Cancer Radiation Therapy Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

Key words: cancer; life; research; literature; cell

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Ahn, S. J., et al. (2012). "Quantitative assessment of tumor responses after radiation therapy in a DLD-1 colon cancer mouse model using serial dynamic contrast-enhanced magnetic resonance imaging." Yonsei Med J **53**(6): 1147-1153.

PURPOSE: The purpose of this study was to investigate the predictability of pretreatment values including Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) derived parameters (K (trans), K (ep) and V (e)), early changes in parameters (K (trans), tumor volume), and heterogeneity (standard deviation of K (trans)) for radiation therapy responses via a human colorectal cancer xenograft model. MATERIALS AND METHODS: A human colorectal cancer xenograft model with DLD-1 cancer cells was produced in the right hind limbs of five mice. Tumors were irradiated with 3 fractions of 3 Gy each for 3 weeks. Baseline and follow up DCE-MRI were performed. Quantitative parameters (K (trans), K (ep) and V (e)) were calculated based on the Tofts model. Early changes in K (trans), standard deviation (SD) of K (trans), and tumor volume were also calculated. Tumor responses were evaluated based on histology. With a cut-off value of 0.4 for necrotic factor, a comparison between good and poor responses was conducted. RESULTS: The good response group (mice #1 and 2) exhibited higher pretreatment K (trans) than the poor response group (mice #3, 4, and 5). The good response group tended to show lower pretreatment K (ep), higher pretreatment V (e), and larger baseline tumor volume than the poor response group. All the mice in the good response group demonstrated marked reductions in K (trans) and SD value after the first radiation. All tumors showed increased volume after the first radiation therapy. CONCLUSION: The good response after radiation therapy group in the DLD-1 colon cancer xenograft nude mouse model exhibited a higher pretreatment K (trans) and showed an early reduction in K (trans), demonstrating a more homogenous distribution.

Albuquerque, K., et al. (2016). "Long-term Benefit of Tumor Volume-Directed Involved Field Radiation Therapy in the Management of Recurrent Ovarian Cancer." Int J Gynecol Cancer **26**(4): 655-660.

OBJECTIVES: This study aimed to report on long-term effectiveness of involved field radiation therapy (IFRT) in the salvage of localized recurrent ovarian cancer (ROC). METHODS: A retrospective analysis of 27 patients with a diagnosis of epithelial ovarian cancer who received tumor volume-directed IFRT for localized extraperitoneal recurrences (either as consolidation after cytoreductive surgery (CRS) or as attempted salvage if unresectable) forms the basis of this report. All patients were heavily pretreated with multiple chemotherapy regimens. Involved field radiation therapy was primarily with external beam (median dose, 50.4 Gy). Local recurrence-free survival (LRFS) was defined as freedom from in-field recurrences and was considered as a measure of effectiveness of radiotherapy. Statistical analyses

evaluated association between disease-free survival, overall survival, LRFS, and various prognostic factors. Comparison was also made with a similar but unmatched cohort with localized recurrences salvaged by additional chemotherapy instead of local therapies (NIFRT group). RESULTS: Of 27 patients, 17 had optimal CRS before RT. The actuarial survival at 5 and 10 years (in parenthesis) from date of radiation were LRFS (70% and 60%), overall survival (30% and 19%), and disease-free survival (33% and 20%). None of the NIFRT patients survived beyond 5 years from initiation of salvage chemotherapy. CONCLUSIONS: Long-term follow-up in this selected series confirmed the benefit of IFRT (+/-CRS) in localized ROC. Chemotherapy salvage in a similar NIFRT group was not equivalent, suggesting a role for locoregional therapies in selected patients with ROC.

Albuquerque, K. V., et al. (2005). "Impact of tumor volume-directed involved field radiation therapy integrated in the management of recurrent ovarian cancer." Gynecol Oncol **96**(3): 701-704.
OBJECTIVES: Assess the role of involved field radiation therapy (IFRT) in recurrent ovarian cancer. METHODS: Thirty-five patients with a diagnosis of epithelial ovarian cancer received radiation therapy at LUMC between 1991 and 2001. Of these, 20 received tumor volume-directed IFRT for localized extraperitoneal recurrences (either as consolidation following debulking surgery or as attempted salvage if unresectable) and form the basis of this report. All patients were heavily pretreated with multiple chemotherapy regimens. Eleven patients had optimal debulking of their recurrences prior to radiation. IFRT was primarily with external beam (median dose 50.4 Gy). Appropriate statistical analyses evaluated association among disease-free (DFS), overall survival (OS), local recurrence-free (LRFS), and various prognostic factors. LRFS was defined as freedom from in-field recurrences and was considered as a measure of effectiveness of radiotherapy. RESULTS: Of 20 patients, 17 had a complete response after RT. The actuarial LRFS, OS, and DFS at 5 years from date of radiation were 66%, 34%, and 34%, respectively. The LRFS at 3 years was 89% for those with optimal resection vs. 42% for those with gross residual/unresectable tumor, which was significantly better (P = 0.04). The corresponding 3-year DFS was 72% vs. 22% and 5-year OS was 50% vs. 19%, respectively. Acute complication of RT was mild, half had Grade 1-2 gastrointestinal (GI) toxicity, three patients had Grade 3-4 late GI effects. CONCLUSION: IFRT is effective in controlling localized recurrences of ovarian cancer, especially after they are optimally debulked (89% local control and 50% 5-year overall

survival in this subgroup), and is relatively well tolerated in these heavily pretreated patients.

Allibhai, Z., et al. (2013). "The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer." Int J Radiat Oncol Biol Phys **87**(5): 1064-1070.
PURPOSE: Stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer (NSCLC) offers excellent control rates. Most published series deal mainly with small (usually <4 cm), peripheral, solitary tumors. Larger tumors are associated with poorer outcomes (ie, lower control rates, higher toxicity) when treated with conventional RT. It is unclear whether SBRT is sufficiently potent to control these larger tumors. We therefore evaluated and examined the influence of tumor size on treatment outcomes after SBRT. METHODS AND MATERIALS: Between October 2004 and October 2010, 185 medically inoperable patients with early (T1-T2N0M0) NSCLC were treated on a prospective research ethics board-approved single-institution protocol. Prescription doses were risk-adapted based on tumor size and location. Follow-up included prospective assessment of toxicity (as per Common Terminology Criteria for Adverse Events, version 3.0) and serial computed tomography scans. Patterns of failure, toxicity, and survival outcomes were calculated using Kaplan-Meier method, and the significance of tumor size (diameter, volume) with respect to patient, treatment, and tumor factors was tested. RESULTS: Median follow-up was 15.2 months. Tumor size was not associated with local failure but was associated with regional failure (P=.011) and distant failure (P=.021). Poorer overall survival (P=.001), disease-free survival (P=.001), and cause-specific survival (P=.005) were also significantly associated with tumor size (with tumor volume more significant than diameter). Gross tumor volume and planning target volume were significantly associated with grade 2 or worse radiation pneumonitis. However, overall rates of grade >/=3 pneumonitis were low and not significantly affected by tumor or target size. CONCLUSIONS: Currently employed stereotactic body radiation therapy dose regimens can provide safe effective local therapy even for larger solitary NSCLC tumors (up to 5.7 cm in tumor diameter or 100 cm (3) in tumor volume) but are associated with more nonlocal failures as well as poorer survival. These observations suggest these patients may benefit from more extensive staging or consideration of adjuvant therapy.

Ardenfors, O., et al. (2018). "Out-of-field doses from secondary radiation produced in proton therapy

and the associated risk of radiation-induced cancer from a brain tumor treatment." Phys Med **53**: 129-136.

PURPOSE: To determine out-of-field doses produced in proton pencil beam scanning (PBS) therapy using Monte Carlo simulations and to estimate the associated risk of radiation-induced second cancer from a brain tumor treatment. METHODS: Simulations of out-of-field absorbed doses were performed with MCNP6 and benchmarked against measurements with tissue-equivalent proportional counters (TEPC) for three irradiation setups: two irradiations of a water phantom using proton energies of 78-147MeV and 177-223MeV, and one brain tumor irradiation of a whole-body phantom. Out-of-field absorbed and equivalent doses to organs in a whole-body phantom following a brain tumor treatment were subsequently simulated and used to estimate the risk of radiation-induced cancer. Additionally, the contribution of absorbed dose originating from radiation produced in the nozzle was calculated from simulations. RESULTS: Out-of-field absorbed doses to the TEPC ranged from 0.4 to 135microGy/Gy. The average deviation between simulations and measurements of the water phantom irradiations was about 17%. The absorbed dose contribution from radiation produced in the nozzle ranged between 0 and 70% of the total dose; the contribution was however small in absolute terms. The absorbed and equivalent doses to the organs ranged between 0.2 and 60microGy/Gy and 0.5-151microSv/Gy. The estimated lifetime risk of radiation-induced second cancer was approximately 0.01%. CONCLUSIONS: The agreement of out-of-field absorbed doses between measurements and simulations was good given the sources of uncertainties. Calculations of out-of-field organ doses following a brain tumor treatment indicated that proton PBS therapy of brain tumors is associated with a low risk of radiation-induced cancer.

Atsumi, K., et al. (2010). "Predictive factors of esophageal stenosis associated with tumor regression in radiation therapy for locally advanced esophageal cancer." J Radiat Res **51**(1): 9-14.

The purpose of this retrospective study was to clarify the predictive factors correlated with esophageal stenosis within three months after radiation therapy for locally advanced esophageal cancer. We enrolled 47 patients with advanced esophageal cancer with T2-4 and stage II-III who were treated with definitive radiation therapy and achieving complete response of primary lesion at Kyushu University Hospital between January 1998 and December 2005. Esophagography was performed for all patients before treatment and within three months after completion of the radiation therapy, the esophageal stenotic ratio was evaluated. The stenotic ratio was used to define four levels of stenosis: stenosis level 1, stenotic ratio of 0-25%; 2, 25-50%; 3,50-75%; 4,75-100%. We then estimated the correlation between the esophageal stenosis level after radiation therapy and each of numerous factors. The numbers and total percentages of patients at each stenosis level were as follows: level 1: n = 14 (30%); level 2: 8 (17%); level 3: 14 (30%); and level 4: 11 (23%). Esophageal stenosis in the case of full circumference involvement tended to be more severe and more frequent. Increases in wall thickness tended to be associated with increases in esophageal stenosis severity and frequency. The extent of involved circumference and wall thickness of tumor region were significantly correlated with esophageal stenosis associated with tumor regression in radiation therapy ($p = 0.0006$, $p = 0.005$). For predicting the possibility of esophageal stenosis with tumor regression within three months in radiation therapy, the extent of involved circumference and esophageal wall thickness of the tumor region may be useful.

Azria, D., et al. (2003). "Enhancement of radiation therapy by tumor necrosis factor alpha in human colon cancer using a bispecific antibody." Int J Radiat Oncol Biol Phys **55**(5): 1363-1373.

PURPOSE: To overcome the systemic side effects of tumor necrosis factor alpha (TNFalpha) injected i.v., we used a bispecific antibody (BAb) directed against carcinoembryonic antigen (CEA) and TNFalpha to target this cytokine in human CEA-expressing colorectal carcinoma treated simultaneously with radiation therapy (RT). METHODS, MATERIALS AND RESULTS: LS174T cell line was used to study the interaction of TNFalpha and radiation on clonogenic cytotoxicity. When TNFalpha (2500 U/mL) was added 12 h before RT, the surviving fraction at 2 Gy was 54% lower than that obtained with irradiation alone (0.23 vs. 0.42, respectively, $p = 0.001$). At 20%, 50%, or 70% survival, data points were within the envelope of additivity. Concerning in vivo experiments, RT as a single agent slowed tumor progression as compared with the control group ($p = 0.027$), whereas TNFalpha, BAb, or BAb + TNFalpha had no effect. BAb + TNFalpha + RT combination enhanced the delay for the tumor to reach 2000 mm (3) as compared with RT alone ($p = 0.033$, for BAb + TNFalpha + RT group vs. RT group). CONCLUSION: These results suggest that TNFalpha in combination with BAb and RT may be beneficial for the treatment of locally advanced colorectal cancer.

Balderson, M., et al. (2016). "Under conditions of large geometric miss, tumor control probability can be higher for static gantry intensity-modulated radiation

therapy compared to volume-modulated arc therapy for prostate cancer." Med Dosim **41**(2): 180-185.

The purpose of this work was to compare static gantry intensity-modulated radiation therapy (IMRT) with volume-modulated arc therapy (VMAT) in terms of tumor control probability (TCP) under scenarios involving large geometric misses, i.e., those beyond what are accounted for when margin expansion is determined. Using a planning approach typical for these treatments, a linear-quadratic-based model for TCP was used to compare mean TCP values for a population of patients who experiences a geometric miss (i.e., systematic and random shifts of the clinical target volume within the planning target dose distribution). A Monte Carlo approach was used to account for the different biological sensitivities of a population of patients. Interestingly, for errors consisting of coplanar systematic target volume offsets and three-dimensional random offsets, static gantry IMRT appears to offer an advantage over VMAT in that larger shift errors are tolerated for the same mean TCP. For example, under the conditions simulated, erroneous systematic shifts of 15mm directly between or directly into static gantry IMRT fields result in mean TCP values between 96% and 98%, whereas the same errors on VMAT plans result in mean TCP values between 45% and 74%. Random geometric shifts of the target volume were characterized using normal distributions in each Cartesian dimension. When the standard deviations were doubled from those values assumed in the derivation of the treatment margins, our model showed a 7% drop in mean TCP for the static gantry IMRT plans but a 20% drop in TCP for the VMAT plans. Although adding a margin for error to a clinical target volume is perhaps the best approach to account for expected geometric misses, this work suggests that static gantry IMRT may offer a treatment that is more tolerant to geometric miss errors than VMAT.

Bando, R., et al. (2013). "Changes of tumor and normal structures of the neck during radiation therapy for head and neck cancer requires adaptive strategy." J Med Invest **60**(1-2): 46-51.

The treatment period over which radiation therapy is administered extends over several weeks. Since tumor shrinkage in response to radiation therapy and weight loss due to radiation-induced mucositis may impact on the dose distribution in both target and organ at risk in patients with head and neck cancer, the anatomical changes of tumor and neck volumes during this period should be taken into consideration. We investigated the anatomical changes that occurred in the target and normal structure of the neck during radiation therapy for pharyngeal cancer, and evaluated the necessity of an adaptive strategy. Ten patients with pharyngeal cancer who underwent radical chemoradiation therapy using 3-dimensional conformal radiation therapy RT (66-70 Gy in 33-35 fractions) between April 2009 and September 2010 were enrolled in the study. Patients underwent CT scans every week during their course of treatment. We analyzed the CT data in the radiation treatment planning system and measured changes of tumor, organ at risk, and neck volume. Gross tumor volume (GTV) was rapidly reduced by 28% of the original volume on average in the first 3 weeks. The right and left submandibular glands volume decreased to 70% and 63% of their initial volumes on average, respectively. The volume of the neck in the radiation fields decreased to 89% of its initial volume on average by the sixth week mainly caused by body weight loss due to acute radiation morbidity. Considerable anatomical change in the radiation filed that will affect dose distribution of the target and organ at risk was observed during radiation therapy for head and neck cancer.

Basaki, K., et al. (2006). "Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume." Int J Radiat Oncol Biol Phys **64**(2): 449-454.

PURPOSE: To investigate the impact of tumor volume on overall survival in patients with Stage III non-small-cell lung cancer (NSCLC) treated with definitive radiation therapy (RT). METHODS AND MATERIALS: Between May 1997 and February 2003, 71 patients with Stage III NSCLC were treated with radiation therapy of 60 Gy or more. The total target dose was between 60 and 77 Gy (average, 66.3 Gy). Chemotherapy was used in 45 cases. The primary tumor and nodal volume were identified in pretreatment computed tomography scans. Univariate and multivariate analyses were used to evaluate the impact of tumor volume on survival after RT. RESULTS: The overall 2-year survival rate was 23%, with a median survival time of 14 months. The median survival times were 10 months and 19 months with large primary tumor volume more than median volume and smaller primary tumor volume, respectively. At a univariate analysis, the total tumor volume (TTV) (p<0.0003) and the primary tumor volume (p<0.00008) were significant and the nodal volume was not. At multivariate analyses, both the TTV and the primary tumor volume were significant prognostic factors. CONCLUSION: The primary tumor volume as well as TTV is a significant prognostic factor on survival in patients with Stage III NSCLC treated with RT and should be recorded in clinical results when the survivals are compared among clinical studies.

Bassalyk, L. S., et al. (1986). "[Effect of radiation and drug therapy on the hormonal status of patients with breast cancer, taking into consideration the receptor level of the tumor]." Med Radiol (Mosk) **31**(4): 48-52.

A study was made of the content of the steroid and peptide hormones in the blood of 115 patients with Stage III a,b,c breast cancer (54 patients at the reproductive age and 61 in the menopause) before treatment and during radio- and chemotherapy. A group of healthy women (28 with preserved menstruation and 20 in the menopause) was taken as controls. Data on the concentration of the steroid hormones in the patients' blood were compared with the presence of the respective receptors in tumor. Before treatment a significant rise of the estradiol concentration was noted in the blood of the menopause patients, that of prolactin both in the menopause patients and in the patients with preserved menstruation. A raised testosterone concentration was also noted in the patients with preserved menstruation. After radiotherapy the blood prolactin level, particularly in the patients with preserved menstruation, increased more than 2-fold. There was no correlation between the levels of the steroid and peptide hormones during therapy and its efficacy. The prolactin level can be used as a criterion of the efficacy of antitumor therapy, its stable rise in operated patients during therapy being an unfavorable prognostic sign.

Belfatto, A., et al. (2016). "Kinetic Models for Predicting Cervical Cancer Response to Radiation Therapy on Individual Basis Using Tumor Regression Measured In Vivo With Volumetric Imaging." Technol Cancer Res Treat **15**(1): 146-158.

This article describes a macroscopic mathematical modeling approach to capture the interplay between solid tumor evolution and cell damage during radiotherapy. Volume regression profiles of 15 patients with uterine cervical cancer were reconstructed from serial cone-beam computed tomography data sets, acquired for image-guided radiotherapy, and used for model parameter learning by means of a genetic-based optimization. Patients, diagnosed with either squamous cell carcinoma or adenocarcinoma, underwent different treatment modalities (image-guided radiotherapy and image-guided chemo-radiotherapy). The mean volume at the beginning of radiotherapy and the end of radiotherapy was on average 23.7 cm (3) (range: 12.7-44.4 cm (3)) and 8.6 cm (3) (range: 3.6-17.1 cm (3)), respectively. Two different tumor dynamics were taken into account in the model: the viable (active) and the necrotic cancer cells. However, according to the results of a preliminary volume regression analysis, we assumed a short dead cell resolving time and the model was simplified to the active tumor volume. Model learning was performed both on the complete patient cohort (cohort-based model learning) and on each single patient (patient-specific model learning). The fitting results (mean error: approximately 16% and approximately 6% for the cohort-based model and patient-specific model, respectively) highlighted the model ability to quantitatively reproduce tumor regression. Volume prediction errors of about 18% on average were obtained using cohort-based model computed on all but 1 patient at a time (leave-one-out technique). Finally, a sensitivity analysis was performed and the data uncertainty effects evaluated by simulating an average volume perturbation of about 1.5 cm (3) obtaining an error increase within 0.2%. In conclusion, we showed that simple time-continuous models can represent tumor regression curves both on a patient cohort and patient-specific basis; this discloses the opportunity in the future to exploit such models to predict how changes in the treatment schedule (number of fractions, doses, intervals among fractions) might affect the tumor regression on an individual basis.

Bernal-Estevez, D., et al. (2016). "Chemotherapy and radiation therapy elicits tumor specific T cell responses in a breast cancer patient." BMC Cancer **16**: 591.

BACKGROUND: Experimental evidence and clinical studies in breast cancer suggest that some anti-tumor therapy regimens generate stimulation of the immune system that accounts for tumor clinical responses, however, demonstration of the immunostimulatory power of these therapies on cancer patients continues to be a formidable challenge. Here we present experimental evidence from a breast cancer patient with complete clinical response after 7 years, associated with responsiveness of tumor specific T cells. METHODS: T cells were obtained before and after anti-tumor therapy from peripheral blood of a 63-years old woman diagnosed with ductal breast cancer (HER2/neu+++, ER-, PR-, HLA-A*02:01) treated with surgery, followed by paclitaxel, trastuzumab (suspended due to cardiac toxicity), and radiotherapy. We obtained a leukapheresis before surgery and after 8 months of treatment. Using in vitro cell cultures stimulated with autologous monocyte-derived dendritic cells (DCs) that produce high levels of IL-12, we characterize by flow cytometry the phenotype of tumor associated antigens (TAAs) HER2/neu and NY-ESO 1 specific T cells. The ex vivo analysis of the TCR-Vbeta repertoire of TAA specific T cells in blood and Tumor Infiltrating Lymphocytes (TILs) were performed in order to correlate both repertoires prior and after therapy. RESULTS: We evidence a

functional recovery of T cell responsiveness to polyclonal stimuli and expansion of TAAs specific CD8+ T cells using peptide pulsed DCs, with an increase of CTLA-4 and memory effector phenotype after anti-tumor therapy. The ex vivo analysis of the TCR-Vbeta repertoire of TAA specific T cells in blood and TILs showed that whereas the TCR-Vbeta04-02 clonotype is highly expressed in TILs the HER2/neu specific T cells are expressed mainly in blood after therapy, suggesting that this particular TCR was selectively enriched in blood after anti-tumor therapy. CONCLUSIONS: Our results show the benefits of anti-tumor therapy in a breast cancer patient with clinical complete response in two ways, by restoring the responsiveness of T cells by increasing the frequency and activation in peripheral blood of tumor specific T cells present in the tumor before therapy.

Bibault, J. E., et al. (2012). "Image-guided robotic stereotactic radiation therapy with fiducial-free tumor tracking for lung cancer." Radiat Oncol 7: 102.
PURPOSE: Stereotactic body radiation therapy (SBRT) for early-stage lung cancer can be achieved with several methods: respiratory gating, body frame, or real-time target and motion tracking. Two target tracking methods are currently available with the CyberKnife (R) System: the first one, fiducial tracking, requires the use of radio-opaque markers implanted near or inside the tumor, while the other, Xsight (R) Lung Tracking System, (XLTS) is fiducial-free. With XLTS, targeting is synchronized directly with target motion, which occurs due to respiration. While the former method (fiducial tracking) is well documented, the clinical relevance of the latter (tracking without fiducials) has never been well described to this date. PATIENTS AND METHODS: A study was performed at our department for each patient treated for lung cancer with CyberKnife using XLTS. Selection criteria were: primary or recurring T1 or T2 stage non-small-cell lung cancer (NSCLC) with 15-60 mm tumor size. Initial staging included CT-Scan and FDG-PET. RESULTS: Fifty-one patients not amenable to surgery were treated with XLTS. Median follow-up was 15 months (range, 5-30 months). Median tumor size was 24 mm (range, 15-60 mm). Median total dose was 60 Gy (36-60 Gy) in three fractions. Actuarial overall survival was 85.5% (95% CI = 74.5-96%) at 1 year and 79.4% (95% CI = 64-94.8%) at 2 years. Actuarial local control rate was 92% (95% CI = 84-99%) at one 1 year and 86% (95% CI = 75-97%) at 2 years. CONCLUSION: Local control and overall survival rates were similar to previous reports that used fiducials for tumor tracking. Toxicity was lower than most studies since tumor tracking did not require fiducial implantion. This fiducial-free method for respiratory motion tracking is a valid option for the most fragile patients.

Blanchard, P., et al. (2017). "Radiation therapy to the primary in metastatic prostate cancer: palliation only or altering tumor biology?" Curr Opin Urol 27(6): 580-586.
PURPOSE OF REVIEW: Despite improvement in systemic treatment, the prognosis of men with de novo metastatic prostate cancer remains poor. Treating the local disease may not only reduce the occurrence of local urologic symptoms, but also slow the metastatic process, either by reducing the seeding from the primary tumor or by altering the microenvironment and thus minimizing the formation of new metastatic sites. RECENT FINDINGS: Retrospective and population-based studies have suggested that the addition of local treatment to systemic therapy may improve survival in this patient group. The aim of this review is to discuss the biologic rationale of such an approach, present and discuss the current available evidence, with a focus on radiation-based treatments. It is key to also address the issue of patient selection as not all patients with metastatic prostate cancer will benefit from the treatment of the primary tumor. SUMMARY: Retrospective and population-based research suggests a survival benefit of prostatectomy or radiotherapy in metastatic prostate cancer patients. Clinical trials evaluating the role of prostate radiotherapy in the metastatic setting are ongoing.

Bowen, S. R., et al. (2018). "Tumor radiomic heterogeneity: Multiparametric functional imaging to characterize variability and predict response following cervical cancer radiation therapy." J Magn Reson Imaging 47(5): 1388-1396.
BACKGROUND: Robust approaches to quantify tumor heterogeneity are needed to provide early decision support for precise individualized therapy. PURPOSE: To conduct a technical exploration of longitudinal changes in tumor heterogeneity patterns on dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI) and FDG positron emission tomography / computed tomography (PET/CT), and their association to radiation therapy (RT) response in cervical cancer. STUDY TYPE: Prospective observational study with longitudinal MRI and PET/CT pre-RT, early-RT (2 weeks), and mid-RT (5 weeks). POPULATION: Twenty-one FIGO IB2 -IVA cervical cancer patients receiving definitive external beam RT and brachytherapy. FIELD STRENGTH/SEQUENCE: 1.5T, precontrast axial T1 -weighted, axial and sagittal T2 -weighted, sagittal DWI (multi-b values), sagittal DCE MRI (<10 sec temporal resolution), postcontrast axial T1 -weighted. ASSESSMENT: Response

assessment 1 month after completion of treatment by a board-certified radiation oncologist from manually delineated tumor volume changes. STATISTICAL TESTS: Intensity histogram (IH) quantiles (DCE SI10% and DWI ADC10%, FDG-PET SUVmax) and distribution moments (mean, variance, skewness, kurtosis) were extracted. Differences in IH features between timepoints and modalities were evaluated by Skillings-Mack tests with Holm's correction. Area under receiver-operating characteristic curve (AUC) and Mann-Whitney testing was performed to discriminate treatment response using IH features. RESULTS: Tumor IH means and quantiles varied significantly during RT (SUVmean: downward arrow28-47%, SUVmax: downward arrow30-59%, SImean: upward arrow8-30%, SI10%: upward arrow8-19%, ADCmean: upward arrow16%, P < 0.02 for each). Among IH heterogeneity features, FDG-PET SUVCoV (downward arrow16-30%, P = 0.011) and DW-MRI ADCskewness decreased (P = 0.001). FDG-PET SUVCoV was higher than DCE-MRI SICoV and DW-MRI ADCCoV at baseline (P < 0.001) and 2 weeks (P = 0.010). FDG-PET SUVkurtosis was lower than DCE-MRI SIkurtosis and DW-MRI ADCkurtosis at baseline (P = 0.001). Some IH features appeared to associate with favorable tumor response, including large early RT changes in DW-MRI ADCskewness (AUC = 0.86). DATA CONCLUSION: Preliminary findings show tumor heterogeneity was variable between patients, modalities, and timepoints. Radiomic assessment of changing tumor heterogeneity has the potential to personalize treatment and power outcome prediction. LEVEL OF EVIDENCE: 2 Technical Efficacy: Stage 3 J. Magn. Reson. Imaging 2018;47:1388-1396.

