The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. Cancer 115:5836-5844, 2009
165. Coit DG, Thompson JA, Algazi A, et al: Melanoma, version 2.2016, NCCN clinical practice guidelines in oncology. J Nat l Compr Cancer Netw 14:450-473, 2016
166. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al: Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med 375:1845-1855, 2016
167. Eggermont AM, Suciu S, Testori A, et al: Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol 30:3810-3818, 2012
168. Robert C, Schachter J, Long GV, et al: Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 372:2521-2532, 2015
169. Schachter J, Ribas A, Long GV, et al: Pembrolizumab versus ipilimumab for advanced melanoma: Final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet* 390:1853-1862, 2017
170. Weber J, Mandala M, Del Vecchio M, et al: Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 377:1824-1835, 2017
171. Petrella TM, Robert C, Richtig E, et al: Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma. Eur J Cancer 86:115-124, 2017
172. Weber JS, Hodi FS, Wolchok JD, et al: Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. J Clin Oncol 35:785-792, 2017
173. Jochems C, Schlom J. Tumor-infiltrating immune cells and prognosis: The potential link between conventional cancer therapy and immunity. Exp Biol Med 236:567-579, 2011
174. Messina JL, Fenstermacher DA, Eschrich S, et al: 12-Chemokine gene signature identifies lymph node-like structures in melanoma: Potential for patient selection for immunotherapy? Sci Rep 2:765, 2012
175. Strom T, Torres-Roca JF, Parekh A, et al: Regional radiation therapy impacts outcome for node-positive cutaneous melanoma. J Natl Compr Cancer Netw 15:473-482, 2017
176. Eschrich S, Zhang H, Zhao H, et al: Systems biology modeling of the radiation sensitivity network: A biomarker discovery platform. Int J Radiat Oncol Biol Phys 75:497-505, 2009
177. Torres-Roca JF, Eschrich S, Zhao H, et al: Prediction of radiation sensitivity using a gene expression classifier. Cancer Res 65:7169-7176, 2005
178. Caudell JJ, Eschrich S, Torres-Roca JF. Radiosensitivity molecular signature is predictive of overall survival in glioblastoma. Int J Radiat Oncol Biol Phys 90:S281, 2014
179. Shridhar R., Hoffe S.E., Coppola D., et al.: Radiosensitivity index shows promise for predicting outcomes with adjuvant radiation in resectable pancreatic cancer patients. Int J Radiat Oncol Biol Phys. 90: S174.
180. Torres-Roca JF, Vergara I, Davicioni E, et al: A molecular signature of radiosensitivity (RSI) is an RT-specific biomarker in prostate cancer. Int J Radiat Oncol Biol Phys 90:S157, 2014
181. Torres-Roca JF, Caudell JJ, Servant N, et al: Integration of a radiosensitivity molecular signature into the assessment of local recurrence risk in breast cancer. Int J Radiat Oncol Biol Phys 93:631-638, 2015
182. Ahmed KA, Chinnaiyan P, Fulp WJ, et al: The radiosensitivity index predicts for overall survival in glioblastoma. Oncotarget 6:34414-34422, 2015
183. Ahmed KA, Fulp WJ, Berglund AE, et al: Differences between colon cancer primaries and metastases using a molecular assay for tumor radiation sensitivity suggest implications for potential oligometastatic SBRT patient selection. Int J Radiat Oncol Biol Phys 92:837-842, 2015
184. Ahmed KA, Caudell JJ, El-Haddad G, et al: Radiosensitivity differences between liver metastases based on primary histology suggest implications for clinical outcomes after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 95:1399-1404, 2016
185. Eschrich SA, Pramana J, Zhang H, et al: A gene expression model of intrinsic tumor radiosensitivity: Prediction of response and prognosis after chemoradiation. Int J Radiat Oncol Biol Phys 75:489-496, 2009
186. Eschrich SA, Fulp WJ, Pawitan Y, et al: Validation of a radiosensitivity molecular signature in breast cancer. Clin Cancer Res 18:5134-5143, 2012
187. Pramana J, Van den Brekel MW, van Velthuysen ML, et al: Gene expression profiling to predict outcome after chemoradiation in head and neck cancer. Int J Radiat Oncol Biol Phys 69:1544-1552, 2007
188. Creelan B, Eschrich S, Fulp W, et al: A Gene expression platform to predict benefit from adjuvant external beam radiation in resected non-small cell lung cancer. Int J Rad Oncol Biol Phys 90:S76-S77, 2014
189. Strom T, Hoffe SE, Fulp W, et al: Radiosensitivity index predicts for survival with adjuvant radiation in resectable pancreatic cancer. Radiother Oncol 117:159-164, 2015

190. Torres-Roca JF, Fulp WJ, Caudell JJ, et al: Integration of a radiosensitivity molecular signature into the assessment of local recurrence risk in breast cancer. Int J Rad Oncol Biol Phys 93:631-638, 2015
191. Anker CJ, Wo JY. Personalized medicine in radiation oncology—A work in progress. Int J Radiat Oncol Biol Phys 92:843-845, 2015
192. Mirjolet C, Boidot R, Saliques S, et al: The role of telomeres in predicting individual radiosensitivity of patients with cancer in the era of personalized radiotherapy. Cancer Treat Rev 41:354-360, 2015
193. Aloia TA, Vauthey JN, Loyer EM, et al: Solitary colorectal liver metastasis: Resection determines outcome. Arch Surg 141:460-466, 2006. discussion 466-467