Bradley, J., et al. (2012). "A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515." Int J Radiat Oncol Biol Phys **82**(1): 435-441 e431.
BACKGROUND: Radiation Therapy Oncology Group (RTOG) 0515 is a Phase II prospective trial designed to quantify the impact of positron emission tomography (PET)/computed tomography (CT) compared with CT alone on radiation treatment plans (RTPs) and to determine the rate of elective nodal failure for PET/CT-derived volumes. METHODS: Each enrolled patient underwent definitive radiation therapy for non-small-cell lung cancer (>/= 60 Gy) and had two RTP datasets generated: gross tumor volume (GTV) derived with CT alone and with PET/CT. Patients received treatment using the PET/CT-derived plan. The primary end point, the impact of PET/CT fusion on treatment plans was measured by differences of the following variables for each patient: GTV, number of involved nodes, nodal station, mean lung dose (MLD), volume of lung exceeding 20 Gy (V20), and mean esophageal dose (MED). Regional failure rate was a secondary end point. The nonparametric Wilcoxon matched-pairs signed-ranks test was used with Bonferroni adjustment for an overall significance level of 0.05. RESULTS: RTOG 0515 accrued 52 patients, 47 of whom are evaluable. The follow-up time for all patients is 12.9 months (2.7-22.2). Tumor staging was as follows: II = 6%; IIIA = 40%; and IIIB = 54%. The GTV was statistically significantly smaller for PET/CT-derived volumes (98.7 vs. 86.2 mL; p < 0.0001). MLDs for PET/CT plans were slightly lower (19 vs. 17.8 Gy; p = 0.06). There was no significant difference in the number of involved nodes (2.1 vs. 2.4), V20 (32% vs. 30.8%), or MED (28.7 vs. 27.1 Gy). Nodal contours were altered by PET/CT for 51% of patients. One patient (2%) has developed an elective nodal failure. CONCLUSIONS: PET/CT-derived tumor volumes were smaller than those derived by CT alone. PET/CT changed nodal GTV contours in 51% of patients. The elective nodal failure rate for GTVs derived by PET/CT is quite low, supporting the RTOG standard of limiting the target volume to the primary tumor and involved nodes.

Braun, D. P., et al. (2013). "Effect of naturopathic and nutritional supplement treatment on tumor response, control, and recurrence in patients with prostate cancer treated with radiation therapy." J Altern Complement Med **19**(3): 198-203.
OBJECTIVES: Use of naturopathic and nutritional supplements (NNS) with antioxidant activity is controversial in patients receiving radiation therapy. The effects of concomitant use of NNS with antioxidant activity during radiation therapy for prostate cancer were investigated in terms of clinical tumor responsiveness, kinetics, and durability. MATERIALS AND METHODS: A retrospective investigation was done of 134 patients treated with curative intent for limited-stage prostate cancer by radiation therapy. Patients self-selected to receive NNS as part of their treatment and maintenance during an extended post-treatment interval of at least 2 years. The outcome measures were the following: prostate-specific antigen (PSA) nadir; >/=24 months post-treatment PSA; time to reach nadir; and time to last follow-up were compared across +NNS and -NNS. RESULTS: Sixty-nine (69) patients elected to receive NNS while 65 did not. Seventy-seven (77) (+NNS 39, -NNS 38) patients received hormone therapy while 57 (+NNS 30, -NNS 27) did not. In the nonhormone cohort, median pretreatment PSA, nadir, post-treatment PSA, time to reach nadir, and time to follow-up were 5.5 ng/mL, 0.56 ng/mL, 0.61 ng/mL, 25

months, and 39.7 months for the -NNS group and 5.1 ng/mL, 0.32 ng/mL, 0.44 ng/mL, 27 months, and 50.1 months for the +NNS group, respectively (p>0.05 for all). Similarly, no significant differences were observed between +NNS and -NNS in the hormone-receiving cohort. CONCLUSIONS: The clinical tumor response to radiation therapy in patients with limited-stage prostate cancer is not inhibited by concomitant NNS based on the magnitude of the PSA response, the velocity of the PSA nadir, and the duration of PSA normalization.

Buglione, M., et al. (2017). "Subgroup Analysis According to Human Papillomavirus Status and Tumor Site of a Randomized Phase II Trial Comparing Cetuximab and Cisplatin Combined With Radiation Therapy for Locally Advanced Head and Neck Cancer." Int J Radiat Oncol Biol Phys **97**(3): 462-472.

PURPOSE: We report a subgroup analysis primarily focused on human papillomavirus (HPV)-related oropharyngeal cancer (OPC) from the Cetuximab Plus Radiotherapy Versus Cisplatin Plus Radiotherapy in Locally Advanced Head and Neck Cancer (CTXMAB+RT; ClinicalTrials.gov identifier NCT01216020) trial comparing radiation therapy with concomitant cisplatin (CDDP) versus concomitant cetuximab (CTX) as first-line treatment of locally advanced head and neck cancer. METHODS AND MATERIALS: The data from all the patients in the CTXMAB+RT trial were reviewed and separately analyzed in 3 groups: p16-positive OPC, p16-negative OPC, and all other cancer sites. The endpoints of interest were locoregional control (LC), metastasis-free survival, cancer-specific survival (CSS), and overall survival (OS). Severe and fatal infectious complications were also reanalyzed to more thoroughly investigate the association between CTX treatment and potentially life-threatening reactions. RESULTS: A total of 33 patients had OPC. The HPV status was available for 30 of the 33 patients. Thus, 3 patients treated with CDDP but with unknown HPV status were excluded from the survival analysis. The small number of patients in each group did not allow for significance to be reached for any of the outcomes analyzed. A trend favored the CDDP arm in the p16-positive group for the 2-year LC and OS/CSS rates (100% vs 72.9% and 100% vs 77.8% for CDDP vs CTX). In this group of patients, the hazard ratio for the treatment arm (CTX vs CDDP) was 4.7 (95% confidence interval [CI] 0.5-40.3) for LC, 3.4 (95% CI 0.4-30.5) for OS, and 2.4 for CSS (95% CI 0.2-23.2). A survival benefit favoring the CDDP arm was not evident in the p16-negative OPC group or for patients with cancer located in other sites. Serious or fatal infectious complications occurred only in the CTX arm. CONCLUSIONS: In patients with p16-positive

OPC in the CTXMAB+RT trial, CTX had lower efficacy than CDDP, with possible implications for treatment selection in this clinical setting.

But-Hadzic, J., et al. (2016). "Acute Toxicity and Tumor Response in Locally Advanced Rectal Cancer After Preoperative Chemoradiation Therapy With Shortening of the Overall Treatment Time Using Intensity-Modulated Radiation Therapy With Simultaneous Integrated Boost: A Phase 2 Trial." Int J Radiat Oncol Biol Phys **96**(5): 1003-1010.

BACKGROUND AND PURPOSE: This phase 2 study investigated the efficacy and safety of preoperative intensity modulated radiation therapy with a simultaneous integrated boost (IMRT-SIB) without dose escalation, concomitant with standard capecitabine chemotherapy in locally advanced rectal cancer. METHODS AND MATERIALS: Between January 2014 and March 2015, 51 patients with operable stage II-III rectal adenocarcinoma received preoperative IMRT with pelvic dose of 41.8 Gy and simultaneously delivered 46.2 Gy to T2/3 and 48.4 Gy to T4 tumor in 22 fractions, concomitant with capecitabine, 825 mg/m (2)/12 hours, including weekends. The primary endpoint was pathologic complete response (pCR). RESULTS: Fifty patients completed preoperative treatment according to the protocol, and 47 underwent surgical resection. The sphincter preservation rate for the low rectal tumors was 62%, and the resection margins were free in all but 1 patient. Decrease in tumor and nodal stage was observed in 32 (68%) and 39 (83%) patients, respectively, with pCR achieved in 12 (25.5%) patients. There were only 2 G >/= 3 acute toxicities, with infectious enterocolitis in 1 patient and dermatitis over the sacral area caused by the bolus effect of the treatment table in the second patient. CONCLUSIONS: Preoperative IMRT-SIB without dose escalation is well tolerated, with a low acute toxicity profile, and can achieve a high rate of pCR and downstaging.

Chinnaiyan, A. M., et al. (2000). "Combined effect of tumor necrosis factor-related apoptosis-inducing ligand and ionizing radiation in breast cancer therapy." Proc Natl Acad Sci U S A **97**(4): 1754-1759.

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a potent endogenous activator of the cell death pathway and functions by activating the cell surface death receptors 4 and 5 (DR4 and DR5). TRAIL is nontoxic in vivo and preferentially kills neoplastically transformed cells over normal cells by an undefined mechanism. Radiotherapy is a common treatment for breast cancer as well as many other cancers. Here we demonstrate that ionizing radiation can sensitize breast carcinoma cells to TRAIL-induced apoptosis. This synergistic effect is p53-dependent and

may be the result of radiation-induced up-regulation of the TRAIL-receptor DR5. Importantly, TRAIL and ionizing radiation have a synergistic effect in the regression of established breast cancer xenografts. Changes in tumor cellularity and extracellular space were monitored in vivo by diffusion-weighted magnetic resonance imaging (diffusion MRI), a noninvasive technique to produce quantitative images of the apparent mobility of water within a tissue. Increased water mobility was observed in combined TRAIL- and radiation-treated tumors but not in tumors treated with TRAIL or radiation alone. Histological analysis confirmed the loss of cellularity and increased numbers of apoptotic cells in TRAIL- and radiation-treated tumors. Taken together, our results provide support for combining radiation with TRAIL to improve tumor eradication and suggest that efficacy of apoptosis-inducing cancer therapies may be monitored noninvasively, using diffusion MRI.

Crane, C. H., et al. (2003). "The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer." Int J Radiat Oncol Biol Phys **57**(1): 84-89.

PURPOSE: To compare the outcome from preoperative chemoradiation (CXRT) and from radiation therapy (RT) in the treatment of rectal cancer in two large, single-institutional experiences. PATIENTS AND METHODS: Between 1978 and 1995, 403 patients with localized, nonmetastatic, clinically staged T3 or T4 rectal cancer patients were treated with preoperative RT alone at two institutions. Patients at institution 1 (n = 207) were treated with pelvic CXRT exclusively, and patients at institution 2 were treated (except for 8 given CXRT) with pelvic RT alone (n = 196). In addition, a third group (n = 61) was treated with CXRT at institution 2 between 1998 and 2000 after a policy change. Both institutions delivered 45 Gy in five fractions as a standard dose, but institution 2 used 20 Gy in five fractions in selected cases (n = 26). At both institutions, concurrent chemotherapy consisted of a continuous infusion of 5-fluorouracil (5-FU) at a dosage of 1500 mg/m(2)/week. The end points were response, sphincter preservation (SP), relapse-free survival (RFS), pelvic disease control (PC), and overall survival (OS). RESULTS: Median follow-up was 63 months for all living patients at institution 1 and in the primary group of institution 2. Multivariate analysis of the patients in these groups showed that the use of concurrent chemotherapy improved tumor response (T-stage downstaging, 62% vs. 42%, p = 0.001, and pathologic complete response, 23% vs. 5% p < 0.0001), but did not significantly improve LC, RFS, or OS. Follow-up for the secondary group at institution 2 was

insufficient to allow the analysis of these endpoints. In the subset of patients receiving 45 Gy who had rectal tumors < or /=6 cm from the anal verge (institution 1: n = 132; institution 2 primary: n = 79; institution 2 secondary: n = 33), there was a significant improvement in SP with the use of concurrent chemotherapy (39% at institution 1 compared with 13% in the primary group at institution 2, p < 0.0001). A logistic regression analysis of clinical prognostic factors indicated that the use of concurrent chemotherapy independently influenced SP in these low tumors (p = 0.002). This finding was supported by a 36% SP rate in the secondary group at institution 2. Thus SP increased after the addition of chemotherapy at institution 2. CONCLUSIONS: The use of concurrent 5-FU with preoperative radiation therapy for T3 and T4 rectal cancer independently increases tumor response and may contribute to increased SP in patients with low rectal cancer.

Crittenden, M. R., et al. (2013). "The peripheral myeloid expansion driven by murine cancer progression is reversed by radiation therapy of the tumor." PLoS One **8**(7): e69527.

Expansion of myeloid-lineage leukocytes in tumor-bearing mice has been proposed as a cause of systemic immunosuppression. We demonstrate that radiation therapy of tumors leads to a decline in myeloid cell numbers in the blood and a decrease in spleen size. The frequency of myeloid cells does not decline to the level seen in tumor-free mice: we demonstrate that metastatic disease can prevent myeloid cell numbers from returning to baseline, and that tumor recurrence from residual disease correlates with re-expansion of myeloid lineage cells. Radiation therapy results in increased proliferation of T cells in the spleen and while T cell responses to foreign antigens are not altered by tumor burden or myeloid cell expansion, responses to tumor-associated antigens are increased after radiation therapy. These data demonstrate that myeloid cell numbers are directly linked to primary tumor burden, that this population contracts following radiation therapy, and that radiation therapy may open a therapeutic window for immunotherapy of residual disease.

Dadey, D. Y. A., et al. (2017). "Antibody Targeting GRP78 Enhances the Efficacy of Radiation Therapy in Human Glioblastoma and Non-Small Cell Lung Cancer Cell Lines and Tumor Models." Clin Cancer Res **23**(10): 2556-2564.

Purpose: Non-small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM) have poor median survival. NSCLC and GBM overexpress glucose regulated protein 78 (GRP78), which has a role in radioresistance and recurrence. In this study,

we determined the effect of anti-GRP78 antibody and the combined effect of the anti-GRP78 antibody with ionizing radiation (XRT) on NSCLC and GBM cell lines both in vitro and in vivoExperimental Design: NSCLC and GBM cancer cell lines were treated with anti-GRP78 antibodies and evaluated for proliferation, colony formation, cell death, and PI3K/Akt/mTOR signaling. The efficacy of anti-GRP78 antibodies on tumor growth in combination with XRT was determined in vivo in mouse xenograft models.Results: GBM and NSCLC cells treated with anti-GRP78 antibodies showed attenuated cell proliferation, colony formation, and enhanced apoptosis. GBM and NSCLC cells treated with anti-GRP78 antibodies also showed global suppression of PI3K/Akt/mTOR signaling. Combining antibody with XRT resulted in significant tumor growth delay in both NSCLC and GBM heterotopic tumor models.Conclusions: Antibodies targeting GRP78 exhibited antitumor activity and enhanced the efficacy of radiation in NSCLC and GBM both in vitro and in vivo GRP78 is a promising novel target, and anti-GRP78 antibodies could be used as an effective cancer therapy alone or in combination with XRT. Clin Cancer Res; 23(10); 2556-64. (c)2016 AACR.

D'Amico, A. V., et al. (2008). "Tumor volume changes on 1.5 tesla endorectal MRI during neoadjuvant androgen suppression therapy for higher-risk prostate cancer and recurrence in men treated using radiation therapy results of the phase II CALGB 9682 study." Int J Radiat Oncol Biol Phys **71**(1): 9-15.

PURPOSE: We prospectively determined whether the change in tumor volume (TV) during 2 months of neoadjuvant androgen suppression therapy (nAST) measured using conventional 1.5 Tesla endorectal magnetic resonance imaging (eMRI) was associated with the risk of recurrence after radiation (RT) and 6 months of AST. PATIENTS AND METHODS: Between 1997 and 2001, 180 men with clinical stage T1c-T3cN0M0 adenocarcinoma of the prostate were registered. Fifteen were found to be ineligible and the institutional MR radiologist could not assess the TV in 32, leaving 133 for analysis. Multivariable Cox regression analysis was used to assess whether a significant association existed between eMRI-defined TV progression during nAST and time to recurrence adjusting for prostate-specific antigen (PSA) level, Gleason score (8 to 10 or 7 vs. 6 or less) and stage (T3 vs. T1-2). RESULTS: After a median follow up of 6.7 years and adjusting for known prognostic factors, there was a significant increase in the risk of PSA failure (HR, 2.3 [95% CI, 1.1-4.5; p = 0.025) in men with eMRI-defined TV progression during nAST. Specifically, adjusted estimates of PSA failure were significantly higher (p = 0.032) in men

with, compared with men without, eMRI-defined TV progression reaching 38% vs. 19%, respectively, by 5 years. CONCLUSION: Eradicating intraprostatic hormone refractory prostate cancer (HRPC) by maximizing local control and randomized trials assessing whether survival is improved when agents active against HRPC are combined with maximal local therapy are needed in men who progress based on eMRI during nAST.

Dholakia, A. S., et al. (2014). "Baseline metabolic tumor volume and total lesion glycolysis are associated with survival outcomes in patients with locally advanced pancreatic cancer receiving stereotactic body radiation therapy." Int J Radiat Oncol Biol Phys **89**(3): 539-546.

PURPOSE: Although previous studies have demonstrated the prognostic value of positron emission tomography (PET) parameters in other malignancies, the role of PET in pancreatic cancer has yet to be well established. We analyzed the prognostic utility of PET for patients with locally advanced pancreatic cancer (LAPC) undergoing fractionated stereotactic body radiation therapy (SBRT). MATERIALS AND METHODS: Thirty-two patients with LAPC in a prospective clinical trial received up to 3 doses of gemcitabine, followed by 33 Gy in 5 fractions of 6.6 Gy, using SBRT. All patients received a baseline PET scan prior to SBRT (pre-SBRT PET). Metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum and peak standardized uptake values (SUVmax and SUVpeak) on pre-SBRT PET scans were calculated using custom-designed software. Disease was measured at a threshold based on the liver SUV, using the equation Livermean + [2 x Liversd]. Median values of PET parameters were used as cutoffs when assessing their prognostic potential through Cox regression analyses. RESULTS: Of the 32 patients, the majority were male (n=19, 59%), 65 years or older (n=21, 66%), and had tumors located in the pancreatic head (n=27, 84%). Twenty-seven patients (84%) received induction gemcitabine prior to SBRT. Median overall survival for the entire cohort was 18.8 months (95% confidence interval [CI], 15.7-22.0). An MTV of 26.8 cm (3) or greater (hazard ratio [HR] 4.46, 95% CI 1.64-5.88, P<.003) and TLG of 70.9 or greater (HR 3.08, 95% CI 1.18-8.02, P<.021) on pre-SBRT PET scan were associated with inferior overall survival on univariate analysis. Both pre-SBRT MTV (HR 5.13, 95% CI 1.19-22.21, P=.029) and TLG (HR 3.34, 95% CI 1.07-10.48, P=.038) remained independently associated with overall survival in separate multivariate analyses. CONCLUSIONS: Pre-SBRT MTV and TLG are potential predictive factors for overall survival in patients with LAPC and may assist in tailoring therapy.

Dorsey, J. F., et al. (2015). "Tracking viable circulating tumor cells (CTCs) in the peripheral blood of non-small cell lung cancer (NSCLC) patients undergoing definitive radiation therapy: pilot study results." Cancer **121**(1): 139-149.

BACKGROUND: Assays identifying circulating tumor cells (CTCs) allow noninvasive and sequential monitoring of the status of primary or metastatic tumors, potentially yielding clinically useful information. However, to the authors' knowledge, the effect of radiation therapy (RT) on CTCs in patients with non-small cell lung cancer (NSCLC) has not been previously explored. METHODS: This report describes results from a pilot study of 30 patients with NSCLC who received RT. Peripheral blood samples obtained from these patients were assayed for CTCs using an assay that identified live cells using an adenoviral probe that detected the elevated telomerase activity present in almost all cancer cells, but not in normal cells, and the validity of the assay was confirmed with secondary tumor-specific markers. Patients were assayed before initiation of RT (pre-RT), during the RT course, and/or after the completion of RT (post-RT). RESULTS: The assay successfully detected CTCs in the majority of patients, including 65% of patients before the start of RT, and in patients with both epidermal growth factor receptor wild-type and mutation-positive tumors. The median CTC counts in patients before RT was 9.1 CTCs per mL (range, undetectable to 571 CTCs per mL) and was significantly higher than the average post-RT count of 0.6 CTCs per mL (range, undetectable to 1.8 CTCs per mL; P<.001). Sequential CTC counts were available in a subset of patients and demonstrated decreases after RT, except for 1 patient who subsequently developed distant failure. CONCLUSIONS: The current pilot data suggest that CTC counts appear to reflect response to RT in patients with localized NSCLC. On the basis of these promising results, the authors have launched a more comprehensive and detailed clinical trial.

Dresen, R. C., et al. (2009). "Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part I. Are we able to predict tumor confined to the rectal wall?" Radiology **252**(1): 71-80.

PURPOSE: To retrospectively assess accuracy of magnetic resonance (MR) imaging after radiation therapy with concomitant chemotherapy for downsizing of the primary lesion to ypT0-2 tumor confined to rectal wall in locally advanced rectal cancer, with histopathologic findings as reference standard, and to evaluate additional value of volumetric analysis. MATERIALS AND METHODS:

The institutional review board approved the study and waived informed consent. Sixty-seven patients met criteria of the study. T2-weighted MR images obtained before and after radiation therapy with concomitant chemotherapy were assessed for tumor stage by expert abdominal radiologist, colorectal surgeon, and general radiologist. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated; tumor volume was measured (compared with Mann-Whitney U test). Findings were correlated with histopathologic findings. RESULTS: Sixty-seven patients (38 men, 29 women; mean age, 63 years) who underwent radiation therapy with concomitant chemotherapy and surgery (all but one) were evaluated. The PPV for prediction of tumor confined to rectal wall (ypT0-2) was 91% (10 of 11), 86% (six of seven), and 88% (seven of eight) for expert abdominal radiologist, surgeon, and general radiologist, respectively. In 24 patients, sensitivity was 42% (10), 25% (six), and 29% (seven). ypT0-2 tumors had significantly smaller volumes than did ypT3-4 tumors before radiation therapy with concomitant chemotherapy (55 vs 92 cm (3), P =.038). Volume reduction rates were significantly higher in ypT0-2 than in ypT3-4 tumors (89% vs 61%, P <.001). If volume before radiation therapy with concomitant chemotherapy was 50 cm (3) or smaller and volume reduction rate was 75% or higher, excised tumor was always confined to rectal wall (ypT0-2). By using these criteria, 43% (six of 14) of cases with overstaging could have been predicted to be ypT0-2 tumors correctly. CONCLUSION: Downsizing to ypT0-2 tumors can be accurately predicted by combining morphologic tumor staging predictions with results from volumetric analyses. MR images obtained after radiation therapy with concomitant chemotherapy might be helpful in more individualized treatment planning.

Eide, H. A., et al. (2018). "Serum cytokine profiles and metabolic tumor burden in patients with non-small cell lung cancer undergoing palliative thoracic radiation therapy." Adv Radiat Oncol **3**(2): 130-138.

Purpose: Radiation therapy effectively kills cancer cells and elicits local effects in the irradiated tissue. The aim of this study was to investigate the kinetics of cytokines in the serum of patients with lung cancer undergoing radiation therapy and to identify associations with metabolic tumor burden as determined by 2-deoxy-2-fluoro-D-glucose ((18)F-FDG) positron emission tomography (PET). Methods and materials: Forty-five patients with advanced non-small cell lung cancer were included in a phase 2 clinical trial and randomized between fractionated thoracic radiation therapy alone or concurrent with an

epidermal growth factor receptor inhibitor. Blood was sampled at 4 different time points: prior to treatment, midtherapy, at the end of therapy, and 6 to 8 weeks after the start of treatment. The serum concentrations of 48 cytokines and 9 matrix metalloproteinases were measured with multiplex immunoassays. A subset of patients was examined by (18)F-FDG PET/computed tomography before, during, and after radiation therapy. The maximum standardized uptake values (SUVmax) of the primary lung tumor, whole-body metabolic tumor volume, and total lesion glycolysis were calculated, and correlations between the PET parameters and cytokines were investigated. Results: The SUVmax decreased from baseline through midtherapy to posttherapy (18)F-FDG PET/computed tomography (P =.018). The serum levels of C-C motif chemokine ligand (CCL) 23, CCL24, C-X3-C motif chemokine ligand 1, and interleukin-8 (C-X-C motif ligand [CXCL]8) were significantly correlated to SUVmax, metabolic tumor volume, and total lesion glycolysis before, during, and after radiation therapy. CXCL2 (P =.030) and CXCL6 (P =.010) decreased after the start of therapy and changed significantly across the sample time points. Serum concentrations of CCL15 (P =.031), CXCL2 (P =.028), and interleukin-6 (P =.007) were positively correlated to the irradiated volume during the second week of treatment. Conclusions: Cytokine serum levels vary and correlate with metabolic tumor burden in patients with advanced non-small cell lung cancer undergoing palliative thoracic radiation therapy.

Formenti, S. C., et al. (2002). "T1 stage breast cancer: adjuvant hypofractionated conformal radiation therapy to tumor bed in selected postmenopausal breast cancer patients--pilot feasibility study." Radiology **222**(1): 171-178.

PURPOSE: To explore the feasibility of a short course of hypofractionated conformal radiation therapy to the tumor bed as part of a breast preservation protocol in postmenopausal patients with nonpalpable pT1N0 stage breast cancer. MATERIALS AND METHODS: The tumor bed was imaged at computed tomography (CT) in the prone position on a dedicated table. The same table and position were used for treatment with a 4-MV linear accelerator. The planning target volume was the tumor bed plus a 1-2-cm margin defined at postmastectomy CT. A regimen of five fractions was tested in this pilot dose study. Cosmesis was assessed by patients and physicians before treatment and 36 months after treatment. RESULTS: Ten consecutive patients who were eligible for the study were assigned to one of three dose-per-fraction regimens; nine were treatable with the proposed technique on the basis of CT findings. Patients received five fractions over 10 days (total

dose range, 25-30 Gy): Three received 5.0 Gy per fraction; four, 5.5 Gy; and two, 6.0 Gy. At minimum follow-up of 36 months (range, 36-53 months), all patients were alive and disease free with good to excellent cosmesis. CONCLUSION: Hypofractionated conformal breast radiation therapy is feasible. Further studies are warranted.

Frenzel, T., et al. (2018). "Locally Ablative Radiation Therapy of a Primary Human Small Cell Lung Cancer Tumor Decreases the Number of Spontaneous Metastases in Two Xenograft Models." Int J Radiat Oncol Biol Phys **100**(4): 1044-1056.

PURPOSE: To investigated the influence of radiation therapy (RT), surgery (OP), radio-chemotherapy (RChT), or chemotherapy (ChT) on small cell lung cancer metastases in 2 xenograft models. METHODS AND MATERIALS: A total of 1 x 10(6) human small cell lung cancer cells (OH1, H69) were subcutaneously injected into severe combined immunodeficiency mice to form a local primary tumor node at the lower trunk. Radiation therapy, OP, RChT, or ChT were started after development of palpable tumors. Chemotherapy was given as a single intraperitoneal injection of cisplatin. Radiation therapy was 5 x 10 Gy on the local tumor node. Two additional groups were implemented to assess primary tumors and distant metastases in untreated mice at the beginning (control group A) and at the end of the experiment (control group B). Proapoptotic, antiproliferative, antiangiogenic, and hypoxic effects were assessed by Feulgen, Ki67, S1P1 receptor, and hypoxia-inducible factor 1alpha staining, respectively. Quantitative Alu-polymerase chain reaction was used to determine circulating tumor cells in the blood, and disseminated tumor cells in the lungs, bone marrow, liver, and brain. RESULTS: In both xenograft models, RT and RChT abrogated local tumor growth, indicated by increased apoptosis, decreased cell proliferation, and reduced microvessel density (equally affecting vessels of all diameters). Regarding metastases, RT and RChT not only counteracted the time-dependent increase of dissemination but also decreased the metastatic load pre-existing at therapy induction in the blood, lungs, and liver. Only in the case of relapse-free surgery could similar effects be achieved by OP. CONCLUSIONS: Our models provide evidence that RT and RChT ablate the primary tumor and inhibit metastasis development over time. Upon local recurrence, RT showed beneficial effects compared with OP with regard to suppression of circulating tumor cells and disseminated tumor cells.

Frick, M. A., et al. (2018). "Circulating Tumor Cell Assessment in Presumed Early Stage Non-Small Cell Lung Cancer Patients Treated with Stereotactic

Body Radiation Therapy: A Prospective Pilot Study." Int J Radiat Oncol Biol Phys **102**(3): 536-542.

PURPOSE: In patients treated with stereotactic body radiation therapy (SBRT) for presumed early stage non-small cell lung cancer (NSCLC), detection and monitoring of circulating tumor cells (CTCs) may be useful for assessing treatment response safely and noninvasively. No published reports of CTC trends in this patient population exist to date. METHODS AND MATERIALS: Patients with clinically diagnosed stage I NSCLC treated with SBRT were eligible for this institutional review board-approved prospective clinical trial. Peripheral blood samples were assayed for CTCs via a green fluorescent protein-expressing adenoviral probe. CTC positivity was defined as 1.3 green fluorescent protein-positive cells/mL of collected blood. Samples were obtained before (pre-radiation therapy [RT]), during, and after SBRT (post-RT; months 1, 3, 6, 12, 18, and 24). SBRT was delivered in </=5 fractions (median dose of 50 Gy in 12.5 Gy fractions) to a biological equivalent dose of >/=100 Gy in all cases. RESULTS: Forty-eight consecutive patients (T1a [73%], T1b [21%], and T2a [6%]) were enrolled. Median follow-up was 14.2 months. Twenty patients (42%) had a positive CTC level pre-RT, with a median CTC count of 4.2 CTCs per mL (interquartile range [IQR], 2.2-18.7). Of these 20 patients, 17 had evaluable post-RT CTC evaluations showing reduced CTC counts at 1 month (median, 0.2; IQR, 0.1-0.8) and 3 months (median, 0.6; IQR, 0-1.1). Three of these 17 patients experienced disease progression at a median of 19.9 months; all 3 experienced >/=1 positive post-RT CTC test predating clinical progression by a median of 16 months (range, 2-17 months). In contrast, among patients presenting with CTC-detectable disease and for whom all post-RT CTC tests were negative, none experienced recurrence or progression. CONCLUSIONS: CTC monitoring after SBRT for presumed early stage NSCLC may give lead-time notice of disease recurrence or progression. Conversely, negative CTC counts after treatment may provide reassurance of disease control. CTC analysis is thus potentially useful in enhancing clinical diagnosis and follow-up in this population.

Gabelov, A. A. and G. M. Zharinov (1983). "[Tumor regression rate and the effectiveness of the radiation therapy of cervical cancer patients]." Vopr Onkol **29**(6): 41-45.

The paper deals with a correlation between the rate of tumor regression in response to radiation and the results of radiation treatment of cancer of the uterine cervix. The period of 50% decrease in tumor size in response to radiation treatment was established in 116 patients with cervical carcinoma by means of a dynamical cytological examination. Acceleration of tumor regression was followed by an increase in 5-year survival rates. A reverse correlation was established between growth and regression rates of cervical carcinoma. Thanks to the determination of tumor regression rates, various modalities of radiation treatment could be evaluated in the course of therapy and their efficacy predicted.

Grabenbauer, G. G., et al. (1998). "Nodal CT density and total tumor volume as prognostic factors after radiation therapy of stage III/IV head and neck cancer." Radiother Oncol **47**(2): 175-183.

PURPOSE: To determine whether the immunohistochemical expression of proliferation-associated antigens (proliferating cell nuclear antigen, MIB1) and the nuclear p53 reactivity in addition to total tumor volume, nodal CT density and T and N category are predictive for overall survival and locoregional tumor control in patients with squamous cell carcinoma of the head and neck region. MATERIALS AND METHODS: Between October 1989 and September 1993, 87 patients with biopsy proven head and neck cancer were randomly allocated to receive radiation alone or simultaneous radiation and chemotherapy as part of a multicenter trial with a total of 298 randomized patients. There were only inoperable lesions in UICC (1992) stage III (8%) and IV (92%). Radiotherapy was delivered with 180 cGy twice daily up to a total dose of 7020 cGy in 51 days. Three cycles of 2340 cGy each were separated by a rest period of 11 days. Chemotherapy consisted of cis-DDP, 5-fluorouracil and leucovorin and was repeated on days 22 and 44. Routinely-processed paraffin-embedded sections were stained using monoclonal antibodies for detection of proliferation-associated antigens (MIB1 and PCNA) and p53 oncoprotein to determine the labeling index (LI). In addition, the total tumor volume and the percentage of necrosis were measured using CT data. The median follow-up was 3.9 years (range 1.9-5.0 years). RESULTS: The overall survival and locoregional control for all 87 patients were 34 and 39% at 3 years, respectively. The addition of chemotherapy resulted in a better overall survival (27 versus 47%, P = 0.03) but did not influence locoregional control (31 versus 47%, P = 0.08). In univariate analysis, nodal CT density (P < 0.0001), total tumor volume (P < 0.0001), age (P = 0.001) and the MIB1-LI (P = 0.04) had a significant impact on overall survival. However, in the final Cox model only the nodal CT density (P = 0.0003) and age (P = 0.05) were independent prognostic factors for survival and only the nodal CT density (P = 0.0006) was an independent prognostic factor for locoregional control. The expression of the p53 oncoprotein was not found to have a clear predictive value. CONCLUSION:

Nodal CT density, total tumor volume and age will remain the relevant prognostic factors in stage III/IV head and neck cancer.

Gulack, B. C., et al. (2016). "Surgical Resection of the Primary Tumor in Stage IV Colorectal Cancer Without Metastasectomy is Associated With Improved Overall Survival Compared With Chemotherapy/Radiation Therapy Alone." Dis Colon Rectum **59**(4): 299-305.

BACKGROUND: Controversy exists over whether resection of the primary tumor in stage IV colorectal cancer with inoperable metastases improves patient outcomes. OBJECTIVE: The purpose of this study was to evaluate whether resection of the primary tumor without metastasectomy in patients with stage IV colorectal cancer is associated with improved overall survival compared with patients undergoing chemotherapy and/or radiation therapy alone. DESIGN: This was a retrospective review of a multi-institutional dataset. SETTINGS: This study was conducted in all participating commission on cancer (CoC)-accredited facilities. PATIENTS: The 2003-2006 National Cancer Data Base was reviewed to identify patients with stage IV adenocarcinoma of the colon or rectum who underwent palliative treatment without curative intent, either in the form of surgical resection of the primary tumor without metastasectomy consisting of a colectomy or rectal resection with or without chemotherapy and/or radiation or chemotherapy and/or radiation alone. MAIN OUTCOME MEASURES: Groups were compared for baseline characteristics. Overall survival was compared using Kaplan-Meier analysis before and after propensity matching with a 1:1 nearest-neighbor algorithm. RESULTS: Of the 1446 patients included in the analysis, 231 (16%) underwent surgical resection of the primary tumor without metastasectomy. Surgical resection was associated with a significant survival benefit on unadjusted analysis (median survival, 9.2 vs. 7.6 months; p < 0.01). After propensity matching to adjust for nonrandom treatment selection, surgical resection continued to be associated with a significant survival benefit (median survival, 9.2 vs. 7.3 months; p < 0.01). LIMITATIONS: This study was limited by the potential for selection bias regarding which patients received surgical resection. There was also a lack of data regarding the indication for operation, specifically whether a patient was symptomatic or asymptomatic before resection. The inability to account for tumor size or grade among patients who did not receive surgical resection was another limitation. CONCLUSIONS: Surgical resection of the primary tumor without metastasectomy in patients with metastatic colorectal cancer is associated with

improved survival as compared with chemotherapy/radiation therapy alone. Additional research is necessary to determine which patients may benefit from this intervention.

Gulec, S. A., et al. (2011). "The prognostic value of functional tumor volume and total lesion glycolysis in patients with colorectal cancer liver metastases undergoing 90Y selective internal radiation therapy plus chemotherapy." Eur J Nucl Med Mol Imaging **38**(7): 1289-1295.

PURPOSE: Functional tumor volume (FTV) and total lesion glycolysis (TLG) are measures of metabolic activity of tumors determined by fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT images. These parameters could potentially have clinical value in response to treatment evaluation and disease prognostication. The objectives of this study were to investigate the relationship between functional tumor parameters (FTV and TLG) and clinical outcomes in patients with colorectal cancer liver metastases (CRCLM) undergoing (90)Y-resin microsphere selective internal radiation therapy (SIRT) (SIR-Spheres (R), Sirtex Medical Limited, Lane Cove, NSW, Australia). METHODS: FDG PET/CT studies of 20 patients with unresectable CRCLM who underwent (90)Y SIRT under a phase II clinical trial were analyzed. FTV and TLG were calculated using PET VCAR (GE Healthcare, Milwaukee, WI, USA) on pretreatment and 4-week posttreatment scans. The effects of pretreatment and posttreatment functional tumor activity on patient survival were evaluated using Kaplan-Meier survival curves. RESULTS: The median survival in the study group was 14.8 months (range 2.0-27.7 months). The median survival for patients with pretreatment FTV values of above and below 200 cc were 11.2 and 26.9 months, respectively (p < 0.05). The median survival for patients with 4-week posttreatment FTV values of above and below 30 cc were 10.9 and 26.9 months, respectively (p < 0.05). The median survival for patients with pretreatment TLG values of above and below 600 g were 11.2 and 26.9 months, respectively (p < 0.05). The median survival for patients with 4-week posttreatment TLG values of above and below 100 g were 10.9 and 26.9 months, respectively (p < 0.05). CONCLUSION: Pretreatment and posttreatment FTV and TLG showed very strong association with survival. These values can be useful quantitative criteria for patient selection and disease prognostication when (90)Y SIRT is contemplated in patients with CRCLM.

Gunter, T., et al. (2015). "Changes in Non-Small Cell Lung Cancer Tumor Location Secondary to Gastric Distension, Implications in the Context of

Stereotactic Body Radiation Therapy." J Okla State Med Assoc **108**(9-10): 398-401.

OBJECTIVE: Stereotactic body radiation therapy (SBRT) facilitates highly conformal dose distributions to a targe tumor volume. Accurate tumor localization is extremely important, and lung tumors pose a unique challenge due to respiratory motion. Patients are required to fast before PET/CT but not before CT simulation and daily treatment, introducing potential variability from gastric distension. METHODS: A case was reviewed involving a patient with early-stage NSCLC which was simulated and treated with SBRT. PET/CT performed while fasting showed an isolated left lower lobe lesion. Following CT simulation, CT and PET/CT images were superimposed for comparison and treatment planning. RESULTS: Tumor location variation was apparent following image superimposition. Simulation CT showed significant gastric distension compared to PET/CT. The patient was resimulated while fasting, resulting in accurate and reproducible tumor localization for treatment planning. CONCLUSIONS: Gastric distension can alter tumor location and treatment volumes for radiotherapy planning, possibly resulting in inaccurate treatment administration.

Hafeez, S., et al. (2016). "Prospective Study Delivering Simultaneous Integrated High-dose Tumor Boost (</=70 Gy) With Image Guided Adaptive Radiation Therapy for Radical Treatment of Localized Muscle-Invasive Bladder Cancer." Int J Radiat Oncol Biol Phys **94**(5): 1022-1030.

PURPOSE: Image guided adaptive radiation therapy offers individualized solutions to improve target coverage and reduce normal tissue irradiation, allowing the opportunity to increase the radiation tumor dose and spare normal bladder tissue. METHODS AND MATERIALS: A library of 3 intensity modulated radiation therapy plans were created (small, medium, and large) from planning computed tomography (CT) scans performed at 30 and 60 minutes; treating the whole bladder to 52 Gy and the tumor to 70 Gy in 32 fractions. A "plan of the day" approach was used for treatment delivery. A post-treatment cone beam CT (CBCT) scan was acquired weekly to assess intrafraction filling and coverage. RESULTS: A total of 18 patients completed treatment to 70 Gy. The plan and treatment for 1 patient was to 68 Gy. Also, 1 patient's plan was to 70 Gy but the patient was treated to a total dose of 65.6 Gy because dose-limiting toxicity occurred before dose escalation. A total of 734 CBCT scans were evaluated. Small, medium, and large plans were used in 36%, 48%, and 16% of cases, respectively. The mean +/- standard deviation rate of intrafraction filling at the start of treatment (ie, week 1) was 4.0 +/- 4.8 mL/min (range

0.1-19.4) and at end of radiation therapy (ie, week 5 or 6) was 1.1 +/- 1.6 mL/min (range 0.01-7.5; P=.002). The mean D98 (dose received by 98% volume) of the tumor boost and bladder as assessed on the post-treatment CBCT scan was 97.07% +/- 2.10% (range 89.0%-104%) and 99.97% +/- 2.62% (range 96.4%-112.0%). At a median follow-up period of 19 months (range 4-33), no muscle-invasive recurrences had developed. Two patients experienced late toxicity (both grade 3 cystitis) at 5.3 months (now resolved) and 18 months after radiation therapy. CONCLUSIONS: Image guided adaptive radiation therapy using intensity modulated radiation therapy to deliver a simultaneous integrated tumor boost to 70 Gy is feasible, with acceptable toxicity, and will be evaluated in a randomized trial.

Hamming-Vrieze, O., et al. (2012). "Evaluation of tumor shape variability in head-and-neck cancer patients over the course of radiation therapy using implanted gold markers." Int J Radiat Oncol Biol Phys **84**(2): e201-207.

PURPOSE: This study quantifies tumor shape variability in head-and-neck cancer patients during radiation therapy using implanted markers. METHODS AND MATERIALS: Twenty-seven patients with oropharyngeal tumors treated with (chemo)radiation were included. Helical gold markers (0.35 x 2 mm, 3-10/patient, average 6) were implanted around the tumor. Markers were identified on planning computed tomography (CT) and daily cone beam CT (CBCT). After bony anatomy registration, the daily vector length on CBCT in reference to the planning CT and daily marker movement perpendicular to the gross tumor volume (GTV) surface at planning CT (d (normal)) of each marker were analyzed. Time trends were assessed with linear regression of the <d (normal)>(markers). In 2 patients, 2 markers were implanted in normal tissue to evaluate migration by measuring intermarker distances. RESULTS: Marker implantation was feasible without complications. Three-dimensional vectors (4827 measurements, mean 0.23 cm, interquartile ratio 0.24 cm) were highest in base of tongue sublocalization (P<.001) and bulky tumors (vectors exceeded 0.5 cm in 5.7% [0-20 mL], 12.0% [21-40 mL], and 21.7% [>/= 41 mL], respectively [P<.001] of measurements). The measured inward time trend in 11/27 patients correlated with the visual observed marker pattern. In patients with an outward trend (5/27) or no trend (11/27), visual observation showed predominantly an inhomogeneous pattern. Remarkably, in 6 patients, outward marker movement was observed in the posterior pharyngeal wall. The difference in distance between normal tissue markers (1 SD) was 0.05-0.06 cm without time trend, indicating that implanted

markers did not migrate. CONCLUSIONS: During head-and-neck radiation therapy, normal tissue markers remained stable. Changes in position of tumor markers depended on sublocalization and tumor volume. Large differences in marker patterns between patients as well as within patients were observed. Based on our study, the cranial and caudal border in the posterior pharyngeal wall are at highest risk to be covered insufficiently. Furthermore, implanted markers could help identify patients with an actual shrinkage of the GTV who might benefit from mid-radiation therapy redelineation to reduce toxicity.

Hannan, R., et al. (2015). "Stereotactic radiation therapy of renal cancer inferior vena cava tumor thrombus." Cancer Biol Ther **16**(5): 657-661.

Renal Cell Carcinoma (RCC) is a common malignancy world-wide that is rising in incidence. Up to 10% of RCC patients present with inferior vena cava (IVC) tumor thrombus (IVC-TT). Although surgery is the only treatment with proven efficacy for IVC-TT, the surgical management of advanced (level III and IV) IVC-TT is difficult with high morbidity and mortality, and offers a poor survival outcome. Currently, there are no treatment options in the setting of recurrent or unresectable RCC IVC-TT. Even though RCC may be resistant to conventionally fractionated radiation therapy, hypofractionated radiation has shown excellent control rates for both primary and metastatic RCC. We report our experience treating 2 RCC patients with Level IV IVC-TT -one recurrent and the other unresectable-with stereotactic ablative radiation therapy (SABR). The first patient is a 75-year-old gentleman with a level IV RCC IVC-TT who presented 9 months after his radical nephrectomy and thrombectomy with a growing level IV IVC-TT that became refractory to 4 targeted agents. He received SABR of 50Gy in 5 fractions and at 2-year follow-up is doing well with a significant decrease in the enhancement and size of the IVC-TT. The second patient is an 83-year-old gentleman who presented with metastatic RCC and level IV IVC-TT but was not a surgical candidate. After progression on temsirolimus, he received SABR of 36Gy in 4 fractions to his IVC-TT and survived 18 months post-SABR. Both patients improved symptomatically and did not experience any acute or late treatment-related toxicity. Their survival of 24 months and 18 months are comparable to the reported median survival of 20 months in patients with level IV IVC-TT that underwent surgical resection. Therefore, SABR can be a potentially safe treatment option in the unresectable setting for RCC patients with IVC-TT and should be further evaluated in prospective trials.

Haque, W., et al. (2017). "Radiation therapy utilization and outcomes for older women with breast cancer: Impact of molecular subtype and tumor grade." Breast **35**: 34-41.

BACKGROUND: Radiation therapy (RT) utilization for elderly women with respect to human epidermal growth factor receptor 2 (HER2) receptor status has not been evaluated. Our purpose was to determine differences in RT utilization and breast cancer specific survival (BCSS) for elderly breast cancer patients with distinct molecular biomarkers. METHODS: The Surveillance, Epidemiology, and End Results database was queried for women >/=70 years of age diagnosed with T1N0M0 breast cancer between 2010 and 2013 receiving breast conservation. Chi-squared analysis was performed to determine the difference in RT utilization between groups. Multivariable logistic regression analysis was performed to determine predictors for RT use. Kaplan-Meier curves were created and the log-rank test done to compare differences in breast cancer specific survival (BCSS) between groups. RESULTS: A total of 12,312 patients met the inclusion criteria. Receipt of RT for patients with distinct tumor biomarkers was as follows: 55.7% for patients with Estrogen Receptor (ER) +/HER2+; 57.1% for patients with ER+/HER2-; 65.6% for patients with ER-/HER2+; and 69.2% for ER-/HER2- patients (p < 0.001). Factors associated with RT use included ER-/HER2- status, 70-74 years of age, and high grade disease, while adjuvant RT was associated with improve BCSS in ER+/HER2- and ER-/HER2- patients. CONCLUSIONS: Patients 70-74 years old and those with ER-/HER2- are more likely to receive adjuvant RT. Moreover, adjuvant RT is associated with improvements in BCSS in ER+/HER2- and ER-/HER2- patients. Given possible poor compliance with hormonal therapy, the omission of RT in ER + patients, without consideration of HER2 status, should be undertaken with care.

Hayakawa, K., et al. (1996). "Impact of tumor extent and location on treatment outcome in patients with stage III non-small cell lung cancer treated with radiation therapy." Jpn J Clin Oncol **26**(4): 221-228.

The results of treatment of 141 patients with stage III non-small cell lung cancer (NSCLC) who received definitive radiation therapy at Gunma University Hospital between 1976 and 1989 were retrospectively analyzed. Radiation was given with standard fractionation for a planned prophylactic dose of 40 Gy over 4 weeks and a definitive dose of 60 Gy over 6 weeks or more. The two- and five-year survival rates were 27% and 12% for stage IIIA, and 18% and 8% for stage IIIB, respectively (P = 0.052). By univariate analysis, a primary tumor less than 5 cm in diameter was also an important predictor of survival (P

= 0.008). As for tumor location, the patients with primary tumors in the upper lobes or the superior segment of the lower lobes of the lung lived longer than those with primary tumors at any other site (P = 0.032). Patients with epidermoid carcinoma had a higher survival rate at 5 years than those with other histologic types (14% vs 3%, P = 0.074). Multivariate analysis showed that among tumor characteristics, the site of the primary tumor, the pattern of tumor spread and N stage were significantly associated with overall survival. Among the patients with stage III NSCLC, those with stage IIIA epidermoid carcinoma in the upper lobe or the superior segment of the lower lobe of the lung were considered to be the most favorable candidates for definitive radiation therapy.

Heerkens, H. D., et al. (2017). "Recommendations for MRI-based contouring of gross tumor volume and organs at risk for radiation therapy of pancreatic cancer." Pract Radiat Oncol 7(2): 126-136.

PURPOSE: Local recurrence is a common and morbid event in patients with unresectable pancreatic adenocarcinoma. A more conformal and targeted radiation dose to the macroscopic tumor in nonmetastatic pancreatic cancer is likely to reduce acute toxicity and improve local control. Optimal soft tissue contrast is required to facilitate delineation of a target and creation of a planning target volume with margin reduction and motion management. Magnetic resonance imaging (MRI) offers considerable advantages in optimizing soft tissue delineation and is an ideal modality for imaging and delineating a gross tumor volume (GTV) within the pancreas, particularly as it relates to conformal radiation planning. Currently, no guidelines have been defined for the delineation of pancreatic tumors for radiation therapy treatment planning. Moreover, abdominal MRI sequences are complex and the anatomy relevant to the radiation oncologist can be challenging. The purpose of this study is to provide recommendations for delineation of GTV and organs at risk (OARs) using MRI and incorporating multiple MRI sequences. METHODS AND MATERIALS: Five patients with pancreatic cancer and 1 healthy subject were imaged with MRI scans either on 1.5T or on 3T magnets in 2 separate institutes. The GTV and OARs were contoured for all patients in a consensus meeting. RESULTS: An overview of MRI-based anatomy of the GTV and OARs is provided. Practical contouring instructions for the GTV and the OARs with the aid of MRI were developed and included in these recommendations. In addition, practical suggestions for implementation of MRI in pancreatic radiation treatment planning are provided. CONCLUSIONS: With this report, we attempt to provide recommendations for MRI-based

contouring of pancreatic tumors and OARs. This could lead to better uniformity in defining the GTV and OARs for clinical trials and in radiation therapy treatment planning, with the ultimate goal of improving local control while minimizing morbidity.

Heerkens, H. D., et al. (2014). "MRI-based tumor motion characterization and gating schemes for radiation therapy of pancreatic cancer." Radiother Oncol 111(2): 252-257.

BACKGROUND AND PURPOSE: To characterize pancreatic tumor motion and to develop a gating scheme for radiotherapy in pancreatic cancer. MATERIALS AND METHODS: Two cine MRIs of 60s each were performed in fifteen pancreatic cancer patients, one in sagittal direction and one in coronal direction. A Minimum Output Sum of Squared Error (MOSSE) adaptive correlation filter was used to quantify tumor motion in craniocaudal, lateral and anteroposterior directions. To develop a gating scheme, stability of the breathing phases was examined and a gating window assessment was created, incorporating tumor motion, treatment time and motion margins. RESULTS: The largest tumor motion was found in craniocaudal direction, with an average peak-to-peak amplitude of 15mm (range 6-34mm). Amplitude of the tumor in the anteroposterior direction was on average 5mm (range 1-13mm). The least motion was seen in lateral direction (average 3mm, range 2-5mm). The end exhale position was the most stable position in the breathing cycle and tumors spent more time closer to the end exhale position than to the end inhale position. On average, a margin of 25% of the maximum craniocaudal breathing amplitude was needed to achieve full target coverage with a duty cycle of 50%. When reducing the duty cycle to 50%, a margin of 5mm was sufficient to cover the target in 11 out of 15 patients. CONCLUSION: Gated delivery for radiotherapy of pancreatic cancer is best performed around the end exhale position as this is the most stable position in the breathing cycle. Considerable margin reduction can be established at moderate duty cycles, yielding acceptable treatment efficiency. However, motion patterns and amplitude do substantially differ between individual patients. Therefore, individual treatment strategies should be considered for radiotherapy in pancreatic cancer.

Hintz, B. L., et al. (1983). "Local control of T1 vocal cord cancer with radiation therapy: the importance of tumor character vs. treatment parameters." Head Neck Surg 5(3): 204-210.

Ninety-one patients with T1 vocal cord carcinoma received primary irradiation treatment. The 5- and 10-year determinate disease-free survival was 80%; the 5- and 10-year determinate survival

including surgical salvage was 92%. Tumors involving more than one-half of a vocal cord or involving the anterior commissure or exhibiting an exophytic growth pattern had numerically, but not statistically, higher local failure rates than tumors without these characteristics. Precise radiation treatment technique appears more important for local control (LC) than tumor character. The crucial treatment factors for high LC with few radiation complications are reproducible daily patient positioning, use of contour-compensating devices (wedges), field size of 5 X 5 cm, and a radiation prescription with a time-dose fractionation value of 101 to 106.

Karava, K., et al. (2017). "Potential dosimetric benefits of adaptive tumor tracking over the internal target volume concept for stereotactic body radiation therapy of pancreatic cancer." Radiat Oncol **12**(1): 175.

BACKGROUND: Radiotherapy for pancreatic cancer has two major challenges: (I) the tumor is adjacent to several critical organs and, (II) the mobility of both, the tumor and its surrounding organs at risk (OARs). A treatment planning study simulating stereotactic body radiation therapy (SBRT) for pancreatic tumors with both the internal target volume (ITV) concept and the tumor tracking approach was performed. The two respiratory motion-management techniques were compared in terms of doses to the target volume and organs at risk. METHODS AND MATERIALS: Two volumetric-modulated arc therapy (VMAT) treatment plans (5 x 5 Gy) were created for each of the 12 previously treated pancreatic cancer patients, one using the ITV concept and one the tumor tracking approach. To better evaluate the overall dose delivered to the moving tumor volume, 4D dose calculations were performed on four-dimensional computed tomography (4DCT) scans. The resulting planning target volume (PTV) size for each technique was analyzed. Target and OAR dose parameters were reported and analyzed for both 3D and 4D dose calculation. RESULTS: Tumor motion ranged from 1.3 to 11.2 mm. Tracking led to a reduction of PTV size (max. 39.2%) accompanied with significant better tumor coverage (p<0.05, paired Wilcoxon signed rank test) both in 3D and 4D dose calculations and improved organ at risk sparing. Especially for duodenum, stomach and liver, the mean dose was significantly reduced (p<0.05) with tracking for 3D and 4D dose calculations. CONCLUSIONS: By using an adaptive tumor tracking approach for respiratory-induced pancreatic motion management, a significant reduction in PTV size can be achieved, which subsequently facilitates treatment planning, and improves organ dose sparing. The dosimetric benefit of tumor tracking is organ and patient-specific.

Karki, K., et al. (2017). "Variabilities of Magnetic Resonance Imaging-, Computed Tomography-, and Positron Emission Tomography-Computed Tomography-Based Tumor and Lymph Node Delineations for Lung Cancer Radiation Therapy Planning." Int J Radiat Oncol Biol Phys **99**(1): 80-89.

PURPOSE: To investigate interobserver delineation variability for gross tumor volumes of primary lung tumors and associated pathologic lymph nodes using magnetic resonance imaging (MRI), and to compare the results with computed tomography (CT) alone- and positron emission tomography (PET)-CT-based delineations. METHODS AND MATERIALS: Seven physicians delineated the tumor volumes of 10 patients for the following scenarios: (1) CT only, (2) PET-CT fusion images registered to CT ("clinical standard"), and (3) postcontrast T1-weighted MRI registered with diffusion-weighted MRI. To compute interobserver variability, the median surface was generated from all observers' contours and used as the reference surface. A physician labeled the interface types (tumor to lung, atelectasis (collapsed lung), hilum, mediastinum, or chest wall) on the median surface. Contoured volumes and bidirectional local distances between individual observers' contours and the reference contour were analyzed. RESULTS: Computed tomography- and MRI-based tumor volumes normalized relative to PET-CT-based volumes were 1.62 +/- 0.76 (mean +/- standard deviation) and 1.38 +/- 0.44, respectively. Volume differences between the imaging modalities were not significant. Between observers, the mean normalized volumes per patient averaged over all patients varied significantly by a factor of 1.6 (MRI) and 2.0 (CT and PET-CT) (P=4.10 x 10(-5) to 3.82 x 10(-9)). The tumor-atelectasis interface had a significantly higher variability than other interfaces for all modalities combined (P=.0006). The interfaces with the smallest uncertainties were tumor-lung (on CT) and tumor-mediastinum (on PET-CT and MRI). CONCLUSIONS: Although MRI-based contouring showed overall larger variability than PET-CT, contouring variability depended on the interface type and was not significantly different between modalities, despite the limited observer experience with MRI. Multimodality imaging and combining different imaging characteristics might be the best approach to define the tumor volume most accurately.

Keruakous, A. R., et al. (2014). "The impact of isolated tumor cells on loco-regional recurrence in breast cancer patients treated with breast-conserving treatment or mastectomy without post-mastectomy radiation therapy." Breast Cancer Res Treat **146**(2): 365-370.

To compare the outcome of patients with invasive breast cancer, who had isolated tumor cells (ITC) in sentinel lymph nodes, pN0(i+), to patients with histologically negative nodes, pN0. We retrospectively studied 1,273 patients diagnosed with T1-T3 breast cancer from 1999 to 2009. Patients were divided into 2 populations: 807 patients treated with breast-conserving surgery (BCS) and radiotherapy (RT), 85(10.5 %) with pN0(i+) and 722(89.5 %) with pN0. And the other population had 466 patients treated with mastectomy without post-mastectomy radiation therapy (PMRT), 80(17.2 %) with pN0(i+),and 386(82.8 %)with pN0. All patients underwent sentinel node biopsy, and the presence of ITC was determined. Patients with axillary dissection only or neoadjuvant chemotherapy were excluded. Among the 1,273 patients studied; 87.3 % received adjuvant systemic therapy. Kaplan-Meier, Cox regression, and log-rank statistical tests were used. Median patient age was 55.7 years. Median follow-up was 69.5 months. The 5- and 10-year cumulative incidence of Loco-regional recurrence (LRR) for patients treated with BCS and RT was 1.6 and 3.5 % for 85 pN0(i+) patients, and 2.4 and 5 % for 722 pN0 patients, respectively. For patients treated with mastectomy without PMRT, 5- and 10-year LRR rates were 2.8 and 2.8 % for 80 pN0(i+) patients, and 1.8 and 3 % for 386 pN0 patients, respectively. There were no statistically significant differences in LRR (p = 0.9), distant recurrence (p = 0.3),and overall survival (p = 0.5) among all groups. On multivariate analysis, ITC were not associated with increased risk of LRR, distant recurrence and overall survival. Grade (p = 0.003) and systemic therapy (p = 0.02) were statistically significantly associated with risk of LRR. Sentinel node ITC have no significant impact on LRR, distant recurrence and overall survival in breast cancer patients. Additional treatments such as axillary dissection, chemotherapy, or regional radiation should not be given solely based on the presence of sentinel node ITC.

Khil, M. S., et al. (1997). "Tumor control of locally advanced prostate cancer following combined estramustine, vinblastine, and radiation therapy." Cancer J Sci Am **3**(5): 289-296.
PURPOSE: A prospective phase II study was carried out to determine whether estramustine phosphate (EMP) plus vinblastine (VBL) in combination with radiotherapy (RT) would improve the control of locally advanced prostate cancer. The rationale for combining EMP plus VBL with RT was based on the clinical and radiobiological data that EMP plus VBL acted as an excellent radiation sensitizer in cultured human prostatic carcinoma cells with the property of tissue selectivity. The combined EMP and VBL were well tolerated in the phase II

clinical study of patients with advanced prostate cancer. MATERIALS AND METHODS: Between January 1991 and July 1996, 65 patients, stage T2 (B2) through stage T4 (D1), were entered into the study. Gleason pattern scores ranged from 4 to 10. Pretreatment prostate-specific antigen (PSA) was as follows: < 20 in 21 patients (32%), 20 to 50 in 23 patients (35%), and > 50 in 21 patients (32%). The median age was 70 years (55-83). All patients were treated with megavoltage beam radiation with a total tumor dose of 65 to 70 Gy. Oral EMP 450 mg/m2 daily and VBL 3 mg/m2 weekly were given concomitantly in 46 patients during the 7- to 7 1/2-week course of radiotherapy. RESULTS: All patients showed prompt and complete tumor regression on digital rectal examination at 6 weeks following the completion of treatment. Median follow-up time is 43 months (3-65). PSA fell to an undetectable level by 6 weeks in 56 of 65 patients (86%). For the whole group at 5 years clinical control was 81%, but biochemical control (PSA < 4 ng/mL) was 48%. The likelihood of being free of biochemical relapse at 5 years was a function of initial PSA value (PSA < 20 in 64% of the cases, 21-50 in 60%, and > 50 in 0%). The biochemical-relapse-free survival at 5 years for each stage was T2, 49%; T3, 38%; and T4, 17%. In particular, a group of patients with pretreatment PSA levels of 20 to 50 ng/mL responded quite favorably to the present combined regimen in that only 40% of the patients showed a biochemical failure at 5 years, considering the high level of initial PSA. CONCLUSIONS: The present combined approach is effective in achieving a high rate of tumor control with no disproportionately enhanced side effects. The rapid regression of the tumor nodules and sustained freedom from biochemical relapse suggest excellent long-term tumor control, especially in the group of patients with pretreatment PSA levels of 20 to 50 ng/mL.

Kitamura, K., et al. (2003). "Reduction in acute morbidity using hypofractionated intensity-modulated radiation therapy assisted with a fluoroscopic real-time tumor-tracking system for prostate cancer: preliminary results of a phase I/II study." Cancer J **9**(4): 268-276.
PURPOSE: The positioning of the prostate is improved with the use of the fluoroscopic real-time tumor-tracking radiation therapy system for prostate cancer. The acute radiation reaction and preliminary tumor response of prostate cancer to hypofractionated intensity-modulated radiation therapy assisted with real-time tumor-tracking radiation therapy were investigated in this study. METHODS: Patients were classified into prognostic risk groups on the basis of the presence of the pretreatment prostate-specific antigen, clinical stage, and histologic differentiation. Neoadjuvant hormonal therapy was administered to

patients in the high-risk group for 6 months before radiation therapy commenced. The intensity-modulated radiation therapy employed a segmental multileaf collimator, which generated a field made up of two or more shaped subfields using forward planning. Real-time tumor-tracking radiation therapy was used for the precise positioning of the prostate to minimize geometric uncertainties, while the dose was escalated in increments of 5 Gy from 65 Gy using a daily dose of 2.5 Gy (65 Gy/2.5 Gy), following the dose-escalation rules. Acute and late gastrointestinal and genitourinary morbidities due to radiation therapy were scored according to the toxicity criteria of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer. RESULTS: Thirty-one patients were enrolled in this study between 1998 and 2001. Eighteen patients were classified as being members of the high-risk group. Total dose was escalated, with 65 Gy/2.5 Gy being administered to 12 patients and 70 Gy/2.5 Gy to 19 patients. The median follow-up period was 37 months (range, 30-43 months), and 19 months (range, 10-27 months), for the 65-Gy and 70-Gy arms, respectively. Patients experienced no acute toxicity and grade 1 late gastrointestinal toxicity (8.3%) in the 65-Gy/2.5-Gy arm. Patients in the 70-Gy/2.5-Gy arm experienced grade 1 acute gastrointestinal toxicity (5.3%) and grade 1 and 2 acute genitourinarytoxicities (15.8%). No patients experienced dose-limiting toxicity (defined as a grade 3 or higher acute toxicity) or a grade 2 or higher late complication in this study period. One and two prostate-specific antigen relapses were observed in the 65-Gy and 70-Gy arms, respectively. CONCLUSION: Up to 70 Gy/2.5 Gy, equivalent to 80 Gy with a daily dose of 2.0 Gy, assuming alpha/beta ratio of 1.5, intensity-modulated radiation therapy assisted with real-time tumor-tracking radiation therapy was administered safely with a reasonable biochemical control rate. A further dose-escalation study using this system is justifiable.

Klement, R. J., et al. (2014). "Support vector machine-based prediction of local tumor control after stereotactic body radiation therapy for early-stage non-small cell lung cancer." Int J Radiat Oncol Biol Phys **88**(3): 732-738.
BACKGROUND: Several prognostic factors for local tumor control probability (TCP) after stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC) have been described, but no attempts have been undertaken to explore whether a nonlinear combination of potential factors might synergistically improve the prediction of local control. METHODS AND MATERIALS: We investigated a support vector machine (SVM) for predicting TCP in a cohort of 399 patients treated at 13

German and Austrian institutions. Among 7 potential input features for the SVM we selected those most important on the basis of forward feature selection, thereby evaluating classifier performance by using 10-fold cross-validation and computing the area under the ROC curve (AUC). The final SVM classifier was built by repeating the feature selection 10 times with different splitting of the data for cross-validation and finally choosing only those features that were selected at least 5 out of 10 times. It was compared with a multivariate logistic model that was built by forward feature selection. RESULTS: Local failure occurred in 12% of patients. Biologically effective dose (BED) at the isocenter (BED (ISO)) was the strongest predictor of TCP in the logistic model and also the most frequently selected input feature for the SVM. A bivariate logistic function of BED (ISO) and the pulmonary function indicator forced expiratory volume in 1 second (FEV1) yielded the best description of the data but resulted in a significantly smaller AUC than the final SVM classifier with the input features BED (ISO), age, baseline Karnofsky index, and FEV1 (0.696 +/- 0.040 vs 0.789 +/- 0.001, P<.03). The final SVM resulted in sensitivity and specificity of 67.0% +/- 0.5% and 78.7% +/- 0.3%, respectively. CONCLUSIONS: These results confirm that machine learning techniques like SVMs can be successfully applied to predict treatment outcome after SBRT. Improvements over traditional TCP modeling are expected through a nonlinear combination of multiple features, eventually helping in the task of personalized treatment planning.

Knol, H. P., et al. (1997). "Effect of radiation therapy alone or in combination with surgery and/or chemotherapy on tumor and symptom control of recurrent rectal cancer." Strahlenther Onkol **173**(1): 43-49.
PURPOSE: To define the value of radiotherapy alone or in combination with other treatment modalities in salvage and/or palliation of locally recurrent rectal cancer with or without concomitant distant metastases. PATIENTS AND METHOD: A series of 280 patients, treated between 1975 and 1990 was retrospectively reviewed. The patients were divided into 2 groups: 166 patients had a local recurrence only (group 1), 114 presented with simultaneously distant metastases (group 2). In group 1, 50 patients had only radiotherapy, 20 had radiation in combination with surgery, 68 patients had radiation and chemotherapy, and 28 patients had a combination of all 3 treatment modalities. In group 2 these numbers were 41, 7, 59 and 7, respectively. The median follow-up time was 11 months (1 to 118). RESULTS: The 2- and 5-year survival of group 1 were 33% and 12%. In group 2 the 2-year survival was 9%. The 2- and 5-year

symptom-free survival for both groups were 18%/12% and 4%/0%, respectively. There was no significant difference in survival and symptom-free survival between treatment including concomitant 5-FU or 5-FU once a week and treatment without chemotherapy. In the combined treatments which included surgery there was a longer survival and symptom-free survival. In both groups a subanalysis of the patients who had radiation only showed a dose-response relationship for symptom-free survival. This was not the case for survival. CONCLUSION: In local recurrence of rectal cancer without detectable distant metastases, radiotherapy and/or surgery have value toward survival and symptom-free survival. Further intense efforts in preventing the local recurrence by improving primary treatment are warranted.

Kocher, M. R., et al. (2018). "Pretreatment 18F-Fluorodeoxyglucose Positron Emission Tomography Standardized Uptake Values and Tumor Size in Medically Inoperable Nonsmall Cell Lung Cancer Is Prognostic of Overall 2-Year Survival After Stereotactic Body Radiation Therapy." J Comput Assist Tomogr **42**(1): 146-150.
OBJECTIVE: The aim of this study was to determine prognostic value of tumor size and metabolic activity on survival for patients with early stage nonsmall cell lung cancer receiving stereotactic body radiation therapy. METHODS: We retrospectively evaluated the patients who underwent positron emission tomography-computed tomography scan before stereotactic body radiation therapy treatment. Tumor diameter, tumor volume, maximum standardized uptake value (SUVmax), standardized uptake value (SUV) average, and SUV volume were obtained. Cox regression analyses were performed to determine the associations between tumor characteristics and survival. RESULTS: The patients with large tumors and high SUVmax have worse survival than patients with small tumors and low SUVmax (hazard ratio [HR] = 3.47, P = 0.007). Patients with small tumors and high SUVmax (HR = 1.80; P = 0.24) and large tumors and low SUVmax (HR = 1.55; P = 0.43) had increased risk of death compared with patients with small tumors and low SUVmax. CONCLUSIONS: Both increased tumor size and metabolic activity are associated with increased risk of death. Combining size and metabolic activity together is superior for predicting 2-year survival and identifying patients for whom survival is statistically worse.

Kochetkova, V. A. and L. E. Voronova (1975). "[The effect of radiation therapy on the course of the tumor process in patients with laryngeal cancer]." Vopr Onkol **21**(6): 44-48.

The authors have studied the effect of radiotherapy on immune responsiveness in 36 patients with laryngeal cancer. The kinetics of variations in the skin cover bacterial picture, as well as some indices of nonspecific (anti-infective) humoral immunity (the titre of agglutinines, general bactericidity of blood sera against the proper staphylococci of the skin and the content of staphylococcic antitoxin) were followed up depending on dosage of irradiation. It was found that radiation therapy with the total focal dosage of 2000 rad in 72% of cases contributed to activation of protective forces of the organism; in larger doses (2001-8000 rad) of irradiation the indices of nonspecific immunity in every patient were found to be reduced.

Komatsu, F. and M. Kajiwara (1997). "Comparison of natural killer (NK) sensitivities of two tumor cell lines established from a cancer patient before and after radiation therapy." Clin Immunol Immunopathol **82**(2): 190-196.
Major histocompatibility complex (MHC) class I positive tumor cells are generally resistant to natural killer (NK) cells. In this report, we compared the NK sensitivities of tumor cell lines H41 and H42, which were established from a cancer patient at surgery. H41 was established before radiation therapy and H42 was established after the radiation therapy in 1985. H41 was resistant to NK cells, whereas H42 was NK-sensitive. Both cell lines reacted with W6/32, which is an antibody to the HLA common epitope determinant. However, H42 did not react to anti-HLA-locus-specific antibodies, although H41 reacted to them. When these cell lines were treated with interferon-gamma, H41 showed an increase in HLA-locus-specific antigenicity, whereas H42 did not show such a tendency. This suggests that there may have been interference in the expression of the HLA-locus-specific determinants on H42. Therefore, it was assumed that the NK sensitivity of H42 may be due to depression of an HLA-locus-specific determinant, and this depression may be related to the radiation therapy. The patient recovered from the disease after the radiation therapy and the last surgery. He is now in a tumor-free state. We propose that his recovery may be related to the conversion of the tumor cells from NK-resistant to NK-sensitive.

Konduri, S., et al. (2009). "Tolfenamic acid enhances pancreatic cancer cell and tumor response to radiation therapy by inhibiting survivin protein expression." Mol Cancer Ther **8**(3): 533-542.
Survivin is overexpressed in most human cancers, including pancreatic adenocarcinoma. Expression of survivin is regulated by specificity protein (Sp) proteins and related to resistance to radiation therapy.

Tolfenamic acid induces Sp protein degradation in several cancer cell lines. The purpose of this study is to investigate whether tolfenamic acid inhibits survivin expression and sensitizes pancreatic cancer cells/tumor to radiotherapy. Panc1 and L3.6pl cells have been used to study the effect of radiation on survivin expression and to investigate the efficacy of tolfenamic acid in enhancing the response to radiation therapy. In addition, an orthotopic model for human pancreatic cancer has been used to confirm the efficacy of tolfenamic acid to enhance tumor response to radiation in vivo. Pancreatic cancer cell lines express variable levels of survivin mRNA/protein, which correlate with their radiosensitivity. Radiation increased survivin promoter activity and protein expression in Panc1 and L3.6pl cells and tolfenamic acid inhibited both constitutive and radiation-induced survivin protein expression and enhanced the response of pancreatic cancer cells to radiation therapy. In vivo studies show that tolfenamic acid enhanced the radiation-induced apoptosis associated with decreased survivin expression in tumors and this correlates with the enhanced response of these tumors to the radiation. Thus, tolfenamic acid significantly enhances pancreatic cancer cells/tumor response to radiation therapy. The underlying mechanism includes tolfenamic acid-induced degradation of Sp proteins, which in tumor decreases expression of the Sp-dependent antiapoptotic protein survivin. These preclinical data suggest that tolfenamic acid has the potential to increase the response of pancreatic adenocarcinoma to radiation therapy.

Kuranishi, F. and T. Ohno (2013). "Eradication of breast cancer with bone metastasis by autologous formalin-fixed tumor vaccine (AFTV) combined with palliative radiation therapy and adjuvant chemotherapy: a case report." World J Surg Oncol **11**: 127.

Skeletal metastasis of breast carcinoma is refractory to intensive chemo-radiation therapy and therefore is assumed impossible to cure. Here, we report an advanced case of breast cancer with vertebra-Th7 metastasis that showed complete response to combined treatments with formalin-fixed autologous tumor vaccine (AFTV), palliative radiation therapy with 36 Gy, and adjuvant chemotherapy with standardized CEF (cyclophosphamide, epirubicin, and 5FU), zoledronic acid, and aromatase inhibitors following mastectomy for the breast tumor. The patient has been disease-free for more than 4 years after the mammary surgery and remains well with no evidence of metastasis or local recurrence. Thus, a combination of AFTV, palliative radiation therapy, and adjuvant chemotherapy may be an effective treatment for this devastating disease.

Leonard, C., et al. (1995). "Are axillary recurrence and overall survival affected by axillary extranodal tumor extension in breast cancer? Implications for radiation therapy." J Clin Oncol **13**(1): 47-53.

PURPOSE: To determine the overall survival and local recurrence significance of axillary lymph node extranodal tumor extension (ETE) and whether axillary/chest-wall irradiation influenced any of these outcomes. MATERIALS AND METHODS: The records of 81 breast cancer patients treated with radical or modified radical mastectomy at a single surgical practice were eligible for study. Thirty-four patients had ETE: 17 with focal ETE (< 10 x high-power field) and 17 with extensive ETE (> 10 x high-power field). RESULTS: With a median follow-up duration of 92 months, only two patients had an axillary recurrence (2%): one had focal ETE and one had no ETE. Neither of these patients received axillary radiation therapy. Overall survival and recurrence-free survival were significantly decreased with ETE in patients whether axillary radiation therapy had been administered or not. Analysis showed that the age of the patient correlated significantly with extensive ETE (P =.04) and that the number of positive lymph nodes (< or = three v > three) correlated significantly with ETE (whether focal or extensive) (P =.0001). A multivariate analysis of extranodal tumor extension and number of positive lymph nodes showed that ETE was associated with decreased survival (P =.05), although to a lesser degree than number of positive lymph nodes (P =.003). CONCLUSION: These results show that ETE is associated with decreased survival and increased recurrence rates regardless of the extent of the radiation therapy field. Also, ETE does not necessarily indicate a significantly increased incidence of axillary recurrence. Therefore, axillary irradiation based on this pathologic finding may not be indicated.

Levegrun, S., et al. (2001). "Fitting tumor control probability models to biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer: pitfalls in deducing radiobiologic parameters for tumors from clinical data." Int J Radiat Oncol Biol Phys **51**(4): 1064-1080.

PURPOSE: The goal of tumor control probability (TCP) models is to predict local control for inhomogeneous dose distributions. All existing fits of TCP models to clinical data have utilized summaries of dose distributions (e.g., prescription dose). Ideally, model fits should be based on dose distributions in the tumor, but usually only dose-volume histograms (DVH) of the planning target volume (PTV) are available. We fit TCP models to biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer using either a dose distribution

66

summary or the full DVH in the PTV. We discuss differences in the radiobiologic parameters and dose-response curves and demonstrate pitfalls in interpreting the results. METHODS AND MATERIAL: Two mechanistic TCP models were fit with a maximum likelihood technique to biopsy outcome from 103 prostate patients treated at Memorial Sloan-Kettering Cancer Center. Fits were performed separately for different patient subgroups defined by tumor-related prognostic factors. Fits were based both on full DVHs, denoted TCP (DVH (calc)), and, alternatively, assuming a homogeneous PTV dose given by the mean dose (Dmean) of each DVH, denoted TCP (Dmean (calc)). Dose distributions for these patients were very homogeneous with any cold spots located on the periphery of the PTV. These cold spots were uncorrelated with biopsy outcome, likely because the low-dose regions may not contain tumor cells. Therefore, fits of TCP models that are potentially sensitive to cold spots (e.g., TCP (DVH (calc))) likely give biologic parameters that diminish this sensitivity. In light of this, we examined differences in fitted clonogenic cell number, N (C), or density, rho (C), surviving fraction after 2 Gy, SF (2), or radiosensitivity, alpha, and their standard deviations in the population, sigma (SF (2)) and sigma (alpha), resulting from fits based on TCP (DVH (calc)) and TCP (Dmean (calc)). Dose-response curves for homogeneous irradiation (characterized by TCD (50), the dose for a TCP of 50%) and differences in TCP predictions calculated from the DVH using alternatively derived parameters were evaluated. RESULTS: Fits of TCP (Dmean (calc)) are better (i.e., have larger likelihood) than fits of TCP (DVH (calc)). For TCP (Dmean (calc)) fits, matching values of SF (2) and sigma (SF (2)) (or alpha and sigma (alpha)) exist for all N (C) (rho (C)) above a threshold that give fits of equal quality, with no maximum in likelihood. In contrast, TCP (DVH (calc)) fits have maximum likelihood for high SF (2) (low alpha) values that minimize effects of cold spots. Consequently, small N (C) (rho (C)) values are obtained to match the observed control rate. For example, for patients in low-, intermediate-, and high-risk groups, optimum values of SF (2) and N (C) are 0.771 and 3.3 x 10(3), 0.736 and 2.2 x 10(4), and 0.776 and 1.0 x 10(4), respectively. The TCD (50) of dose-response curves for intermediate-risk patients is 2.6 Gy lower using TCP (DVH (calc)) parameters (TCD (50) = 67.8 Gy) than for TCP (Dmean (calc)) parameters (TCD (50) = 70.4 Gy). TCP predictions calculated from the DVH using risk group-dependent TCP (Dmean (calc)) parameters are up to 53% lower than corresponding calculations with TCP (DVH (calc)) parameters. CONCLUSION: For our data, TCP parameters derived from DVHs likely do not reflect true radiobiologic

parameters in the tumor, but are a consequence of the reduced importance of low-dose regions at the periphery of the PTV. Deriving radiobiologic parameters from TCP (Dmean (calc)) fits is not possible unless one parameter is already known. TCP predictions using TCP (DVH (calc)) and TCP (Dmean (calc)) parameters may differ substantially, requiring consistency in the derivation and application of model parameters. The proper derivation of radiobiologic parameters from clinical data requires both substantial dose inhomogeneities and understanding of how these coincide with tumor location.

Levegrun, S., et al. (2000). "Analysis of biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer using dose-distribution variables and tumor control probability models." Int J Radiat Oncol Biol Phys **47**(5): 1245-1260.
PURPOSE: To investigate tumor control following three-dimensional conformal radiation therapy (3D-CRT) of prostate cancer and to identify dose-distribution variables that correlate with local control assessed through posttreatment prostate biopsies. METHODS AND MATERIAL: Data from 132 patients, treated at Memorial Sloan-Kettering Cancer Center (MSKCC), who had a prostate biopsy 2.5 years or more after 3D-CRT for T1c-T3 prostate cancer with prescription doses of 64.8-81 Gy were analyzed. Variables derived from the dose distribution in the PTV included: minimum dose (Dmin), maximum dose (Dmax), mean dose (Dmean), dose to n% of the PTV (Dn), where n = 1%,...,99%. The concept of the equivalent uniform dose (EUD) was evaluated for different values of the surviving fraction at 2 Gy (SF (2)). Four tumor control probability (TCP) models (one phenomenologic model using a logistic function and three Poisson cell kill models) were investigated using two sets of input parameters, one for low and one for high T-stage tumors. Application of both sets to all patients was also investigated. In addition, several tumor-related prognostic variables were examined (including T-stage, Gleason score). Univariate and multivariate logistic regression analyses were performed. The ability of the logistic regression models (univariate and multivariate) to predict the biopsy result correctly was tested by performing cross-validation analyses and evaluating the results in terms of receiver operating characteristic (ROC) curves. RESULTS: In univariate analysis, prescription dose (Dprescr), Dmax, Dmean, dose to n% of the PTV with n of 70% or less correlate with outcome (p < 0.01). The area under the ROC curve for Dmean is 0.64. In contrast, Dmin (p = 0.6), D98 (p = 0.2) or D95 (p = 0.1) are not significantly correlated with outcome. The results for EUD depend on the input parameter SF (2): EUD correlates significantly

with outcome for SF (2) of 0.4 or more, but not for lower SF (2) values. Using either of the two input parameters sets, all TCP models correlate with outcome (p < 0.05; ROC areas 0.60-0.62). Using T-stage dependent input parameters, the correlation is improved (logistic function: p < 0.01, ROC area 0.67, Poisson models: p < 0.01, ROC areas 0.64-0.66). In comparison, the ROC area is 0.68 for the combination of Dmean and T-stage. After multivariate analysis, a model based on TCP, D20 and Gleason score is the best overall model (ROC area 0.73). However, an alternative model based on Dmean, Gleason score, and T-stage is competitive (ROC area 0.70). CONCLUSION: Biopsy outcome after 3D-CRT of prostate cancer at MSKCC is not correlated with Dmin in the PTV and appears to be insensitive to cold spots in the dose distribution. This observation likely reflects the fact that much of the PTV, especially at the periphery, may not contain viable tumor cells and that the treatment margins were sufficiently large. Therefore, the predictive power of all variables which are sensitive to cold spots, like TCPs with Poisson models and EUD for low SF (2), is limited because the low dose region may not coincide with the tumor location. Instead, for MSKCC prostate cancer patients with their standardized CTV definition, substantial target motion and small dose inhomogeneities, Dmean (or any variable that downplays the effect of cold spots) is a very good predictor of biopsy outcome. While our findings may indicate a general problem in the application of current TCP models to clinical data, these conclusions should not be extrapolated to other disease sites without careful analysis.

Levendag, P. C., et al. (2006). "Interstitial radiation therapy for early-stage nasal vestibule cancer: a continuing quest for optimal tumor control and cosmesis." Int J Radiat Oncol Biol Phys **66**(1): 160-169.
INTRODUCTION: This article reports on the effectiveness, cosmetic outcome, and costs of interstitial high-dose-rate (HDR) brachytherapy for early-stage cancer of the nasal vestibule (NV) proper and/or columella high-dose-rate (HDR). METHODS AND MATERIALS: Tumor control, survival, cosmetic outcome, functional results, and costs were established in 64 T1/T2N0 nasal vestibule cancers treated from 1991-2005 by fractionated interstitial radiation therapy (IRT) only. Total dose is 44 Gy: 2 fractions of 3 Gy per day, 6-hour interval, first and last fraction 4 Gy. Cosmesis is noted in the chart by the medical doctor during follow-up, by the patient (visual analog scale), and by a panel. Finally, full hospital costs are computed. RESULTS: A local relapse-free survival rate of 92% at 5 years was obtained. Four local failures were observed; all four patients were

salvaged. The neck was not treated electively; no neck recurrence in follow-up was seen. Excellent cosmetic and functional results were observed. With 10 days admission for full treatment, hospital costs amounted to euro5772 (7044 US dollars). CONCLUSION: Excellent tumor control, cosmesis, and function of nasal airway passage can be achieved when HDR-IRT for T1/T2N0 NV cancers is used. For the more advanced cancers (Wang classification: T3 tumor stage), we elect to treat by local excision followed by a reconstructive procedure. The costs, admission to hospital inclusive, for treatment by HDR-IRT amounts to euro5772 (7044 US dollars). This contrasts substantially with the full hospital costs when NV cancers are treated by plastic reconstructive surgery, being on average threefold as expensive.

Lowes, L. E., et al. (2015). "The significance of circulating tumor cells in prostate cancer patients undergoing adjuvant or salvage radiation therapy." Prostate Cancer Prostatic Dis **18**(4): 358-364.
BACKGROUND: Following radical prostatectomy, success of adjuvant and salvage radiation therapy (RT) is dependent on the absence of micrometastatic disease. However, reliable prognostic/predictive factors for determining this are lacking. Therefore, novel biomarkers are needed to assist with clinical decision-making in this setting. Enumeration of circulating tumor cells (CTCs) using the regulatory-approved CellSearch System (CSS) is prognostic in metastatic prostate cancer. We hypothesize that CTCs may also be prognostic in the post-prostatectomy setting. METHODS: Patient blood samples (n=55) were processed on the CSS to enumerate CTCs at 0, 6, 12 and 24 months after completion of RT. CTC values were correlated with predictive/prognostic factors and progression-free survival. RESULTS: CTC status (presence/absence) correlated significantly with positive margins (increased likelihood of CTC (neg) disease; P=0.032), and trended toward significance with the presence of seminal vesicle invasion (CTC (pos); P=0.113) and extracapsular extension (CTC (neg); P=0.116). Although there was a trend toward a decreased time to biochemical failure (BCF) in baseline CTC-positive patients (n=9), this trend was not significant (hazard ratio (HR)=0.3505; P=0.166). However, CTC-positive status at any point (n=16) predicted for time to BCF (HR=0.2868; P=0.0437). CONCLUSIONS: One caveat of this study is the small sample size utilized (n=55) and the low number of patients with CTC-positive disease (n=16). However, our results suggest that CTCs may be indicative of disseminated disease and assessment of CTCs during RT may be helpful in clinical decision-making to determine, which patients

may benefit from RT versus those who may benefit more from systemic treatments.

Matsuda, T., et al. (2013). "Impact of adjuvant radiation therapy for microscopic residual tumor after resection of extrahepatic bile duct cancer." Am J Clin Oncol **36**(5): 461-465.

OBJECTIVES: The effect of adjuvant radiation therapy (RT) in extrahepatic bile duct (EHBD) cancer patients with microscopic-positive resection margins (R1 resection) is still controversial. METHODS: Between January 2000 and March 2010, 52 patients with EHBD cancer underwent surgery at our institution, of whom 36 were subjected to a retrospective analysis. Eleven patients received adjuvant RT after resection [surgery (S)+RT group], which included 9 patients with R1 resection and 2 with para-aortic lymph node metastasis. Their oncological outcomes were analyzed and compared with those of the 25 patients with R0 resection who did not receive adjuvant RT (S group). RESULTS: Patients in the S+RT group had significantly more advanced disease than those in the S group. However, there was no significant difference in disease-free survival or overall survival between the 2 groups. Median survival times for the S+RT and the S groups were 44 and 47 months, respectively, whereas the 5-year survival rates were 38.9% and 46%, respectively (P=0.707). Locoregional recurrence was less frequent in the S+RT group as compared with the S group, but the incidence of distant metastasis was unaffected by the adjuvant RT. CONCLUSIONS: Our results support the beneficial effect of adjuvant RT in EHBD cancer patients with R1 resection. This effect seems to result from an improved control of the locoregional tumor by adjuvant RT.

Mayr, N. A., et al. (2010). "Longitudinal changes in tumor perfusion pattern during the radiation therapy course and its clinical impact in cervical cancer." Int J Radiat Oncol Biol Phys **77**(2): 502-508.

PURPOSE: To study the temporal changes of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) perfusion patterns during the radiation therapy (RT) course and their influence on local control and survival in cervical cancer. METHODS AND MATERIALS: DCE-MRI was performed in 98 patients with Stage IB (2)-IVA cervical cancer before RT (pre-RT) and during early RT (20-25 Gy) and mid-RT (45-50 Gy). Signal intensity (SI) from the DCE-MRI time-SI curve was derived for each tumor voxel. The poorly perfused low-DCE tumor subregions were quantified as lower 10th percentiles of SI (SI10). Local control, disease-specific survival, and overall survival were correlated with DCE parameters at pre-RT, early RT, and mid-

RT. Median follow-up was 4.9 (range, 0.2-9.0) years. RESULTS: Patients (16/98) with initial pre-RT high DCE (SI10 >or=2.1) had 100% 5-year local control, 81% disease-specific survival, and 81% overall survival, compared with only 79%, 61%, and 55%, respectively, in patients with pre-RT low DCE. Conversion from pre-RT low DCE to high DCE in early RT (28/82 patients) was associated with higher local control, disease-specific survival, and overall survival (93%, 74%, and 67%, respectively). In comparison with all other groups, outcome was worst in patients with persistently low DCE from pre-RT throughout the mid-RT phase (66%, 44%, and 43%; p = 0.003, 0.003, and 0.020; respectively). CONCLUSION: Longitudinal tumor perfusion changes during RT correlate with treatment outcome. Persistently low perfusion in pre-RT, early RT, and mid-RT indicates a high risk of treatment failure, whereas outcome is favorable in patients with initially high perfusion or subsequent improvements of initially low perfusion. These findings likely reflect reoxygenation and may have potential for noninvasive monitoring of intra-treatment radio-responsiveness and for guiding adaptive therapy.

Miller, J. A., et al. (2017). "The impact of tumor biology on survival and response to radiation therapy among patients with non-small cell lung cancer brain metastases." Pract Radiat Oncol **7**(4): e263-e273.

PURPOSE: To investigate the natural history and response to radiation therapy among ALK-rearranged, EGFR-mutated, wild-type adenocarcinoma, and squamous cell non-small cell lung cancer (NSCLC) brain metastases. METHODS AND MATERIALS: Patients with NSCLC brain metastasis diagnosed from 1989 through 2014 at a single tertiary-care institution were included. The primary outcome was overall survival, whereas secondary outcomes included local failure, distant intracranial failure, and radiation necrosis. Cox proportional hazards regression was used to model overall survival; multivariate competing risks regression was used to model secondary outcomes. RESULTS: Within the study period, 1920 patients presented with 6312 brain metastases. Squamous histology was associated with poorer median survival compared with adenocarcinomas (5.4 vs 8.8 months, P <.01). Median survival was greatest among ALK+ patients (49.2 months), followed by EGFR+ (20.3 months), and wild-type adenocarcinomas (10.0 months, P <.01). Treatment with estimated glomerular filtration rate inhibitors (hazard ratio [HR], 0.66; P <.01) and vascular endothelial growth factor antibodies (HR, 0.65; P <.01) increased survival independent of mutational status. Among 2056 lesions treated with stereotactic radiosurgery, the 12-month cumulative incidence of

local failure was significantly greater among squamous cell carcinomas relative to adenocarcinomas (15% vs 10%, HR, 1.26; P =.04). Patients with ALK+ metastases experienced higher rates of local failure (10%; HR, 2.00; P =.05), distant failure (39%; HR, 2.94; P <.01), and radiation necrosis (18%; HR, 5.77; P <.01), whereas EGFR+ patients experienced the lowest rates of local failure (5%; HR, 0.46; P =.04) and distant failure (3%; HR, 0.13; P =.04). CONCLUSIONS: Advances in precision medicine have increased survival among select patients with NSCLC. In the present investigation, ALK+ and EGFR+ status were associated with improved survival. However, patients with ALK+ metastases have poor intracranial control relative to EGFR+ metastases, possibly because of limited intracranial penetration of crizotinib compared with estimated glomerular filtration rate inhibitors. Future investigations are warranted to determine the optimal management of ALK+ brain metastases with the introduction of second-generation ALK inhibitors.

Miller, T. R. and P. W. Grigsby (2002). "Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy." Int J Radiat Oncol Biol Phys **53**(2): 353-359.
PURPOSE: This study evaluated the usefulness of tumor volume measurement with positron emission tomography (PET) in patients with advanced cervical cancer treated by radiation therapy. METHODS AND MATERIALS: Fifty-one patients underwent PET before treatment. Primary tumor volume was determined, and volume, FIGO stage, and presence of lymph nodes on the PET study were compared to progression-free survival (PFS) and overall survival (OS). RESULTS: Tumor volume, lymph node disease, and stage were predictive of PFS, whereas volume and lymph node involvement predicted OS. Lymph node status did not correlate with volume. Dividing patients according to whether the tumor volume was more or less than 60 cm (3) predicted PFS and OS. Separation of patients with tumor volumes <or=60 cm (3) and no lymph node disease vs. any other combination was strongly predictive of PFS and OS. CONCLUSIONS: The following conclusions were drawn regarding patients with advanced cervical cancer treated with radiation therapy: (1) Tumor volume can be accurately measured by PET; (2) Tumor volume separates patients with a good prognosis from those with a poorer prognosis; (3) A subset of patients with relatively small tumors and no lymph node involvement does remarkably well; (4) Tumor volume does not correlate with the presence of lymph node disease.

Milosevic, M. F., et al. (2016). "Sorafenib Increases Tumor Hypoxia in Cervical Cancer Patients Treated With Radiation Therapy: Results of a Phase 1 Clinical Study." Int J Radiat Oncol Biol Phys **94**(1): 111-117.
PURPOSE: Preclinical studies have shown that angiogenesis inhibition can improve response to radiation therapy (RT). The purpose of this phase 1 study was to examine the angiogenesis inhibitor sorafenib in patients with cervical cancer receiving radical RT and concurrent cisplatin (RTCT). METHODS AND MATERIALS: Thirteen patients with stage IB to IIIB cervical cancer participated. Sorafenib was administered daily for 7 days before the start of standard RTCT in patients with early-stage, low-risk disease and also during RTCT in patients with high-risk disease. Biomarkers of tumor vascularity, perfusion, and hypoxia were measured at baseline and again after 7 days of sorafenib alone before the start of RTCT. The median follow-up time was 4.5 years. RESULTS: Initial complete response was seen in 12 patients. One patient died without achieving disease control, and 4 experienced recurrent disease. One patient with an extensive, infiltrative tumor experienced pelvic fistulas during treatment. The 4-year actuarial survival was 85%. Late grade 3 gastrointestinal toxicity developed in 4 patients. Sorafenib alone produced a reduction in tumor perfusion/permeability and an increase in hypoxia, which resulted in early closure of the study. CONCLUSIONS: Sorafenib increased tumor hypoxia, raising concern that it might impair rather than improve disease control when added to RTCT.

Muijs, C., et al. (2014). "Residual tumor after neoadjuvant chemoradiation outside the radiation therapy target volume: a new prognostic factor for survival in esophageal cancer." Int J Radiat Oncol Biol Phys **88**(4): 845-852.
PURPOSE/OBJECTIVE (S): The aim of this study was to analyze the accuracy of gross tumor volume (GTV) delineation and clinical target volume (CTV) margins for neoadjuvant chemoradiation therapy (neo-CRT) in esophageal carcinoma at pathologic examination and to determine the impact on survival. METHODS AND MATERIALS: The study population consisted of 63 esophageal cancer patients treated with neo-CRT. GTV and CTV borders were demarcated in situ during surgery on the esophagus, using anatomical reference points to provide accurate information regarding tumor location at pathologic evaluation. To identify prognostic factors for disease-free survival (DFS) and overall survival (OS), a Cox regression analysis was performed. RESULTS: After resection, macroscopic residual tumor was found outside the GTV in 7 patients (11%). Microscopic

residual tumor was located outside the CTV in 9 patients (14%). The median follow-up was 15.6 months. With multivariate analysis, only microscopic tumor outside the CTV (hazard ratio [HR], 4.96; 95% confidence interval [CI], 1.03-15.36), and perineural growth (HR, 5.77; 95% CI, 1.27-26.13) were identified as independent prognostic factors for OS. The 1-year OS was 20% for patients with tumor outside the CTV and 86% for those without (P<.01). For DFS, microscopic tumor outside the CTV (HR, 5.92; 95% CI, 1.89-18.54) and ypN+ (HR, 3.36; 95% CI, 1.33-8.48) were identified as independent adverse prognostic factors. The 1-year DFS was 23% versus 77% for patients with or without tumor outside the CTV (P<.01). CONCLUSIONS: Microscopic tumor outside the CTV is associated with markedly worse OS after neo-CRT. This may either stress the importance of accurate tumor delineation or reflect aggressive tumor behavior requiring new adjuvant treatment modalities.

Nishibuchi, I., et al. (2014). "Time-adjusted internal target volume: a novel approach focusing on heterogeneity of tumor motion based on 4-dimensional computed tomography imaging for radiation therapy planning of lung cancer." Int J Radiat Oncol Biol Phys **89**(5): 1129-1137.
PURPOSE: To consider nonuniform tumor motion within the internal target volume (ITV) by defining time-adjusted ITV (TTV), a volume designed to include heterogeneity of tumor existence on the basis of 4-dimensional computed tomography (4D-CT). METHODS AND MATERIALS: We evaluated 30 lung cancer patients. Breath-hold CT (BH-CT) and free-breathing 4D-CT scans were acquired for each patient. The tumors were manually delineated using a lung CT window setting (window, 1600 HU; level, -300 HU). Tumor in BH-CT images was defined as gross tumor volume (GTV), and the sum of tumors in 4D-CT images was defined as ITV-4D. The TTV images were generated from the 4D-CT datasets, and the tumor existence probability within ITV-4D was calculated. We calculated the TTV80 value, which is the percentage of the volume with a tumor existence probability that exceeded 80% on ITV-4D. Several factors that affected the TTV80 value, such as the ITV-4D/GTV ratio or tumor centroid deviation, were evaluated. RESULTS: Time-adjusted ITV images were acquired for all patients, and tumor respiratory motion heterogeneity was visualized. The median (range) ITV-4D/GTV ratio and median tumor centroid deviation were 1.6 (1.0-4.1) and 6.3 mm (0.1-30.3 mm), respectively. The median TTV80 value was 43.3% (2.9-98.7%). Strong correlations were observed between the TTV80 value and the ITV-4D/GTV ratio (R=-0.71) and tumor centroid deviation (R=-0.72). The TTV images revealed the tumor motion pattern

features within ITV. CONCLUSIONS: The TTV images reflected nonuniform tumor motion, and they revealed the tumor motion pattern features, suggesting that the TTV concept may facilitate various aspects of radiation therapy planning of lung cancer while incorporating respiratory motion in the future.

Nougaret, S., et al. (2012). "MR volumetric measurement of low rectal cancer helps predict tumor response and outcome after combined chemotherapy and radiation therapy." Radiology **263**(2): 409-418.
PURPOSE: To retrospectively determine whether magnetic resonance (MR) volumetry of rectal cancer is a reproducible method for predicting disease-free survival (DFS) in patients with locally advanced low or midrectal tumors who undergo combined chemotherapy and radiation therapy (CRT) before total mesorectal excision. MATERIALS AND METHODS: The institutional review board does not require approval for the use of patient data obtained for an observational retrospective study. Fifty-eight patients were included in the study; 42 patients had low-lying tumors. Two radiologists independently measured tumor volumes before and after CRT with use of semiautomated software. The radiologists were blinded to the clinical information for each patient. The tumor volume reduction ratio, circumferential resection margin, T stage, and occurrence of downstaging were compared with the histopathologic response and DFS. The threshold of tumor volume reduction for predicting DFS was assessed with receiver operating characteristic curve analysis. DFS was estimated with the Kaplan-Meier method and compared between groups with the log-rank test. RESULTS: The interobserver correlation coefficient between the two radiologists was 0.87 (95% confidence interval [CI]: 0.76, 0.93) for pre-CRT volumetry and 0.81 (95% CI: 0.74, 0.90) for post-CRT volumetry. A tumor volume reduction of at least 70% was significantly associated with good histologic regression (tumor regression grade [TRG], 3 or 4) (P <.0001) compared with a volume reduction rate of less than 70%. DFS was studied in 51 patients. The mean follow-up of survivors at the time of analysis was 52 months +/- 20 (standard deviation). Patients with a volume reduction ratio of at least 70% had a higher DFS (P <.0001). Tumor volume reduction was an independent prognostic parameter in multivariate analysis for DFS (P =.003; 95% CI: 0.01, 0.4). CONCLUSION: The results demonstrate that volumetric measurements are reliable markers of rectal cancer prognosis, enabling the prediction of DFS and TRG. The cutoff of 70% is an easy parameter to use as a surrogate for clinical response to predict both TRG and outcome.

Ohri, N., et al. (2018). "Stereotactic body radiation therapy for stage I non-small cell lung cancer: The importance of treatment planning algorithm and evaluation of a tumor control probability model." Pract Radiat Oncol **8**(2): e33-e39.

BACKGROUND: Stereotactic body radiation therapy (SBRT) is increasingly used to treat early-stage non-small cell lung cancer (NSCLC). A previous report introduced the term size-adjusted biologically effective dose (sBED), which accounts for tumor diameter and biologically effective dose (BED) and may be used to predict the likelihood of local control following SBRT. Here we seek to replicate those findings using a separate dataset. METHODS AND MATERIALS: We queried the RSSearch Patient Registry for patients treated with SBRT for stage I NSCLC. Kaplan-Meier survival curves, log-rank testing, and Cox proportional hazards modeling were used to evaluate tumor diameter, BED, and treatment planning algorithm as predictors of local control. sBED was defined as BED minus 10 times the tumor diameter (in centimeters). Tumor control probability (TCP) modeling was performed to characterize the relationship between sBED and the likelihood of local control 2 years after SBRT. RESULTS: A total of 928 patients met inclusion criteria. Median BED was 115.5 Gy, and 59% of patients had T1 tumors. Local control rates following treatments planned using a pencil beam algorithm were inferior to those observed following treatments planned using a Monte Carlo algorithm (89% vs 96% at 2 years, log-rank P =.022). In a multivariable Cox model adjusted for tumor diameter and BED, the use of a pencil beam planning algorithm was associated with increased risk of local failure (hazard ratio, 2.39; 95% confidence interval, 1.08-5.29; P =.032). TCP modeling, restricted to patients treated using a Monte Carlo algorithm, demonstrated that sBED values of 60, 80, and 100 Gy yield predicted TCP rates of 91%, 95%, and 97%, respectively. CONCLUSIONS: Using a large, multi-institutional database, we found a strong association between treatment planning algorithm and local control rates following SBRT for early-stage NSCLC. sBED is a useful tool for predicting the likelihood of local control following SBRT in this setting.

Olberg, S., et al. (2018). "Optimization of treatment planning workflow and tumor coverage during daily adaptive magnetic resonance image guided radiation therapy (MR-IGRT) of pancreatic cancer." Radiat Oncol **13**(1): 51.

BACKGROUND: To simplify the adaptive treatment planning workflow while achieving the optimal tumor-dose coverage in pancreatic cancer patients undergoing daily adaptive magnetic resonance image guided radiation therapy (MR-IGRT).

METHODS: In daily adaptive MR-IGRT, the plan objective function constructed during simulation is used for plan re-optimization throughout the course of treatment. In this study, we have constructed the initial objective functions using two methods for 16 pancreatic cancer patients treated with the ViewRay MR-IGRT system: 1) the conventional method that handles the stomach, duodenum, small bowel, and large bowel as separate organs at risk (OARs) and 2) the OAR grouping method. Using OAR grouping, a combined OAR structure that encompasses the portions of these four primary OARs within 3 cm of the planning target volume (PTV) is created. OAR grouping simulation plans were optimized such that the target coverage was comparable to the clinical simulation plan constructed in the conventional manner. In both cases, the initial objective function was then applied to each successive treatment fraction and the plan was re-optimized based on the patient's daily anatomy. OAR grouping plans were compared to conventional plans at each fraction in terms of coverage of the PTV and the optimized PTV (PTV OPT), which is the result of the subtraction of overlapping OAR volumes with an additional margin from the PTV. RESULTS: Plan performance was enhanced across a majority of fractions using OAR grouping. The percentage of the volume of the PTV covered by 95% of the prescribed dose (D95) was improved by an average of 3.87 +/- 4.29% while D95 coverage of the PTV OPT increased by 3.98 +/- 4.97%. Finally, D100 coverage of the PTV demonstrated an average increase of 6.47 +/- 7.16% and a maximum improvement of 20.19%. CONCLUSIONS: In this study, our proposed OAR grouping plans generally outperformed conventional plans, especially when the conventional simulation plan favored or disregarded an OAR through the assignment of distinct weighting parameters relative to the other critical structures. OAR grouping simplifies the MR-IGRT adaptive treatment planning workflow at simulation while demonstrating improved coverage compared to delivered pancreatic cancer treatment plans in daily adaptive radiation therapy.

Parekh, A., et al. (2013). "Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer." Gastrointest Cancer Res **6**(5-6): 137-143.

BACKGROUND: Preoperative chemoradiotherapy (preopCRT) for locally advanced rectal cancer is associated with grade 3 or higher acute gastrointestinal (GI) toxicity. This study was conducted to determine whether intensity-modulated radiation therapy (IMRT) significantly reduces acute GI toxicity, compared to 3-dimensional conformal RT (3D-CRT) in preopCRT for rectal cancer. METHODS:

A retrospective analysis was conducted of 48 patients treated between January 2002 and August 2010 with preopCRT for rectal cancer. 3D-CRT or IMRT was administered at a planned dose of 45-50.4 Gy to patients positioned prone on a bowel-displacement device. Data regarding patient and tumor characteristics, treatment, acute toxicity, and tumor response were collected. Comparisons of acute toxicity and treatment response between 3D-CRT and IMRT were performed with the Chi-square or Fisher's exact test. RESULTS: There were no significant differences in radiation dose, median age, race, gender, stage, type of concurrent chemotherapy, pathologic complete response (pCR), or type of surgery (lower anterior or abdominal perineal resection) between 3D-CRT and IMRT. There was a significant reduction in grade 2 or higher GI toxicity (3D-CRT, 60.7%; IMRT, 30%; P =.036) and grade 2 or higher diarrhea (3D-CRT, 42.8%; IMRT, 10%; P =.014). Two patients who underwent 3D-CRT required a treatment break (grade 3 diarrhea and grade 3 dehydration). Radiation duration was significantly less (IMRT, 35 days; 3D-CRT, 39 days; P </=.0001). pCR rates were 16.7% for 3D-CRT and 21.4% for IMRT (nonsignificant [NS]); pCR+microscopic residual rates were 57.1% for IMRT and 27.8% for 3D-CRT (P =.093). CONCLUSION: Maximal bowel displacement with IMRT yields favorable acute GI toxicity and pathologic downstaging profiles, as compared to 3D-CRT in preoperative CRT for rectal cancer and warrants further prospective investigation.

Park, M. J., et al. (2011). "Locally advanced rectal cancer: added value of diffusion-weighted MR imaging for predicting tumor clearance of the mesorectal fascia after neoadjuvant chemotherapy and radiation therapy." Radiology 260(3): 771-780.

PURPOSE: To evaluate the added value of diffusion-weighted (DW) imaging in combination with T2-weighted magnetic resonance (MR) imaging compared with T2-weighted imaging alone for predicting tumor clearance of the mesorectal fascia (MRF) after neoadjuvant chemotherapy and radiation therapy (CRT) in patients with locally advanced rectal cancer. MATERIALS AND METHODS: This retrospective study was approved by the institutional review board, and informed consent was waived. Forty-five patients with rectal cancer with clinically suspected MRF invasion who underwent neoadjuvant CRT and subsequent surgery were enrolled. All patients underwent pre- and post-CRT 3.0-T rectal MR imaging with DW imaging. Two observers independently reviewed a set of T2-weighted images and a combined set of T2-weighted and DW images and rated them by using a five-point scale. Diagnostic performance was evaluated for each observer with

receiver operating characteristic (ROC) curve analysis. Accuracy, sensitivity, specificity, positive predictive value, and negative predictive value (NPV) were assessed. The standard of reference was histopathologic findings in the surgical specimen. Pairwise comparison of the ROC curves was used to compare diagnostic performance between the two image sets; the McNemar test was used to compare accuracy, sensitivity, and specificity. RESULTS: The diagnostic performance (area under the ROC curve [A (z)]) with respect to MRF tumor clearance of both observers improved significantly after additional review of DW images: A (z) improved from 0.770 to 0.918 (P =.017) for observer 1 and from 0.847 to 0.960 (P =.026) for observer 2. The diagnostic accuracy of DW combined with T2-weighted imaging (observer 1, 89% [40 of 45]; observer 2, 93% [42 of 45]), sensitivity (observer 1, 94% [31 of 33]; observer 2, 97% [32 of 33]) and NPV (observer 1, 82% [nine of 11]; observer 2, 91% [10 of 11]) were significantly higher than those of T2-weighted imaging alone (accuracy: observer 1, 40% [18 of 45], P <.001; observer 2, 69% [31 of 45], P =.022; sensitivity: observer 1, 21% [seven of 33], P <.001; observer 2, 67% [22 of 33], P =.002; NPV: observer 1, 30% [11 of 37], P =.013; observer 2, 45% [nine of 20], P =.025). Interobserver agreement of confidence levels was fair for T2-weighted imaging alone (kappa = 0.212) but was excellent for the combined set of DW and T2-weighted images (kappa = 0.880). CONCLUSION: Adding DW imaging to T2-weighted imaging can improve the prediction of tumor clearance in the MRF after neoadjuvant CRT compared with T2-weighted imaging alone in patients with locally advanced rectal cancer.

Pezner, R. D., et al. (1988). "To boost or not to boost: decreasing radiation therapy in conservative breast cancer treatment when "inked" tumor resection margins are pathologically free of cancer." Int J Radiat Oncol Biol Phys 14(5): 873-877.

A retrospective study was performed to compare local treatment approaches for 108 treated breasts in 105 patients with Stage I or II breast cancer. Six cases with intraductal carcinoma have shown no evidence of recurrence. The other 102 cases had invasive cancer. In 54 treated breasts in 53 patients, the treatment approach involved surgical resection of the primary tumor, pathological determination of tumor-free "inked" specimen margins and 5000 cGy to the whole breast. Local radiation therapy (RT) boosts to the primary site were not given. This approach produced a 100% local control rate (mean follow-up of 38 months). In 28 treated breasts in 27 patients, the treatment approach involved tumor excision without evaluation of specimen margins followed by RT which

included a local boost by either interstitial Iridium-192 implant or electron beam. This approach yielded an actuarial local control rate of 87% at 48 months (mean follow-up of 47 months). The difference in local control rate between the two groups was statistically significant (p less than 0.03). Among patients with clear surgical margins who received a local RT boost, 1 of 9 developed a local recurrence. Among those with tumor involving specimen margins who received a local boost, 1 of 8 developed local recurrence. Local recurrence developed more frequently among patients with poorly differentiated cancers (2 of 11 cases) than among those with other invasive cancers (3 of 91 cases). Comparison of treatment approaches was limited since poorly differentiated cancer was present in 25% of cases with unknown specimen margins, as compared with only 2% of those with clear surgical margins who did not receive a local RT boost. Our preliminary findings suggest that when "inked" primary tumor resection margins are pathologically free of cancer, 5000 cGy whole breast RT appears to be highly effective for local tumor control in patients with Stage I or II disease. Our results are inconclusive as to whether patients with poorly differentiated cancers should receive a local RT boost even when surgical margins are clear.

Pezner, R. D., et al. (1989). "The reverse hockey stick technique: postmastectomy radiation therapy for breast cancer patients with locally advanced tumor presentation or extensive loco-regional recurrence." Int J Radiat Oncol Biol Phys **17**(1): 191-197.
A combination of photon and electron radiation therapy (RT) fields was devised to treat patients with initial or recurrent breast cancer presentations which extensively involved the chest wall (CW) and/or the axilla. The ipsilateral supraclavicular, infraclavicular, axillary, and lateral CW regions are treated in continuity by anterior and posterior opposed photon beam "reverse hockey stick" fields. The internal mammary and medial chest wall regions are treated by an anterior electron beam field which is tightly junctioned to the photon beam fields. Electron beam energy and thickness of applied bolus are selected so that the electron beam 80% depth isodose curve matches the anterior pleural surface and/or deepest extent of tumor. The goal of treatment is to deliver 4400-5000 cGy to regions at risk of microscopic tumor with local boosts to 6000-7500 cGy to sites of gross disease. Between January 1977, and June 1985, this technique was selectively used in 46 patients, 31 patients with loco-regional tumor recurrence and 15 post-mastectomy patients who initially presented with locally advanced disease. A minimum tumor dose of 4400 cGy was delivered in all except five patients. A diffuse moist skin reaction developed in 31 of the 44

(70%) patients who received at least 3800 cGy. This healed in less than 1 month in all except seven. Frequency of CW diffuse moist skin reaction within the electron beam field was related to the daily applied RT dose. Diffuse moist skin reactions were also noted to be more frequent among patients who had received prior or concurrent Adriamycin. Significant complications included symptomatic arm lymphedema in seven; CW ulcer in two; and acute radiation pneumonitis; steroid-withdrawal radiation pneumonitis, pleuritis, and marked thrombocytopenia in one patient each. With a follow-up of 36-100 months, there was no evidence of loco-regional tumor relapse in 55% of patients treated for recurrent disease and in 73% treated following mastectomy for locally advanced presentations. In summary, we find the reverse hockey stick technique to be a simple, highly reproducible and effective RT approach for postmastectomy breast cancer patients with extensive initial presentation or recurrent disease.

Pezner, R. D., et al. (2013). "Radiation therapy for breast cancer patients who undergo oncoplastic surgery: localization of the tumor bed for the local boost." Am J Clin Oncol **36**(6): 535-539.
INTRODUCTION: Oncoplastic reconstructive surgery is performed in select patients with breast cancer to allow conservation treatment when the lumpectomy would be expected to have a poor cosmetic outcome. These techniques not only rearrange the breast tissue but may also shift the position of the tumor bed. The oncoplastic incision may have no relationship to the tumor bed. Although use of whole-breast radiation therapy (RT) is straightforward, difficulties in localization of the tumor bed for the local RT boost have not been investigated. MATERIALS AND METHODS: A retrospective review was performed of 25 patients with 26 cancers who received RT after breast conservation surgery with oncoplastic reconstruction. RESULTS: Among 11 patients with a minimum of 4 surgical clips placed at tumor resection, 8 (73%) had the final tumor bed extend beyond the original breast quadrant or be completely relocated into a different region. In 3 (27%) cases, the clinical treatment volume was 2 to 3 separated regions within the breast. DISCUSSION: For breast cancer patients who have had oncoplastic surgery, the tumor bed is frequently more extensive and possibly relocated compared with original presentation. Placement of surgical clips after tumor resection and before oncoplastic reconstruction may be the most accurate method to localize the RT local boost field.

Philpotts, L. E., et al. (1996). "Mammographic findings of recurrent breast cancer after lumpectomy

and radiation therapy: comparison with the primary tumor." Radiology **201**(3): 767-771.

PURPOSE: To compare the mammographic findings of recurrent breast cancer with those of the primary tumor in patients who underwent lumpectomy and radiation therapy. MATERIALS AND METHODS: Mammograms were reviewed of primary and recurrent tumors in 25 patients (26 lesions). Mammographic appearance, location, and histopathologic characteristics were retrospectively compared between primary and recurrent tumors. RESULTS: Primary and recurrent tumors were mammographically similar in 21 (81%) of the 26 lesions. Of 14 primary tumors with calcifications, 12 (86%) recurred with calcifications, and of the 12 masses, nine (75%) recurred as masses. Recurrent tumors that occurred in the lumpectomy quadrant were more often similar in mammographic appearance to the primary tumor (20 of 22 tumors) than those in other quadrants (one of four tumors) (P <.02). CONCLUSION: After conservative treatment of breast cancer, the majority of recurrent tumors appear to be mammographically similar to primary tumors. It is prudent to review preoperative mammograms during follow-up of patients after lumpectomy and radiation therapy.

Pirogov, A. I. and S. N. Nered (1989). "[Preoperative diagnosis of residual tumor in esophageal cancer following radiation therapy]." Grudn Khir (5): 69-74.

The authors analyse 100 operations for resection of the esophagus after radiotherapy. Morphological examination before irradiation showed squamous cell carcinoma in all patients. Difficulties arise in the diagnosis of a residual esophageal tumor after radiotherapy, as a result of which 11 (14.5%) of 76 patients irradiated with a dose of 30-40 GY and 1 (4.2%) of 24 patients who received a dose of 50-70 Gy were exposed to the risk of a surgical intervention in the absence of morphological signs of a tumor in the removed esophagus. The difficulties of the diagnosis are due to resorption of the tumor under the effect of radiotherapy, its exophytic component in particular, the frequent submucosal position of the tumor, signs of therapeutic pathomorphosis of the tumor, and fibrosis of the esophageal wall.

Pucar, D., et al. (2007). "Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence." Int J Radiat Oncol Biol Phys **69**(1): 62-69.

PURPOSE: To determine whether prostate cancer local recurrence after radiation therapy (RT) occurs at the site of primary tumor by retrospectively comparing the tumor location on pre-RT and post-RT magnetic resonance imaging (MRI) and using step-section pathology after salvage radical prostatectomy (SRP) as the reference standard. METHODS AND MATERIALS: Nine patients with localized prostate cancer were treated with intensity modulated RT (69-86.4 Gy), and had pre-RT and post-RT prostate MRI, biopsy-proven local recurrence, and SRP. The location and volume of lesions on pre-RT and post-RT MRI were correlated with step-section pathology findings. Tumor foci >0.2 cm (3) and/or resulting in extraprostatic disease on pathology were considered clinically significant. RESULTS: All nine significant tumor foci (one in each patient; volume range, 0.22-8.63 cm (3)) were detected both on pre-RT and post-RT MRI and displayed strikingly similar appearances on pre-RT and post-RT MRI and step-section pathology. Two clinically insignificant tumor foci (</=0.06 cm (3)) were not detected on imaging. The ratios between tumor volumes on pathology and on post-RT MRI ranged from 0.52 to 2.80. CONCLUSIONS: Our study provides a direct visual confirmation that clinically significant post-RT local recurrence occurs at the site of primary tumor. Our results are in agreement with reported clinical and pathologic results and support the current practice of boosting the radiation dose within the primary tumor using imaging guidance. They also suggest that monitoring of primary tumor with pre-RT and post-RT MRI could lead to early detection of local recurrence amenable to salvage treatment.

Quackenbush, K., et al. (2017). "Regression of a Fungating Tumor After Hypofractionated Radiation Therapy in a Patient With Metastatic Breast Cancer." Cureus **9**(7): e1417.

Radiation therapy is a well-established palliative treatment for symptomatic metastases from breast cancer. This is also true of symptomatic primary breast tumors in patients with metastatic disease or in those who are medically inoperable. Further, local progression in the chest wall can severely impair quality of life, with local pain, bleeding, and significant impact on one's self-image. Here, we present the case of a patient who showed an exceptional response to a palliative hypofractionated radiation course to her bleeding, fungating breast primary.

Ragazzi, G., et al. (1997). "Variations of tumor control and rectum complication probabilities due to random set-up errors during conformal radiation therapy of prostate cancer." Radiother Oncol **44**(3): 259-263.

BACKGROUND AND PURPOSE: The effect of random set-up errors on tumor control probability

(TCP) and rectum complication probability (NTCP) on 3D conformal treatment planning of prostate cancer has been investigated by applying the convolution method originally proposed by Leong (Leong, J. Implementation of random positioning error in computerized radiation treatment planning systems as a result of fractionation. Phys. Med. Biol. 32: 327-334, 1987). MATERIALS AND METHODS: The combined influence of the standard deviation of the random shifts probability distribution (sigma) of the dose and of the Beam's-eye-view margin (M) between the clinical target volume (CTV) and the edge of the blocks have been investigated in two patients. RESULTS AND CONCLUSIONS: Random set-up error has been found to decrease TCP (for a typical 70 Gy CTV mean dose) by up to 6% for a 1 cm margin (sigma = 7 mm). When M is equal to or larger than 1.5 cm, no relevant effects on TCP are obtained. Maximum acceptable TCP values (corresponding to a rectum NTCP equal to 5%) have been derived and the dependence on sigma and M has been investigated.

Rombouts, A. J. M., et al. (2018). "Tumor response after long interval comparing 5x5Gy radiation therapy with chemoradiation therapy in rectal cancer patients." Eur J Surg Oncol 44(7): 1018-1024.
BACKGROUND: In the era of organ preserving strategies in rectal cancer, insight into the efficacy of preoperative therapies is crucial. The goal of the current study was to evaluate and compare tumor response in rectal cancer patients according to their type of preoperative therapy. METHODS: All rectal cancer patients diagnosed between 2005 and 2014, receiving radiation therapy (RT, 5 x 5Gy; N = 764) or chemoradiation therapy (CRT; N = 5070) followed by total mesorectal excision after an interval of 5-15 weeks were retrieved from the nationwide Netherlands Cancer registry. Logistic regression was used for multivariable analysis. RESULTS: Median age of patients treated with RT was 76 years (range 28-92) compared to 64 years (range 21-92) for patients treated with CRT (P < 0.001). Patients treated with RT had a significantly lower clinical stage (P < 0.001). A complete pathologic response (ypT0N0) was found in 9.3% of patients treated with RT, significantly less than in patients treated with CRT (17.5%; odds ratio [OR] 0.37, 95% confidence interval [CI] 0.24-0.57). A good response (ypT0-1N0) was observed in 17.5% of patients treated with RT and in 22.6% of patients treated with CRT (OR 0.70, 95% CI 0.51-0.95). Histological subtype, clinical stage and distance to anus were identified as independent predictors for tumor response. CONCLUSIONS: Despite a more advanced clinical stage, complete pathologic response was more common in patients treated with CRT than in patients treated with RT. Prospective trials are needed to establish the differences in other outcome parameters, including the impact on organ preserving strategies.

Rwigema, J. C., et al. (2015). "4pi noncoplanar stereotactic body radiation therapy for head-and-neck cancer: potential to improve tumor control and late toxicity." Int J Radiat Oncol Biol Phys 91(2): 401-409.
PURPOSE: To evaluate the potential benefit of 4pi radiation therapy in recurrent, locally advanced, or metastatic head-and-neck cancer treated with stereotactic body radiation therapy (SBRT). METHODS AND MATERIALS: Twenty-seven patients with 29 tumors who were treated using SBRT were included. In recurrent disease (n=26), SBRT was delivered with a median 44 Gy (range, 35-44 Gy) in 5 fractions. Three patients with sinonasal mucosal melanoma, metastatic breast cancer, and primary undifferentiated carcinoma received 35 Gy, 22.5 Gy, and 40 Gy in 5 fractions, respectively. Novel 4pi treatment plans were created for each patient to meet the objective that 95% of the planning target volume was covered by 100% of the prescription dose. Doses to organs at risk (OARs) and 50% dose spillage volumes were compared against the delivered clinical SBRT plans. Local control (LC), late toxicity, tumor control probability (TCP), and normal tissue complication probability were determined. RESULTS: Using 4pi plans, mean/maximum doses to all OARs were reduced by 22% to 89%/10% to 86%. With 4pi plans, the 50% dose spillage volume was decreased by 33%. Planning target volume prescription dose escalation by 10 Gy and 20 Gy were achieved while keeping doses to OARs significantly improved or unchanged from clinical plans, except for the carotid artery maximum dose at 20-Gy escalation. At a median follow-up of 10 months (range, 1-41 months), crude LC was 52%. The 2-year LC of 39.2% approximated the predicted mean TCP of 42.2%, which increased to 45.9% with 4pi plans. For 10-Gy and 20-Gy dose escalation, 4pi plans increased TCP from 80.1% and 88.1% to 85.5% and 91.4%, respectively. The 7.4% rate of grade >/=3 late toxicity was comparable to the predicted 5.6% mean normal tissue complication probability for OARs, which was significantly reduced by 4pi planning at the prescribed and escalated doses. CONCLUSIONS: 4pi plans may allow dose escalation with significant and consistent improvements in critical organ sparing, tumor control, and coverage.

Sakakibara-Konishi, J., et al. (2011). "Phase I study of concurrent real-time tumor-tracking thoracic radiation therapy with paclitaxel and carboplatin in locally advanced non-small cell lung cancer." Lung Cancer 74(2): 248-252.

INTRODUCTION: Although paclitaxel with carboplatin and thoracic radiotherapy has improved survival for patients with locally advanced unresectable non-small cell lung cancer (NSCLC), the optimal dose of paclitaxel has not been well defined in Japan. This study was conducted to determine the maximum tolerated dose (MTD) and recommended dose (RD) of paclitaxel in combination with carboplatin and concurrent real-time tumor-tracking thoracic radiation therapy (thoracic RTRT). PATIENTS AND METHODS: Previously untreated patients with histologically confirmed, locally advanced unresectable NSCLC were eligible. Before treatment, gold markers were inserted into the lung and the mediastinum of all patients. RTRT comprised a total of 66 Gy at 2 Gy/fraction, 5 days/week, for 7 weeks. Patients received paclitaxel at a starting dose of 40 mg/m (2) followed by carboplatin at a fixed area under the curve (AUC) of 2, as a weekly regimen with RTRT. The dose of paclitaxel was escalated by 5mg/m (2) per level. RESULTS: Eight patients with locally advanced unresectable NSCLC were enrolled and treated with two dose levels of paclitaxel (40 mg/m (2) and 45 mg/m (2)), carboplatin (AUC=2) and RTRT. No dose limiting toxicities (DLTs) were observed at Level 1 (paclitaxel, 40 mg/m (2) and carboplatin, AUC=2). At Level 2 (paclitaxel, 45 mg/m (2) and carboplatin, AUC=2), two of five patients experienced DLTs, in the form of esophagitis and discontinuation of chemotherapy more than twice. The MTD and RD of paclitaxel were thus defined as 45 mg/m (2) and 40 mg/m (2), respectively. CONCLUSIONS: This phase I study was well tolerated and the RD of paclitaxel and carboplatin with RTRT is 40 mg/m (2) at AUC=2, respectively. Further studies are warranted to evaluate the efficacy of this regimen.

Sandler, H. M., et al. (1990). "The influence of tumor size and pre-treatment staging on outcome following radiation therapy alone for stage I non-small cell lung cancer." Int J Radiat Oncol Biol Phys **19**(1): 9-13.

From 1970 through 1987, 77 patients with Stage I lung cancer were treated with definitive radiation therapy (RT) alone at the Fox Chase Cancer Center or the Hospital of The University of Pennsylvania. All patients had a pathologic diagnosis of non-small cell lung cancer and were not candidates for surgical resection because of premorbid medical problems or patient refusal. The median age was 72 years, although 10 patients were over 80. The histologic cell type was squamous in 44, adenocarcinoma in 15, large cell in 3, adenosquamous in 1, non-small cell in 11, and bronchioli-alveolar in 3. Tumor size was retrievable in 75 patients and 25 were less than or equal to 3 cm, 41 from 3-6 cm, and 9 greater than 6 cm. Diagnostic

staging varied during the study period. Twelve patients, evaluated with a CT scan of the chest, including the liver, and a bone scan were classified as having "excellent" staging, 24 patients with conventional tomography, liver-spleen scan and a bone scan had "good" staging, and 41 patients were staged less rigorously. The RT was of megavoltage energy in all patients. The median dose was 60 Gy. The mediastinum was treated in all but eight patients who had poor pulmonary function. Survival was measured from the date of pathologic diagnosis. The actuarial 3-year survival rate of the entire group of patients is 17% with a median survival time of 20 months. Of the 61 deaths, 51 were due to disease and 10 were due to intercurrent disease without evidence of tumor recurrence. The actuarial 3-year disease-specific survival (DSS) was 22%. The 3-year disease-specific survival for patients with tumors less than 3 cm and from 3-6 cm was 30% and 17%, respectively. All nine patients with tumors greater than 6 cm were dead of disease. Local progression occurred in 33 patients, resulting in a 44%, 3-year actuarial freedom from local progression. The median time to local failure was 28 months and there were no local failures after 3 years in the 18 patients eligible for observation beyond this point. Of the patients with "excellent" staging, only 2 of 12 were dead of disease compared with 22 of 24 with "good" staging and 30 of 41 of the remainder. In this large group of Stage I non-small cell lung cancer, thorough pre-treatment staging and smaller tumor size are associated with a more favorable outcome.

Sasaoka, M., et al. (1997). "[Radiation therapy for uterine cervix cancer: importance of evaluation of pre-treatment tumor size with MR imaging]." Nihon Igaku Hoshasen Gakkai Zasshi **57**(8): 505-509.

From May 1992 through December 1995, a total of 42 patients with previously untreated squamous cell carcinoma of the uterine cervix were treated by using middle-dose-rate intracavitary therapy, and their previously treated local tumor volume was evaluated with MRI. According to the staging of FIGO, 2 patients were classified as Stage IB, 2 as IIA, 18 as IIB, 1 as IIIA, 14 as IIIB, 2 as IVA and 3 as IVB. Cumulative 3-year survival rates were 89% in Stage IIB and 54% in IIIB. 3-year local control rates were 100% in Stage IIB and 67% in IIIB. On the other hand, the cumulative survival rate for the local control group in all stages was 100% at 2 years and 82% at 3 years. For the pelvic failure group it was 41% at 2 years. All of those in the pelvic failure group had bulky local tumor sizes of more than 60 mm in the previous treatment MRI study. The 3-year cumulative survival rate and local control rate for tumors less than 60 mm were 84% and 100%, but for tumors over 60 mm the respective rates were 45% and 33% (p < 0.01). The a

results showed that the group with pretreatment of local tumors over 60 mm on MRI had a poor outcome. We concluded that pretreatment tumor volume is an important factor in prognosis and the evaluation of pretreatment tumor volume by imaging study (MRI) is necessary.

Sharabi, A., et al. (2017). "Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center." Oncologist **22**(6): 631-637.

Neuroendocrine carcinoma of the cervix is an ultra-rare malignancy with a poor prognosis and limited treatment options. Checkpoint blockade immunotherapy has rapidly developed into an emerging standard of care for several common disease types. Interestingly, in preclinical and retrospective clinical data, radiation therapy has been demonstrated to synergize with checkpoint inhibitors. Here we report a patient with metastatic, chemotherapy-refractory neuroendocrine carcinoma who presented with partial bowel obstruction due to a large tumor burden. Genomic analysis demonstrated a high number of alterations on liquid biopsy (circulating tumor DNA [ctDNA]), which prompted treatment with stereotactic body radiation therapy (SBRT) combined with anti-programmed cell death protein 1 antibody. Tissue rebiopsy and comprehensive genomic profiling confirmed high tumor mutational burden and a mismatch repair gene defect. The patient manifested near-complete systemic resolution of disease, ongoing at 10+ months. We discuss the novel treatment modality of SBRT combined with a checkpoint inhibitor and the implications of molecular profiling and tumor mutational burden as potential predictors of response. KEY POINTS: High-grade, large-cell neuroendocrine carcinoma of the cervix is an ultra-rare malignancy that carries a grim prognosis.Next-generation sequencing may reveal key mutations in MSH2 genes amongst others. MSH2 mutations target the DNA mismatch repair process and can predispose patients to malignancies with high mutational burdens.Immunotherapy combined with radiation therapy can elicit a significant response, both within and outside the field of radiation. The latter is termed the "abscopal" effect, perhaps mediated by radiation-induced cross presentation of tumor antigens resulting in immune activation.Sequencing of blood-derived ctDNA showed a high number of alterations, and tissue sequencing confirmed a high tumor mutational burden as a consequence of a mismatch repair gene defect. This observation led to a therapeutic "match" with an anti- programmed cell death protein 1

antibody combined with SBRT, resulting in a durable (10+ months), near-complete remission in a patient with advanced chemotherapy-refractory disease.

Shimizu, S., et al. (2014). "Early results of urethral dose reduction and small safety margin in intensity-modulated radiation therapy (IMRT) for localized prostate cancer using a real-time tumor-tracking radiotherapy (RTRT) system." Radiat Oncol **9**: 118.

BACKGROUND: We prospectively assessed the utility of intensity-modulated radiation therapy (IMRT) with urethral dose reduction and a small margin between the clinical target volume (CTV) and the planning target volume (PTV) for patients with localized prostate cancer. METHODS: The study population was 110 patients in low- (14.5%), intermediate- (41.8%), and high-risk (43.6%) categories. Three gold fiducial markers were inserted into the prostate. A soft guide-wire was used to identify the urethra when computed tomography (CT) scan for treatment planning was performed. A dose constraint of V70 < 10% was applied to the urethral region. Margins between the CTV-PTV were set at 3 mm in all directions. Patients were treated with 70 Gy IMRT in 30 fractions (D95 of PTV) over 7.5 weeks. The patient couch was adjusted to keep the gold markers within 2.0 mm from their planned positions with the use of frequent on-line verification. RESULTS: The median follow-up period was 31.3 (3.2 to 82.1) months. The biochemical relapse-free survival (bRFS) rates at 3 years were 100%, 93.8% and 89.5% for the low-, intermediate-, and high-risk patients, respectively. The incidences of acute adverse events (AEs) were 45.5% and 0.9% for grades 1 and 2, respectively. The late AEs were grade 1 cystitis in 10.0% of the patients, rectal bleeding in 7.3%, and urinary urgency in 6.4%. Only three patients (2.7%) developed grade 2 late AEs. CONCLUSIONS: On-line image guidance with precise correction of the table position during radiotherapy achieved one of the lowest AEs rates with a bRFS equal to the highest in the literature.

Shinohara, N., et al. (2013). "Longitudinal comparison of quality of life after real-time tumor-tracking intensity-modulated radiation therapy and radical prostatectomy in patients with localized prostate cancer." J Radiat Res **54**(6): 1095-1101.

The purpose of this study was to compare the quality of life (QOL) in patients with localized prostate cancer (PC) after intensity-modulated radiation therapy assisted with a fluoroscopic real-time intensity-modulated radiation therapy (RT-IMRT) tumor-tracking system versus the QOL after radical prostatectomy (RP). Between 2003 and 2006, 71 patients were enrolled in this longitudinal prospective

study. Each patient was allowed to decide which treatment modality they would receive. Of the 71 patients, 23 patients underwent RT-IMRT, while 48 opted for RP. No patient received neo-adjuvant or adjuvant hormone therapy. The global QOL and disease-specific-QOL were evaluated before treatment and again at 1, 3 and 5 years after treatment. There was no significant difference in the background characteristics between the two groups. The 5-year biochemical progression-free survival was 90% in the RT-IMRT and 79% in the RP group. In the RT-IMRT group, there was no significant deterioration of the global QOL or disease-specific QOL through 5 years post-treatment. In the RP group, the urinary function, sexual function, and sexual bother indicators significantly deteriorated after treatment. Urinary and sexual function was significantly better in the RT-IMRT group at 1, 3 and 5 years post-treatment compared to the RP group. RT-IMRT may be a preferable treatment for localized PC because of similar efficacy to RP but better post-treatment QOL.

Shintani, S., et al. (2001). "The influence of blood arterial oxygen condition on the tumor response to preoperative radiation therapy in oral cancer patients." Oncol Rep **8**(1): 99-102.
The relationship between clinicopathological factors and response of radiation therapy in oral squamous cell carcinoma has been studied. It has been suggested that factors such as tumor site, extent and tumor differentiation determine the response to radiation therapy. It is known that oxygenation is related to the therapeutic effects of radiation therapy. However, there are few reports on the relationship between oxygen condition and the response to radiation therapy. The present study was carried out to assess whether any clinicopathological factors, including an evaluation of the oxygen condition can be used to predict the effects of preoperative radiation therapy in oral squamous cell carcinomas. Forty-seven patients with oral cancer treated with external radiation therapy preoperatively were evaluated. There were no significant differences in response to the radiation with respect to age, sex, tumor site, stage, macroscopic shape of tumors, and the histological factors. The hemoglobin (Hb) and arterial oxygen content (CaO (2)) levels of favorable cases (Hb: 14.4 g/dl, CaO (2) 19.1 ml/dl) were significantly higher than those of unfavorable cases (Hb: 11.0 g/dl, CaO (2): 16.1 ml/dl). These findings suggest that oxygen conditions of oral cancer patients predict tumor response to preoperative radiation therapy.

Shipley, W. U., et al. (1987). "Intraoperative radiation therapy in patients with bladder cancer. A review of techniques allowing improved tumor doses and providing high cure rates without loss of bladder function." Cancer **60**(7): 1485-1488.
Conventional external beam irradiation, using modern megavoltage techniques and doses that do not harm bladder function, will permanently eradicate local bladder cancer in 30% to 50% of patients, compared with 70% to 90% with cystectomy. In appropriately chosen patients, open surgery can safely provide excellent exposure for the selective delivery of more radiant energy directly to the tumor and less to the uninvolved portion of the bladder. Intraoperative radiation therapy, by either a removable radium or iridium implant or a large single dose of electrons, has been reported to be safe and can permanently cure the bladder of cancer and also preserve bladder function in more than 75% of patients with solitary tumors that invade into but not beyond the bladder muscle. With the increasing interest in and availability of intraoperative radiation therapy in the US, this curative and bladder-sparing treatment for operable patients with bladder cancer invading the trigone is appropriate for careful clinical trial.

Stephans, K. L., et al. (2018). "Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer." Int J Radiat Oncol Biol Phys **100**(2): 462-469.
PURPOSE: To examine the impact of stereotactic body radiation therapy (SBRT) dose on outcomes in early-stage non-small cell lung cancer in a large single-institution series. METHODS AND MATERIALS: We reviewed 600 patients treated from 2003 to 2012 for early-stage non-small cell lung cancer. The SBRT dose was at physician discretion on the basis of tumor size and location. Peripheral tumors were treated to 60 Gy in 3 fractions (homogeneous planning), 48-50 Gy in 4-5 fractions, or 30-34 Gy in 1 fraction. Central tumors were treated to 50 Gy in 5 fractions, 60 Gy in 8 fractions, or 50 Gy in 10 fractions. Patient, tumor, and treatment factors were assessed for their impact on patterns of failure, toxicity, and survival. RESULTS: An SBRT dose of 54-60 Gy in 3 fractions was associated with a statistically significant lower rate of local failure (LF) (4.3% at 2 years) compared with 30-34 Gy in 1 fraction (21%), 48-50 Gy in 4-5 fractions (15.5%), and 50-60 Gy in 8-10 fractions (13.3%). Lower pre-SBRT hemoglobin and higher positron emission tomography standardized uptake value were also associated with LF. Nodal failure, distant failure, and overall survival were similar between fractionation groups. Pulmonary toxicity (crude rate, any grade) was slightly higher for 3 fractions (5.0%) compared with 1 (3.2%) or 4-5 fractions (3.8%). Chest wall toxicity was also higher for 3 (23.7%) compared with 1 (8.6%) or 4-5 (7.7%)

fraction regimens. CONCLUSIONS: Although higher biologically equivalent dose SBRT (150-180 Gy10) may be associated with slightly lower LF, it was also associated with mildly increased toxicity and no difference in other patterns of failure or overall survival.

Stokes, C. L., et al. (2018). "Timing of Radiation Therapy in Pediatric Wilms Tumor: A Report From the National Cancer Database." Int J Radiat Oncol Biol Phys **101**(2): 453-461.

PURPOSE: To determine, using the National Cancer Database (NCDB), the impact of the surgery to radiation therapy interval (SRI) on survival in contemporary patients with Wilms tumor (WT). METHODS AND MATERIALS: The NCDB was queried for patients aged </=25 years diagnosed from 2004 to 2013 with unilateral WT who underwent definitive surgery and radiation therapy. The SRI was calculated for each patient. A stratified analysis was performed based on presence of metastasis using logistic regression to calculate risk factors for prolonged SRI, with a focus on the recommended SRI according to recent Children's Oncology Group trials (by day 14) and National Wilms Tumor Study-5 (by day 9). Cox regression was performed to assess the association of SRI with overall survival. RESULTS: A total of 1488 patients were included; 32.1% had metastasis at diagnosis. Among both metastatic and nonmetastatic groups, older patients were more likely to have prolonged SRI. For those without metastasis, SRI > 14 days was associated with increased risk of mortality (hazard ratio 2.13, P =.013). Analyzing SRI as a continuous variable also demonstrated an increased risk of death with longer SRI (hazard ratio 1.04 per day, P =.006) in this group. In contrast, among patients with metastasis, no significant association between SRI and mortality was found. CONCLUSION: Early initiation of radiation therapy remains a critical component of multimodal treatment for patients with nonmetastatic WT. For nonmetastatic patients, SRI </= 14 days correlates with improved overall survival. However, no such association was noted for patients with metastases. These results may inform the development of future WT trials.

Straughn, J. M., Jr., et al. (2006). "Anti-tumor activity of TRA-8 anti-death receptor 5 (DR5) monoclonal antibody in combination with chemotherapy and radiation therapy in a cervical cancer model." Gynecol Oncol **101**(1): 46-54.

OBJECTIVES: There is substantial evidence that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) causes apoptosis via activation of death receptors 4 and 5 (DR4 and DR5). We sought to determine the therapeutic potential of TRA-8 (anti-DR5 monoclonal antibody) in combination with chemotherapy and radiation therapy in a cervical cancer model. METHODS: DR5 expression in 7 human cervical cancer cell lines was analyzed by indirect immunofluorescence using murine TRA-8 in combination with flow cytometry. Cell lines were treated with TRA-8 alone or in combination with cisplatin, topotecan, or radiation, and cytotoxicity assays were performed. Mice were inoculated with ME-180 cancer cells and treated with different combinations of therapy. Animals receiving antibody were injected intraperitoneally with 200 microg of TRA-8. Animals received 9 Gy 60Co radiation divided into 3 fractions and 3 intraperitoneal doses of cisplatin (6 mg/kg) 1 h before radiation. A similar experiment was performed using topotecan (2 mg/kg) as the chemotherapeutic agent. RESULTS: DR5 was expressed to a varying degree on the cervical cancer cell lines. Combination treatment with TRA-8 and chemotherapy or radiation resulted in synergistic cytotoxicity in vitro. In vivo, combination therapy with TRA-8, cisplatin, and radiation produced tumor growth inhibition that was significantly greater than the other groups. Similar results were seen in combination studies with topotecan. CONCLUSIONS: These data suggest that DR5 is a good target for activation of the apoptotic pathway. Monoclonal antibodies such as TRA-8 may play an important role in the development of an effective treatment strategy for patients with advanced cervical cancer.

Swisher, S. G., et al. (2003). "Induction of p53-regulated genes and tumor regression in lung cancer patients after intratumoral delivery of adenoviral p53 (INGN 201) and radiation therapy." Clin Cancer Res **9**(1): 93-101.

PURPOSE: We designed a prospective single arm Phase II study to evaluate the feasibility and mechanisms of apoptosis induction after Ad-p53 (INGN 201) gene transfer and radiation therapy in patients with non-small cell lung cancer. EXPERIMENTAL DESIGN: Nineteen patients with nonmetastatic non-small cell lung cancer who were not eligible for chemoradiation or surgery were treated as outpatients with radiation therapy to 60 Gy over 6 weeks in conjunction with three intratumoral injections of Ad-p53 (INGN 201) on days 1, 18, and 32. RESULTS: Seventeen of 19 patients completed all planned radiation and Ad-p53 (INGN 201) gene therapy as outpatients. The most common adverse events were grade 1 or 2 fevers (79%) and chills (53%). Three months after completion of therapy, pathologic biopsies of the primary tumor revealed no viable tumor (12 of 19 patients, 63%), viable tumor (3 of 19 patients, 16%), and not assessed (4 of 19 patients, 21%). Computed tomography and bronchoscopic

findings at the primary injected tumor revealed complete response (1 of 19 patients, 5%), partial response (11 of 19 patients, 58%), stable disease (3 of 19 patients, 16%), progressive disease (2 of 19 patients, 11%), and not evaluable (2 of 19 patients, 11%). Quantitative reverse transcription-PCR analysis of the four p53 related genes [p21 (CDKN1A), FAS, BAK, and MDM2] revealed that Bak expression was increased significantly 24 h after Ad-p53 (INGN 201) injection and levels of CDKN1A and MDM2 expression were increased over the course of treatment. CONCLUSIONS: Intratumoral injection of Ad-p53 (INGN 201) in combination with radiation therapy is well tolerated and demonstrates evidence of tumor regression at the primary injected tumor. Serial biopsies of the tumor suggest that BAK gene expression is most closely related to Ad-p53 (INGN 201) gene transfer.

Tabi, Z., et al. (2010). "Resistance of CD45RA- T cells to apoptosis and functional impairment, and activation of tumor-antigen specific T cells during radiation therapy of prostate cancer." J Immunol **185**(2): 1330-1339.

The effect of radiation therapy (RT) to the pelvis on circulating T cells was studied in prostate cancer (PCa) patients to provide a baseline for a more informed design of combination radioimmunotherapy. Peripheral blood samples taken from 12 PCa patients with locally advanced tumor before, during, and after hypofractionated RT were analyzed for T cell phenotype and function. There was significantly more loss of naive and early memory compared with more differentiated T cells during RT. The proportions of annexin-V (+) and Fas-expressing T cells were elevated in patients during RT and in PBMC irradiated in vitro (< or = 5.0 Gy), with preferential increases in CD45RA (+) T cells. The baseline level of apoptosis of CD45RA (-) T cells increased > 2-fold in the presence of an IkappaB-kinase inhibitor, indicating a protective effect via this pathway. T cell proliferation was impaired during RT with IL-2-dependent recovery post-RT. Recall T cell responses to common viral Ags, measured by IFN-gamma production, were little affected by RT. In vitro irradiation of healthy donor PBMCs resulted in a significantly increased frequency of responding T cells, due at least partly to the preferential elimination of CD45RA (+) T cells. Most importantly, antitumor CD4(+) and CD8(+) T cell responses were detectable after, but not before or during RT. The results indicate that generating tumor-specific T cell responses before RT and boosting their activity post-RT are ways likely to amplify the frequency and function of antitumor T cells, with implications for scheduling immunotherapy in PCa.

Tai, A., et al. (2016). "An analysis of tumor control probability of stereotactic body radiation therapy for lung cancer with a regrowth model." Phys Med Biol **61**(10): 3903-3913.

We report a modeling study of tumor response after stereotactic body radiation therapy (SBRT) for early-stage non-small-cell lung carcinoma using published clinical data with a regrowth model. A linear-quadratic inspired regrowth model was proposed to analyze the tumor control probability (TCP) based on a series of published data of SBRT, in which a tumor is controlled for an individual patient if number of tumor cells is smaller than a critical value K cr. The regrowth model contains radiobiological parameters such as alpha, alpha/beta the potential doubling time T p. This model also takes into account the heterogeneity of tumors and tumor regrowth after radiation treatment. The model was first used to fit TCP data from a single institution. The extracted fitting parameters were then used to predict the TCP data from another institution with a similar dose fractionation scheme. Finally, the model was used to fit the pooled TCP data selected from 48 publications available in the literature at the time when this manuscript was written. Excellent agreement between model predictions and single-institution data was found and the extracted radiobiological parameters were alpha = 0.010 +/- 0.001 Gy (-1), alpha /beta = 21.5 +/- 1.0 Gy and T p = 133.4 +/- 7.6 d. These parameters were alpha = 0.072 +/- 0.006 Gy (-1), alpha/beta = 15.9 +/- 1.0 Gy and T p = 85.6 +/- 24.7 d when extracted from multi-institution data. This study shows that TCP saturates at a BED of around 120 Gy. A few new dose-fractionation schemes were proposed based on the extracted model parameters from multi-institution data. It is found that the regrowth model with an alpha/beta around 16 Gy can be used to predict the dose response of lung tumors treated with SBRT. The extracted radiobiological parameters may be useful for comparing clinical outcome data of various SBRT trials and for designing new treatment regimens.

Takahashi, N., et al. (2016). "Metabolic tumor volume on FDG-PET/CT is a possible prognostic factor for Stage I lung cancer patients treated with stereotactic body radiation therapy: a retrospective clinical study." J Radiat Res **57**(6): 655-661.

The aim of this study was to determine whether metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are associated with outcomes in Stage I lung cancer patients treated with stereotactic body radiation therapy (SBRT). Thirty-eight patients underwent [(18)F] fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG-PET/CT) within 60 days before SBRT at our institution between January 2001 and December 2011.

The maximum standardized uptake value (SUVmax), MTV2, MTV4, MTV6, TLG40%, TLG50% and TLG60% were calculated. Prognostic factors for overall survival (OS) and local control (LC) were analyzed using Cox's proportional hazards model, and survival curves were calculated using the Kaplan-Meier method. Receiver operating characteristics (ROC) curves of PET parameters for OS and LC were calculated. The median follow-up period for survivors was 37.7 months. Three-year OS and LC rates were 56.4% and 70.5%, respectively, and 5-year OS and LC rates were 36.8% and 70.5%, respectively. In univariate analyses, tumor diameter ($P = 0.019$), single dose $>/=10$ Gy ($P = 0.017$), MTV2 ($P = 0.030$) and MTV4 ($P = 0.048$) were significant predictors for OS. Tumor diameter ($P < 0.001$), single dose $>/=10$ Gy ($P = 0.007$), SUVmax ($P = 0.035$), MTV2 ($P < 0.001$), MTV4 ($P = 0.003$), MTV6 ($P = 0.017$), TLG40% ($P < 0.001$), TLG50% ($P = 0.001$) and TLG60% ($P = 0.003$) were significant predictors for LC. SUVmax was not a significant predictor for OS. We made the ROC curves at PET parameters, and the largest area under the curve value for OS was MTV2 and for LC was TLG40% Tumor diameter, single dose $>/=10$ Gy, MTV2 and MTV4 are prognostic factors for OS and LC rates and MTV2 is a better prognostic factor for OS than other PET parameters.

Tennyson, N., et al. (2017). "Effect of variations in atelectasis on tumor displacement during radiation therapy for locally advanced lung cancer." Adv Radiat Oncol **2**(1): 19-26.

PURPOSE: Atelectasis (AT), or collapsed lung, is frequently associated with central lung tumors. We investigated the variation of atelectasis volumes during radiation therapy and analyzed the effect of AT volume changes on the reproducibility of the primary tumor (PT) position. METHODS AND MATERIALS: Twelve patients with lung cancer who had AT and 10 patients without AT underwent repeated 4-dimensional fan beam computed tomography (CT) scans during radiation therapy per protocols that were approved by the institutional review board. Interfraction volume changes of AT and PT were correlated with PT displacements relative to bony anatomy using both a bounding box (BB) method and change in center of mass (COM). Linear regression modeling was used to determine whether PT and AT volume changes were independently associated with PT displacement. PT displacement was compared between patients with and without AT. RESULTS: The mean initial AT volume on the planning CT was 189 cm (3) (37-513 cm (3)), and the mean PT volume was 93 cm (3) (12-176 cm (3)). During radiation therapy, AT and PT volumes decreased on average 136.7 cm (3) (20-369 cm (3)) for AT and 40 cm (3) (-7 to 131 cm (3)) for PT. Eighty-

three percent of patients with AT had at least one unidirectional PT shift that was greater than 0.5 cm outside of the initial BB during treatment. In patients with AT, the maximum PT COM shift was $>/=0.5$ cm in all patients and >1 cm in 58% of patients (0.5-2.4 cm). Changes in PT and AT volumes were independently associated with PT displacement ($P <.01$), and the correlation was smaller with COM (R (2) = 0.58) compared with the BB method (R (2) = 0.80). The median root mean squared PT displacement with the BB method was significantly less for patients without AT (0.45 cm) compared with those with AT (0.8cm, $P =.002$). CONCLUSIONS: Changes in AT and PT volumes during radiation treatment were significantly associated with PT displacements that often exceeded standard setup margins. Repeated 3-dimensional imaging is recommended in patients with AT to evaluate for PT displacements during treatment.

Timar, J., et al. (2003). "The effect of leukocyte interleukin injection (Multikine) treatment on the peritumoral and intratumoral subpopulation of mononuclear cells and on tumor epithelia: a possible new approach to augmenting sensitivity to radiation therapy and chemotherapy in oral cancer--a multicenter phase I/II clinical Trial." Laryngoscope **113**(12): 2206-2217.

OBJECTIVES/HYPOTHESIS: The main objective of this study was to investigate the effect of the administration of a novel immunoadjuvant, leukocyte interleukin injection, as part of an immuno-augmenting treatment regimen on the peritumoral and intratumoral subpopulations of the tumor infiltrating mononuclear cells and on the epithelial and stromal components, when administered to patients with advanced primary oral squamous cell carcinoma classified as T2-3N0-2M0, as compared with disease-matched control patients (not treated with leukocyte interleukin injection). STUDY DESIGN: Multicenter Phase I/II clinical trial. Fifty-four patients from four clinical centers were included in the dose-escalating study (27 in each group [leukocyte interleukin injection-treated and control groups]). Cumulative leukocyte inter-leukin injection doses were 2400, 4800, and 8000 IU (as interleukin-2 equivalent). METHODS: Paraffin-embedded tumor samples obtained at surgical resection of the residual tumor (between days 21 and 28 after treatment initiation) were used. Histological analysis, necrosis evaluation, and American Joint Committee on Cancer grading were performed from H & E-stained sections. Immunohistochemical analysis was performed on three different tumor regions (surface, zone 1; center, zone 2; and tumor-stroma interface, zone 3). Trichrome staining was used to evaluate connective tissue, and morphometric measurements were made using ImagePro analysis

software. Cell cycling was determined by the use of Ki-67 marker. RESULTS: Leukocyte interleukin injection treatment induced a shift from stromal infiltrating T cells toward intraepithelial T cells and posted a significant (P <.05) increase in intraepithelial CD3-positive T cells independent of the leukocyte interleukin injection dose, whereas the increase in CD25 (interleukin-2 receptor alpha [IL-2Ralpha])-positive lymphoid cells was significant only at the lowest leukocyte interleukin injection dose (P <.05). Furthermore, both low- and medium-dose leukocyte interleukin injection treatment induced a significant (P <.05) increase in the number of cycling tumor cells, as compared with control values. CONCLUSION: The results could be highly beneficial for patients with oral squamous cell carcinoma. First, leukocyte interleukin injection treatment induces T-cell migration into cancer nests and, second, noncycling cancer cells may enter cell cycling on administration of leukocyte interleukin injection. This latter effect may modulate the susceptibility of cancer cells to radiation therapy and chemotherapy. The findings may indicate a need to re-evaluate the way in which follow-up treatment (with radiation therapy and chemotherapy) of patients with head and neck cancer is currently approached.

Tjebbes, G. W., et al. (2002). "P53 tumor suppressor gene mutations in laryngeal cancer and in recurrent disease following radiation therapy." Oral Oncol **38**(3): 296-300.

In this study we performed p53 sequencing based mutation analysis in laryngeal cancers and matched recurrent disease following irradiation. The question is if irradiation affects the DNA and introduces or deletes mutations so that p53 cannot be used as a clonal marker anymore. P53 mutations were identified in fresh-frozen laryngectomy specimens with either primary laryngeal cancers, treated by surgery and irradiation post-operative with local failure during follow-up, or with recurrent laryngeal cancers following primary irradiation. In 21 tumors the p53 status was analyzed by direct sequencing full-length mRNA through RT-PCR. DNA sequencing analysis of exons 2 through 11 was performed when RNA isolation could not be performed. The marker mutation identified in this way was detected by DNA sequencing of the corresponding exon in formalin-fixed deparaffinized tumor biopsy samples in respectively matched recurrent disease following surgery and irradiation or primary tumor before irradiation. DNA sequencing analysis of the corresponding exon of peripheral blood leukocytes excluded the presence of germline mutations or polymorphisms. In 16 out of 21 tumors (71%), a mutation was identified. Fifteen of these marker mutations were detected in the matched tumor biopsy

sample (94%). The only case lacking the marker mutation probably was a second primary tumor. We conclude that we find no direct evidence for induction or loss of p53 mutations following irradiation. Consequently, p53 may be used as a diagnostic tool when histological examination fails, for example in discriminating between the presence of a second primary tumor in the same area versus recurrent disease.

VanderBeek, L., et al. (2017). "Primary Breast Cancer Tumor and Patient Characteristics as Predictors of Adjuvant Radiation Therapy." Breast J **23**(1): 40-48.

Adjuvant radiation therapy reduces the risk of local recurrence of breast cancer. Our study identifies patient and tumor characteristics that guide the use of adjuvant radiation therapy and evaluates our adherence to recommended guidelines. A retrospective review was undertaken of 1,667 stage I-III breast cancer patients treated at a regional cancer center from 2004 to 2007. Univariate analysis was used to select factors for entry into a multivariate stepwise logistic regression model. Descriptive statistics was used to compare use of radiation therapy of 382 stage I-III breast cancer patients diagnosed in 2013 to those from 2004 to 2007. The primary indicators for any radiation therapy (n = 935) were breast conserving surgery (OR 79.5, 95% CI [47.6-132.9]), four to nine positive lymph nodes (71.9, [17.0-304.7]), and greater than nine positive lymph nodes (60.5, [7.9-460.8]). In post-mastectomy patients (n = 408), the indicators for radiation therapy were four to nine positive lymph nodes (29.4, [12.9-67.4]) and greater than nine positive lymph nodes (108.3, [14.5-807.5]). In breast conserving surgery patients (n = 1,081) 96.1% were offered radiation therapy. Patients offered local-regional radiation therapy were more likely to have any positive nodes (ORs 4.3-91.0), have had a mastectomy (4.3, [2.2-8.4]), and had larger tumors (1.6, [1.3-2.0]). Local-regional radiation therapy was recommended less frequently in node positive patients in 2004-2007 (35.0%) compared to in 2013 (70.5%) [p < 0.001]. Patients who had a breast conserving surgery or had four or more positive lymph nodes were more likely to receive radiation therapy. Patients with any positive lymph nodes, larger tumors, or who had a mastectomy were more likely to receive local-regional radiation therapy. Our institution was more likely to offer local-regional radiation therapy in node positive breast cancer in 2013 compare to 2004-2007.

Vargo, J. A., et al. (2018). "Head and Neck Tumor Control Probability: Radiation Dose-Volume Effects in Stereotactic Body Radiation Therapy for Locally Recurrent Previously-Irradiated Head and

Neck Cancer: Report of the AAPM Working Group." Int J Radiat Oncol Biol Phys.

PURPOSE: Stereotactic body radiation therapy (SBRT) has emerged as a viable reirradiation strategy for locally recurrent previously-irradiated head and neck cancer. Doses in the literature have varied, which challenges clinical application of SBRT as well as clinical trial design. MATERIAL & METHODS: A working group was formed through the American Association of Physicists in Medicine to study tumor control probabilities for SBRT in head and neck cancer. We herein present a systematic review of the available literature addressing the dose/volume data for tumor control probability with SBRT in patients with locally recurrent previously-irradiated head and neck cancer. Dose-response models are generated that present tumor control probability as a function of dose. RESULTS: Data from more than 300 cases in 8 publications suggest that there is a dose-response relationship, with superior local control and possibly improved overall survival for doses of 35 to 45 Gy (in 5 fractions) compared with <30 Gy. CONCLUSION: Stereotactic body radiation therapy doses equivalent to 5-fraction doses of 40 to 50 Gy are suggested for retreatment.

Veenhof, A. A., et al. (2009). "The relationship of histological tumor regression grade (TRG) and two different time intervals to surgery following radiation therapy for locally advanced rectal cancer." Int J Colorectal Dis 24(9): 1091-1096.

BACKGROUND: The objective of this study was to assess the effect of two different time intervals between radiation therapy and surgery for rectal cancer on the histological tumor regression grade (TRG) in the resected specimen. METHODS: Between 1995 and 2000, patients undergoing preoperative radiation therapy and TME for locally advanced (T3N0 and T3N1) mid and low rectal tumors treated in the VU University Medical Center or the Zaans Medical Center were entered into this study. All patients received identical radiation treatment (5 x 5 Gy) in the VU University medical center and were subsequently operated on within 2 weeks in the Zaans Medical Center (SI group) and after 6-8 weeks in the VU University Medical Center (LI group). All available histological material was reevaluated for TRG and correlated to survival. RESULTS: Sixty-seven patients were included in the present study, 28 in the LI group and 39 in the SI group. Patient gender was comparable for both groups with 21 (75%) male patients in the LI group versus 26 (67%) male patients in the SI group (p = 0.46). A T3N0 preoperative tumor stage was found in 21 (75%) patients in the LI group and in 33 (85%) patients in the SI group (p = 0.36). All tumors were histologically proven adenocarcinoma. Patients in the

SI group were significantly older (67 vs. 58 years). In the LI group, a significantly more pronounced histological tumor regression was found. A complete response (TRG1), combined with a near complete histological response (TRG 2), were present in 12 patients in the LI group and in four patients in the SI group (p = 0.002). Radicality of resection was comparable for both groups. With a follow-up of over 60 months, there were no statistically significant differences between the SI and LI groups regarding local control, overall, or disease-free survival. CONCLUSION: Although histological tumor regression is significantly more pronounced following a long interval between radiation therapy and surgery, in the present study, this is not reflected in a better radical resection rate, local control or better overall and disease-free survival.

Verma, V., et al. (2017). "Influence of Fractionation Scheme and Tumor Location on Toxicities After Stereotactic Body Radiation Therapy for Large (>/=5 cm) Non-Small Cell Lung Cancer: A Multi-institutional Analysis." Int J Radiat Oncol Biol Phys 97(4): 778-785.

PURPOSE: To describe the impact of fractionation scheme and tumor location on toxicities in stereotactic body radiation therapy (SBRT) for >/=5-cm non-small cell lung cancer (NSCLC), as part of a multi-institutional analysis. METHODS: Patients with primary >/=5-cm N0 M0 NSCLC who underwent </=5-fraction SBRT were examined across multiple high-volume SBRT centers. Collected data included clinical/treatment parameters; toxicities were prospectively assessed at each institution according to the Common Terminology Criteria for Adverse Events. Patients treated daily were compared with those treated every other day (QOD)/other nondaily regimens. Stratification between central and peripheral tumors was also performed. RESULTS: Ninety-two patients from 12 institutions were evaluated (2004-2016), with median follow-up of 12 months. In total there were 23 (25%) and 6 (7%) grade >/=2 and grade >/=3 toxicities, respectively. Grades 2 and 3 pulmonary toxicities occurred in 9% and 4%, respectively; 1 patient treated daily experienced grade 5 radiation pneumonitis. Of the entire cohort, 46 patients underwent daily SBRT, and 46 received QOD (n=40)/other nondaily (n=6) regimens. Clinical/treatment parameters were similar between groups; the QOD/other group was more likely to receive 3-/4-fraction schemas. Patients treated QOD/other experienced significantly fewer grade >/=2 toxicities as compared with daily treatment (7% vs 43%, P<.001). Patients treated daily also had higher rates of grade >/=2 pulmonary toxicities (P=.014). Patients with peripheral tumors (n=66) were more

likely to receive 3-/4-fraction regimens than those with central tumors (n=26). No significant differences in grade >/=2 toxicities were identified according to tumor location (P>.05). CONCLUSIONS: From this multi-institutional study, toxicity of SBRT for >/=5-cm lesions is acceptable, and daily treatment was associated with a higher rate of toxicities.

Vu, C. C., et al. (2013). "Prognostic value of metabolic tumor volume and total lesion glycolysis from (1) (8)F-FDG PET/CT in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer." Nucl Med Commun **34**(10): 959-963.

OBJECTIVES: The aim of this study was to evaluate the prognostic value of pretreatment F-fluorodeoxyglucose PET/computed tomography (CT), particularly in the assessment of metabolic tumor burden markers such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), with respect to clinical outcomes in stage I non-small-cell lung cancer (NSCLC) patients undergoing stereotactic body radiation therapy (SBRT). METHODS: This retrospective study evaluated 50 patients who underwent SBRT for stage I NSCLC from May 2007 to December 2012. The maximum standardized uptake value (SUVmax), average SUV (SUVavg), MTV, and TLG were measured from the PET/CT scan. The study population was dichotomized at the median into high and low groups. Kaplan-Meier log-rank tests were then used to compare high with low PET/CT parameter groups, and univariate Cox proportional hazards regression analysis was carried out to identify predictors of overall survival. RESULTS: The 2-year local control rate was 93.7%. After a median follow-up of 25.1 months, the 2-year overall survival was 79.3%. Eight patients (16%) had disease recurrence. There were three local failures (6%), three mediastinal failures (6%), and six cases of distant metastases (12%). Both Kaplan-Meier actuarial analysis and Cox proportional hazards regression found no correlation between SUVmax, SUVavg, MTV, and TLG and overall survival. CONCLUSION: Standard PET/CT measures, such as SUVmax, as well as newer measures of metabolic tumor burden, such as MTV and TLG, were not correlated with overall survival in our study population of stage I NSCLC patients undergoing SBRT. Larger studies with longer follow-up periods are needed to confirm these results.

Walker, G. V., et al. (2013). "Muddy water? Variation in reporting receipt of breast cancer radiation therapy by population-based tumor registries." Int J Radiat Oncol Biol Phys **86**(4): 686-693.

PURPOSE: To evaluate, in the setting of breast cancer, the accuracy of registry radiation therapy (RT) coding compared with the gold standard of Medicare claims. METHODS AND MATERIALS: Using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we identified 73,077 patients aged >/=66 years diagnosed with breast cancer in the period 2001-2007. Underascertainment (1 - sensitivity), sensitivity, specificity, kappa, and chi (2) were calculated for RT receipt determined by registry data versus claims. Multivariate logistic regression characterized patient, treatment, and geographic factors associated with underascertainment of RT. Findings in the SEER-Medicare registries were compared with three non-SEER registries (Florida, New York, and Texas). RESULTS: In the SEER-Medicare registries, 41.6% (n=30,386) of patients received RT according to registry coding, versus 49.3% (n=36,047) according to Medicare claims (P<.001). Underascertainment of RT was more likely if patients resided in a newer SEER registry (odds ratio [OR] 1.70, 95% confidence interval [CI] 1.60-1.80; P<.001), rural county (OR 1.34, 95% CI 1.21-1.48; P<.001), or if RT was delayed (OR 1.006/day, 95% CI 1.006-1.007; P<.001). Underascertainment of RT receipt in SEER registries was 18.7% (95% CI 18.6-18.8%), compared with 44.3% (95% CI 44.0-44.5%) in non-SEER registries. CONCLUSIONS: Population-based tumor registries are highly variable in ascertainment of RT receipt and should be augmented with other data sources when evaluating quality of breast cancer care. Future work should identify opportunities for the radiation oncology community to partner with registries to improve accuracy of treatment data.

Werner-Wasik, M., et al. (2008). "Increasing tumor volume is predictive of poor overall and progression-free survival: secondary analysis of the Radiation Therapy Oncology Group 93-11 phase I-II radiation dose-escalation study in patients with inoperable non-small-cell lung cancer." Int J Radiat Oncol Biol Phys **70**(2): 385-390.

PURPOSE: Patients with non-small-cell lung cancer (NSCLC) in the Radiation Therapy Oncology Group (RTOG) 93-11 trial received radiation doses of 70.9, 77.4, 83.8, or 90.3 Gy. The locoregional control and survival rates were similar among the various dose levels. We investigated the effect of the gross tumor volume (GTV) on the outcome. METHODS AND MATERIALS: The GTV was defined as the sum of the volumes of the primary tumor and involved lymph nodes. The tumor response, median survival time (MST), and progression-free survival (PFS) were analyzed separately for smaller (< or =45 cm (3)) vs. larger (>45 cm (3)) tumors. RESULTS: The distribution of the GTV was as follows: < or =45 cm (3) in 79 (49%) and >45 cm (3) in 82 (51%) of 161 patients. The median GTV was 47.3 cm (3). N0 status

and female gender were associated with better tumor responses. Patients with smaller (< or =45 cm (3)) tumors achieved a longer MST and better PFS than did patients with larger (>45 cm (3)) tumors (29.7 vs. 13.3 months, p < 0.0001; and 15.8 vs. 8.3 months, p < 0.0001, respectively). Increasing the radiation dose had no effect on the MST or PFS. On multivariate analysis, only a smaller GTV was a significant prognostic factor for improved MST and PFS (hazard ratio [HR], 2.12, p = 0.0002; and HR, 2.0, p = 0.0002, respectively). The GTV as a continuous variable was also significantly associated with the MST and PFS (HR, 1.59, p < 0.0001; and HR, 1.39, p < 0.0001, respectively). CONCLUSIONS: Radiation dose escalation up to 90.3 Gy did not result in improved MST or PFS. The tumor responses were greater in node-negative patients and women. An increasing GTV was strongly associated with decreased MST and PFS. Future radiotherapy trials patients might need to use stratification by tumor volume.

Westphalen, A. C., et al. (2011). "Prostate cancer: prediction of biochemical failure after external-beam radiation therapy--Kattan nomogram and endorectal MR imaging estimation of tumor volume." Radiology **261**(2): 477-486.

PURPOSE: To determine whether magnetic resonance (MR) imaging and MR spectroscopic imaging findings can improve predictions made with the Kattan nomogram for radiation therapy. MATERIALS AND METHODS: The institutional review board approved this retrospective HIPAA-compliant study. Ninety-nine men who underwent endorectal MR and MR spectroscopy before external-beam radiation therapy for prostate cancer (January 1998 to June 2007) were included. Linear predictors were calculated with input variables from the study sample and the Kattan original coefficients. The linear predictor is a single weighted value that combines information of all predictor variables in a model, where the weight of each value is its association with the outcome. Two radiologists independently reviewed all MR images to determine extent of disease; a third independent reader resolved discrepancies. Biochemical failure was defined as a serum prostate-specific antigen level of 2 ng/mL (2 mug/L) or more above nadir. Cox proportional hazard models were used to determine the probabilities of treatment failure (biochemical failure) in 5 years. One model included only the Kattan nomogram data; the other also incorporated imaging findings. The discrimination performance of all models was determined with receiver operating characteristics (ROC) curve analyses. These analyses were followed by an assessment of net risk reclassification. RESULTS: The areas under the ROC curve for the Kattan nomogram and the model incorporating MR imaging findings were 61.1% (95% confidence interval: 58.1%, 64.0%) and 78.0% (95% confidence interval: 75.7%, 80.4%), respectively. Comparison of performance showed that the model with imaging findings performed significantly better than did the model with clinical variables alone (P <.001). Overall, the addition of imaging findings led to an improvement in risk classification of about 28%, ranging from approximately a minimum of 16% to a maximum of 39%, depending on the risk change considered important. CONCLUSION: MR imaging data improve the prediction of biochemical failure with the Kattan nomogram after external-beam radiation therapy for prostate cancer. The number needed to image to improve the prediction of biochemical failure in one patient ranged from three to six.

Wheeler, J. A., et al. (1993). "Dedifferentiation of locally recurrent prostate cancer after radiation therapy. Evidence for tumor progression." Cancer **71**(11): 3783-3787.

BACKGROUND: Untreated or unsuccessfully treated prostatic adenocarcinoma may develop more malignant characteristics as time passes--the phenomenon of tumor progression. Whether this occurs after unsuccessful radiation therapy has not been answered. This study was designed to address that issue. METHODS: The histologic grades at initial diagnosis and at local recurrence were compared in 49 patients who experienced local recurrence after external beam radiation therapy. RESULTS: Tumor grades were assigned using the M. D. Anderson grading system. At the initial diagnosis, the grades were distributed as follows: Grade 1, 18 (37%), Grade 2, 22 (45%); Grade 3, 8 (16%); and Grade 4, 1 (2%). At recurrence, the grades were: Grade 1, 3 (6%); Grade 2, 14 (29%); Grade 3, 14 (29%); and Grade 4, 18 (37%). The shift to higher grades at recurrence was highly significant (P < 0.001). This dedifferentiation could not be accounted for by possible tissue sampling variability, and stepwise multiple variable logistic regression revealed that the only factor predicting for dedifferentiation was the time since treatment. The tumors that recurred later had a significantly higher likelihood to be dedifferentiated than those that recurred early. Patients whose tumors dedifferentiated had a poorer survival than those whose tumors retained their original grade. CONCLUSIONS: The possibilities were considered that the dedifferentiation could arise by tissue sampling error, by persistence and regrowth of high-grade components, by the development of new tumors, or by radiation-induced transformation. None of these mechanisms appeared to explain the data adequately, and it was concluded that the observed dedifferentiation was indeed a

manifestation of time-dependent tumor progression. Eradication of the primary tumor is therefore important, not only to allay local symptoms, but also to prevent the emergence of more virulent and potentially lethal tumors.

Wieder, H. A., et al. (2007). "Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival." Radiology **243**(3): 744-751.

PURPOSE: To retrospectively evaluate the prognostic importance of involvement of the circumferential resection margin predicted by using magnetic resonance (MR) imaging before neoadjuvant treatment in patients with rectal cancer. MATERIALS AND METHODS: The local institutional review board approved the retrospective analysis of the data and waived informed consent. Sixty-eight patients (52 men, 16 women; mean age +/- standard deviation, 58.9 years +/- 9.4) with cT3 NX M0 tumors were included. T2-weighted MR images were analyzed in consensus by two radiologists with respect to the shortest distance between the outermost parts of the tumor to the adjacent mesorectal fascia (as the potential circumferential resection margin in total mesorectal excision). Histopathologic and follow-up data were available for all patients (mean follow-up time, 54 months; range, 31-77 months). To compare local recurrence and survival rates, the population was divided into three groups categorized according to the minimum distance of the tumor to the mesorectal fascia (group 1, <or=1 mm; group 2, >1 to 5 mm; group 3, >5 mm). Univariate Cox and multivariate proportional hazard regression models were used to test the prognostic importance of clinical, histopathologic regression, and histopathologic tumor parameters. RESULTS: MR imaging led to accurate prediction of a histologically involved circumferential resection margin (sensitivity, 100%; specificity, 88%). The rates for local recurrence (group 1, 33%; group 2, 5%; group 3, 6%; P<.02) and 5-year overall survival (group 1, 39%; group 2, 70%; group 3, 90%; P<.001) differed significantly among the predefined groups. The distance to the mesorectal fascia was an independent prognostic parameter in multivariate analysis (P<.001), and histopathologic response to treatment provided no additional information. CONCLUSION: Prediction of the tumor-free circumferential resection margin assessed with MR imaging before initiation of neoadjuvant chemotherapy and radiation therapy proved to be a prognostic factor in rectal cancer.

Witek, M., et al. (2014). "Tumor radiation therapy creates therapeutic vaccine responses to the colorectal cancer antigen GUCY2C." Int J Radiat Oncol Biol Phys **88**(5): 1188-1195.

PURPOSE: Radiation therapy (RT) is thought to produce clinical responses in cancer patients, not only through direct toxicity to cancer cells and supporting tumor stroma cells, but also through activation of immunologic effectors. More recently, RT has potentiated the local and systemic effects of cancer immunotherapy (IT). However, combination regimens that maximize immunologic and clinical efficacy remain undefined. METHODS AND MATERIALS: We evaluated the impact of local RT on adenoviral-mediated vaccination against the colorectal cancer antigen GUCY2C (Ad5-GUCY2C) in a murine subcutaneous tumor model using mouse CT26 colon cancer cells (CT26-GUCY2C). Immune responses were assessed by ELISpot, and clinical responses were assessed by tumor size and incidence. RESULTS: The specific sequence of tumor-directed RT preceding Ad5-GUCY2C IT transformed inactive therapeutic Ad5-GUCY2C vaccination into a curative vaccine. GUCY2C-specific T cell responses were amplified (P<.05), tumor eradication was maximized (P<.01), and tumor volumes were minimized (P<.001) in mice whose tumors were irradiated before, compared with after, Ad5-GUCY2C vaccination. The immunologic and antitumor efficacy of Ad5-GUCY2C was amplified comparably by unfractionated (8 Gy x 1), or biologically equivalent doses of fractionated (3.5 Gy x 3), RT. The antitumor effects of sequential RT and IT (RT-IT) depended on expression of GUCY2C by tumor cells and the adenoviral vaccine vector, and tumor volumes were inversely related to the magnitude of GUCY2C-specific T cell responses. Moreover, mice cured of CT26-GUCY2C tumors by RT-IT showed long-lasting antigen-dependent protection, resisting tumors formed by GUCY2C-expressing 4T1 breast cancer cells inoculated 50 days after CT26 cells. CONCLUSIONS: Optimal sequencing of RT and IT amplifies antigen-specific local and systemic immune responses, revealing novel acute and long-term therapeutic antitumor protection. These observations underscore the importance of modality sequence optimization before the initiation of clinical trials of RT and IT to maximize immune and antitumor responses.

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References

1. Ahn, S. J., et al. (2012). "Quantitative assessment of tumor responses after radiation therapy in a DLD-1 colon cancer mouse model using serial

dynamic contrast-enhanced magnetic resonance imaging." Yonsei Med J 53(6): 1147-1153.

2. Albuquerque, K. V., et al. (2005). "Impact of tumor volume-directed involved field radiation therapy integrated in the management of recurrent ovarian cancer." Gynecol Oncol 96(3): 701-704.

3. Albuquerque, K., et al. (2016). "Long-term Benefit of Tumor Volume-Directed Involved Field Radiation Therapy in the Management of Recurrent Ovarian Cancer." Int J Gynecol Cancer 26(4): 655-660.

4. Allibhai, Z., et al. (2013). "The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer." Int J Radiat Oncol Biol Phys 87(5): 1064-1070.

5. Ardenfors, O., et al. (2018). "Out-of-field doses from secondary radiation produced in proton therapy and the associated risk of radiation-induced cancer from a brain tumor treatment." Phys Med 53: 129-136.

6. Atsumi, K., et al. (2010). "Predictive factors of esophageal stenosis associated with tumor regression in radiation therapy for locally advanced esophageal cancer." J Radiat Res 51(1): 9-14.

7. Azria, D., et al. (2003). "Enhancement of radiation therapy by tumor necrosis factor alpha in human colon cancer using a bispecific antibody." Int J Radiat Oncol Biol Phys 55(5): 1363-1373.

8. Baidu. http://www.baidu.com. 2018.

9. Balderson, M., et al. (2016). "Under conditions of large geometric miss, tumor control probability can be higher for static gantry intensity-modulated radiation therapy compared to volume-modulated arc therapy for prostate cancer." Med Dosim 41(2): 180-185.

10. Bando, R., et al. (2013). "Changes of tumor and normal structures of the neck during radiation therapy for head and neck cancer requires adaptive strategy." J Med Invest 60(1-2): 46-51.

11. Basaki, K., et al. (2006). "Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume." Int J Radiat Oncol Biol Phys 64(2): 449-454.

12. Bassalyk, L. S., et al. (1986). "[Effect of radiation and drug therapy on the hormonal status of patients with breast cancer, taking into consideration the receptor level of the tumor]." Med Radiol (Mosk) 31(4): 48-52.

13. Belfatto, A., et al. (2016). "Kinetic Models for Predicting Cervical Cancer Response to Radiation Therapy on Individual Basis Using

Tumor Regression Measured In Vivo With Volumetric Imaging." Technol Cancer Res Treat 15(1): 146-158.

14. Bernal-Estevez, D., et al. (2016). "Chemotherapy and radiation therapy elicits tumor specific T cell responses in a breast cancer patient." BMC Cancer 16: 591.

15. Bibault, J. E., et al. (2012). "Image-guided robotic stereotactic radiation therapy with fiducial-free tumor tracking for lung cancer." Radiat Oncol 7: 102.

16. Blanchard, P., et al. (2017). "Radiation therapy to the primary in metastatic prostate cancer: palliation only or altering tumor biology?" Curr Opin Urol 27(6): 580-586.

17. Bowen, S. R., et al. (2018). "Tumor radiomic heterogeneity: Multiparametric functional imaging to characterize variability and predict response following cervical cancer radiation therapy." J Magn Reson Imaging 47(5): 1388-1396.

18. Bradley, J., et al. (2012). "A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515." Int J Radiat Oncol Biol Phys 82(1): 435-441 e431.

19. Braun, D. P., et al. (2013). "Effect of naturopathic and nutritional supplement treatment on tumor response, control, and recurrence in patients with prostate cancer treated with radiation therapy." J Altern Complement Med 19(3): 198-203.

20. Buglione, M., et al. (2017). "Subgroup Analysis According to Human Papillomavirus Status and Tumor Site of a Randomized Phase II Trial Comparing Cetuximab and Cisplatin Combined With Radiation Therapy for Locally Advanced Head and Neck Cancer." Int J Radiat Oncol Biol Phys 97(3): 462-472.

21. But-Hadzic, J., et al. (2016). "Acute Toxicity and Tumor Response in Locally Advanced Rectal Cancer After Preoperative Chemoradiation Therapy With Shortening of the Overall Treatment Time Using Intensity-Modulated Radiation Therapy With Simultaneous Integrated Boost: A Phase 2 Trial." Int J Radiat Oncol Biol Phys 96(5): 1003-1010.

22. Chinnaiyan, A. M., et al. (2000). "Combined effect of tumor necrosis factor-related apoptosis-inducing ligand and ionizing radiation in breast cancer therapy." Proc Natl Acad Sci U S A 97(4): 1754-1759.

23. Crane, C. H., et al. (2003). "The addition of continuous infusion 5-FU to preoperative

radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer." Int J Radiat Oncol Biol Phys 57(1): 84-89.

24. Crittenden, M. R., et al. (2013). "The peripheral myeloid expansion driven by murine cancer progression is reversed by radiation therapy of the tumor." PLoS One 8(7): e69527.

25. Dadey, D. Y. A., et al. (2017). "Antibody Targeting GRP78 Enhances the Efficacy of Radiation Therapy in Human Glioblastoma and Non-Small Cell Lung Cancer Cell Lines and Tumor Models." Clin Cancer Res 23(10): 2556-2564.

26. D'Amico, A. V., et al. (2008). "Tumor volume changes on 1.5 tesla endorectal MRI during neoadjuvant androgen suppression therapy for higher-risk prostate cancer and recurrence in men treated using radiation therapy results of the phase II CALGB 9682 study." Int J Radiat Oncol Biol Phys 71(1): 9-15.

27. Dholakia, A. S., et al. (2014). "Baseline metabolic tumor volume and total lesion glycolysis are associated with survival outcomes in patients with locally advanced pancreatic cancer receiving stereotactic body radiation therapy." Int J Radiat Oncol Biol Phys 89(3): 539-546.

28. Dorsey, J. F., et al. (2015). "Tracking viable circulating tumor cells (CTCs) in the peripheral blood of non-small cell lung cancer (NSCLC) patients undergoing definitive radiation therapy: pilot study results." Cancer 121(1): 139-149.

29. Dresen, R. C., et al. (2009). "Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part I. Are we able to predict tumor confined to the rectal wall?" Radiology 252(1): 71-80.

30. Eide, H. A., et al. (2018). "Serum cytokine profiles and metabolic tumor burden in patients with non-small cell lung cancer undergoing palliative thoracic radiation therapy." Adv Radiat Oncol 3(2): 130-138.

31. Formenti, S. C., et al. (2002). "T1 stage breast cancer: adjuvant hypofractionated conformal radiation therapy to tumor bed in selected postmenopausal breast cancer patients--pilot feasibility study." Radiology 222(1): 171-178.

32. Frenzel, T., et al. (2018). "Locally Ablative Radiation Therapy of a Primary Human Small Cell Lung Cancer Tumor Decreases the Number of Spontaneous Metastases in Two Xenograft Models." Int J Radiat Oncol Biol Phys 100(4): 1044-1056.

33. Frick, M. A., et al. (2018). "Circulating Tumor Cell Assessment in Presumed Early Stage Non-Small Cell Lung Cancer Patients Treated with Stereotactic Body Radiation Therapy: A Prospective Pilot Study." Int J Radiat Oncol Biol Phys 102(3): 536-542.

34. Gabelov, A. A. and G. M. Zharinov (1983). "[Tumor regression rate and the effectiveness of the radiation therapy of cervical cancer patients]." Vopr Onkol 29(6): 41-45.

35. Google. http://www.google.com. 2018.

36. Grabenbauer, G. G., et al. (1998). "Nodal CT density and total tumor volume as prognostic factors after radiation therapy of stage III/IV head and neck cancer." Radiother Oncol 47(2): 175-183.

37. Gulack, B. C., et al. (2016). "Surgical Resection of the Primary Tumor in Stage IV Colorectal Cancer Without Metastasectomy is Associated With Improved Overall Survival Compared With Chemotherapy/Radiation Therapy Alone." Dis Colon Rectum 59(4): 299-305.

38. Gulec, S. A., et al. (2011). "The prognostic value of functional tumor volume and total lesion glycolysis in patients with colorectal cancer liver metastases undergoing 90Y selective internal radiation therapy plus chemotherapy." Eur J Nucl Med Mol Imaging 38(7): 1289-1295.

39. Gunter, T., et al. (2015). "Changes in Non-Small Cell Lung Cancer Tumor Location Secondary to Gastric Distension, Implications in the Context of Stereotactic Body Radiation Therapy." J Okla State Med Assoc 108(9-10): 398-401.

40. Hafeez, S., et al. (2016). "Prospective Study Delivering Simultaneous Integrated High-dose Tumor Boost (</=70 Gy) With Image Guided Adaptive Radiation Therapy for Radical Treatment of Localized Muscle-Invasive Bladder Cancer." Int J Radiat Oncol Biol Phys 94(5): 1022-1030.

41. Hamming-Vrieze, O., et al. (2012). "Evaluation of tumor shape variability in head-and-neck cancer patients over the course of radiation therapy using implanted gold markers." Int J Radiat Oncol Biol Phys 84(2): e201-207.

42. Hannan, R., et al. (2015). "Stereotactic radiation therapy of renal cancer inferior vena cava tumor thrombus." Cancer Biol Ther 16(5): 657-661.

43. Haque, W., et al. (2017). "Radiation therapy utilization and outcomes for older women with breast cancer: Impact of molecular subtype and tumor grade." Breast 35: 34-41.

44. Hayakawa, K., et al. (1996). "Impact of tumor extent and location on treatment outcome in patients with stage III non-small cell lung cancer

treated with radiation therapy." Jpn J Clin Oncol 26(4): 221-228.

45. Heerkens, H. D., et al. (2014). "MRI-based tumor motion characterization and gating schemes for radiation therapy of pancreatic cancer." Radiother Oncol 111(2): 252-257.

46. Heerkens, H. D., et al. (2017). "Recommendations for MRI-based contouring of gross tumor volume and organs at risk for radiation therapy of pancreatic cancer." Pract Radiat Oncol 7(2): 126-136.

47. Hintz, B. L., et al. (1983). "Local control of T1 vocal cord cancer with radiation therapy: the importance of tumor character vs. treatment parameters." Head Neck Surg 5(3): 204-210.

48. Karava, K., et al. (2017). "Potential dosimetric benefits of adaptive tumor tracking over the internal target volume concept for stereotactic body radiation therapy of pancreatic cancer." Radiat Oncol 12(1): 175.

49. Karki, K., et al. (2017). "Variabilities of Magnetic Resonance Imaging-, Computed Tomography-, and Positron Emission Tomography-Computed Tomography-Based Tumor and Lymph Node Delineations for Lung Cancer Radiation Therapy Planning." Int J Radiat Oncol Biol Phys 99(1): 80-89.

50. Keruakous, A. R., et al. (2014). "The impact of isolated tumor cells on loco-regional recurrence in breast cancer patients treated with breast-conserving treatment or mastectomy without post-mastectomy radiation therapy." Breast Cancer Res Treat 146(2): 365-370.

51. Khil, M. S., et al. (1997). "Tumor control of locally advanced prostate cancer following combined estramustine, vinblastine, and radiation therapy." Cancer J Sci Am 3(5): 289-296.

52. Kitamura, K., et al. (2003). "Reduction in acute morbidity using hypofractionated intensity-modulated radiation therapy assisted with a fluoroscopic real-time tumor-tracking system for prostate cancer: preliminary results of a phase I/II study." Cancer J 9(4): 268-276.

53. Klement, R. J., et al. (2014). "Support vector machine-based prediction of local tumor control after stereotactic body radiation therapy for early-stage non-small cell lung cancer." Int J Radiat Oncol Biol Phys 88(3): 732-738.

54. Knol, H. P., et al. (1997). "Effect of radiation therapy alone or in combination with surgery and/or chemotherapy on tumor and symptom control of recurrent rectal cancer." Strahlenther Onkol 173(1): 43-49.

55. Kocher, M. R., et al. (2018). "Pretreatment 18F-Fluorodeoxyglucose Positron Emission Tomography Standardized Uptake Values and Tumor Size in Medically Inoperable Nonsmall Cell Lung Cancer Is Prognostic of Overall 2-Year Survival After Stereotactic Body Radiation Therapy." J Comput Assist Tomogr 42(1): 146-150.

56. Kochetkova, V. A. and L. E. Voronova (1975). "[The effect of radiation therapy on the course of the tumor process in patients with laryngeal cancer]." Vopr Onkol 21(6): 44-48.

57. Komatsu, F. and M. Kajiwara (1997). "Comparison of natural killer (NK) sensitivities of two tumor cell lines established from a cancer patient before and after radiation therapy." Clin Immunol Immunopathol 82(2): 190-196.

58. Konduri, S., et al. (2009). "Tolfenamic acid enhances pancreatic cancer cell and tumor response to radiation therapy by inhibiting survivin protein expression." Mol Cancer Ther 8(3): 533-542.

59. Kuranishi, F. and T. Ohno (2013). "Eradication of breast cancer with bone metastasis by autologous formalin-fixed tumor vaccine (AFTV) combined with palliative radiation therapy and adjuvant chemotherapy: a case report." World J Surg Oncol 11: 127.

60. Leonard, C., et al. (1995). "Are axillary recurrence and overall survival affected by axillary extranodal tumor extension in breast cancer? Implications for radiation therapy." J Clin Oncol 13(1): 47-53.

61. Levegrun, S., et al. (2000). "Analysis of biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer using dose-distribution variables and tumor control probability models." Int J Radiat Oncol Biol Phys 47(5): 1245-1260.

62. Levegrun, S., et al. (2001). "Fitting tumor control probability models to biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer: pitfalls in deducing radiobiologic parameters for tumors from clinical data." Int J Radiat Oncol Biol Phys 51(4): 1064-1080.

63. Levendag, P. C., et al. (2006). "Interstitial radiation therapy for early-stage nasal vestibule cancer: a continuing quest for optimal tumor control and cosmesis." Int J Radiat Oncol Biol Phys 66(1): 160-169.

64. Lowes, L. E., et al. (2015). "The significance of circulating tumor cells in prostate cancer patients undergoing adjuvant or salvage radiation therapy." Prostate Cancer Prostatic Dis 18(4): 358-364.

65. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.

66. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.

67. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15.

68. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.

69. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.

70. Marsland Press. http://www.sciencepub.net. 2018.

71. Matsuda, T., et al. (2013). "Impact of adjuvant radiation therapy for microscopic residual tumor after resection of extrahepatic bile duct cancer." Am J Clin Oncol 36(5): 461-465.

72. Mayr, N. A., et al. (2010). "Longitudinal changes in tumor perfusion pattern during the radiation therapy course and its clinical impact in cervical cancer." Int J Radiat Oncol Biol Phys 77(2): 502-508.

73. Miller, J. A., et al. (2017). "The impact of tumor biology on survival and response to radiation therapy among patients with non-small cell lung cancer brain metastases." Pract Radiat Oncol 7(4): e263-e273.

74. Miller, T. R. and P. W. Grigsby (2002). "Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy." Int J Radiat Oncol Biol Phys 53(2): 353-359.

75. Milosevic, M. F., et al. (2016). "Sorafenib Increases Tumor Hypoxia in Cervical Cancer Patients Treated With Radiation Therapy: Results of a Phase 1 Clinical Study." Int J Radiat Oncol Biol Phys 94(1): 111-117.

76. Muijs, C., et al. (2014). "Residual tumor after neoadjuvant chemoradiation outside the radiation therapy target volume: a new prognostic factor for survival in esophageal cancer." Int J Radiat Oncol Biol Phys 88(4): 845-852.

77. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2018.

78. Nishibuchi, I., et al. (2014). "Time-adjusted internal target volume: a novel approach focusing on heterogeneity of tumor motion based on 4-dimensional computed tomography imaging for radiation therapy planning of lung cancer." Int J Radiat Oncol Biol Phys 89(5): 1129-1137.

79. Nougaret, S., et al. (2012). "MR volumetric measurement of low rectal cancer helps predict tumor response and outcome after combined chemotherapy and radiation therapy." Radiology 263(2): 409-418.

80. Ohri, N., et al. (2018). "Stereotactic body radiation therapy for stage I non-small cell lung cancer: The importance of treatment planning algorithm and evaluation of a tumor control probability model." Pract Radiat Oncol 8(2): e33-e39.

81. Olberg, S., et al. (2018). "Optimization of treatment planning workflow and tumor coverage during daily adaptive magnetic resonance image guided radiation therapy (MR-IGRT) of pancreatic cancer." Radiat Oncol 13(1): 51.

82. Parekh, A., et al. (2013). "Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer." Gastrointest Cancer Res 6(5-6): 137-143.

83. Park, M. J., et al. (2011). "Locally advanced rectal cancer: added value of diffusion-weighted MR imaging for predicting tumor clearance of the mesorectal fascia after neoadjuvant chemotherapy and radiation therapy." Radiology 260(3): 771-780.

84. Pezner, R. D., et al. (1988). "To boost or not to boost: decreasing radiation therapy in conservative breast cancer treatment when "inked" tumor resection margins are pathologically free of cancer." Int J Radiat Oncol Biol Phys 14(5): 873-877.

85. Pezner, R. D., et al. (1989). "The reverse hockey stick technique: postmastectomy radiation therapy for breast cancer patients with locally advanced tumor presentation or extensive loco-regional recurrence." Int J Radiat Oncol Biol Phys 17(1): 191-197.

86. Pezner, R. D., et al. (2013). "Radiation therapy for breast cancer patients who undergo oncoplastic surgery: localization of the tumor bed for the local boost." Am J Clin Oncol 36(6): 535-539.

87. Philpotts, L. E., et al. (1996). "Mammographic findings of recurrent breast cancer after lumpectomy and radiation therapy: comparison with the primary tumor." Radiology 201(3): 767-771.

88. Pirogov, A. I. and S. N. Nered (1989). "[Preoperative diagnosis of residual tumor in esophageal cancer following radiation therapy]." Grudn Khir (5): 69-74.

89. Pucar, D., et al. (2007). "Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence." Int J Radiat Oncol Biol Phys 69(1): 62-69.

90. Quackenbush, K., et al. (2017). "Regression of a Fungating Tumor After Hypofractionated Radiation Therapy in a Patient With Metastatic Breast Cancer." Cureus 9(7): e1417.

91. Ragazzi, G., et al. (1997). "Variations of tumor control and rectum complication probabilities

due to random set-up errors during conformal radiation therapy of prostate cancer." Radiother Oncol 44(3): 259-263.

92. Rombouts, A. J. M., et al. (2018). "Tumor response after long interval comparing 5x5Gy radiation therapy with chemoradiation therapy in rectal cancer patients." Eur J Surg Oncol 44(7): 1018-1024.

93. Rwigema, J. C., et al. (2015). "4pi noncoplanar stereotactic body radiation therapy for head-and-neck cancer: potential to improve tumor control and late toxicity." Int J Radiat Oncol Biol Phys 91(2): 401-409.

94. Sakakibara-Konishi, J., et al. (2011). "Phase I study of concurrent real-time tumor-tracking thoracic radiation therapy with paclitaxel and carboplatin in locally advanced non-small cell lung cancer." Lung Cancer 74(2): 248-252.

95. Sandler, H. M., et al. (1990). "The influence of tumor size and pre-treatment staging on outcome following radiation therapy alone for stage I non-small cell lung cancer." Int J Radiat Oncol Biol Phys 19(1): 9-13.

96. Sasaoka, M., et al. (1997). "[Radiation therapy for uterine cervix cancer: importance of evaluation of pre-treatment tumor size with MR imaging]." Nihon Igaku Hoshasen Gakkai Zasshi 57(8): 505-509.

97. Sharabi, A., et al. (2017). "Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center." Oncologist 22(6): 631-637.

98. Shimizu, S., et al. (2014). "Early results of urethral dose reduction and small safety margin in intensity-modulated radiation therapy (IMRT) for localized prostate cancer using a real-time tumor-tracking radiotherapy (RTRT) system." Radiat Oncol 9: 118.

99. Shinohara, N., et al. (2013). "Longitudinal comparison of quality of life after real-time tumor-tracking intensity-modulated radiation therapy and radical prostatectomy in patients with localized prostate cancer." J Radiat Res 54(6): 1095-1101.

100. Shintani, S., et al. (2001). "The influence of blood arterial oxygen condition on the tumor response to preoperative radiation therapy in oral cancer patients." Oncol Rep 8(1): 99-102.

101. Shipley, W. U., et al. (1987). "Intraoperative radiation therapy in patients with bladder cancer. A review of techniques allowing improved tumor doses and providing high cure rates without loss of bladder function." Cancer 60(7): 1485-1488.

102. Stephans, K. L., et al. (2018). "Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer." Int J Radiat Oncol Biol Phys 100(2): 462-469.

103. Stokes, C. L., et al. (2018). "Timing of Radiation Therapy in Pediatric Wilms Tumor: A Report From the National Cancer Database." Int J Radiat Oncol Biol Phys 101(2): 453-461.

104. Straughn, J. M., Jr., et al. (2006). "Anti-tumor activity of TRA-8 anti-death receptor 5 (DR5) monoclonal antibody in combination with chemotherapy and radiation therapy in a cervical cancer model." Gynecol Oncol 101(1): 46-54.

105. Swisher, S. G., et al. (2003). "Induction of p53-regulated genes and tumor regression in lung cancer patients after intratumoral delivery of adenoviral p53 (INGN 201) and radiation therapy." Clin Cancer Res 9(1): 93-101.

106. Tabi, Z., et al. (2010). "Resistance of CD45RA-T cells to apoptosis and functional impairment, and activation of tumor-antigen specific T cells during radiation therapy of prostate cancer." J Immunol 185(2): 1330-1339.

107. Tai, A., et al. (2016). "An analysis of tumor control probability of stereotactic body radiation therapy for lung cancer with a regrowth model." Phys Med Biol 61(10): 3903-3913.

108. Takahashi, N., et al. (2016). "Metabolic tumor volume on FDG-PET/CT is a possible prognostic factor for Stage I lung cancer patients treated with stereotactic body radiation therapy: a retrospective clinical study." J Radiat Res 57(6): 655-661.

109. Tennyson, N., et al. (2017). "Effect of variations in atelectasis on tumor displacement during radiation therapy for locally advanced lung cancer." Adv Radiat Oncol 2(1): 19-26.

110. Timar, J., et al. (2003). "The effect of leukocyte interleukin injection (Multikine) treatment on the peritumoral and intratumoral subpopulation of mononuclear cells and on tumor epithelia: a possible new approach to augmenting sensitivity to radiation therapy and chemotherapy in oral cancer--a multicenter phase I/II clinical Trial." Laryngoscope 113(12): 2206-2217.

111. Tjebbes, G. W., et al. (2002). "P53 tumor suppressor gene mutations in laryngeal cancer and in recurrent disease following radiation therapy." Oral Oncol 38(3): 296-300.

112. VanderBeek, L., et al. (2017). "Primary Breast Cancer Tumor and Patient Characteristics as Predictors of Adjuvant Radiation Therapy." Breast J 23(1): 40-48.

113. Vargo, J. A., et al. (2018). "Head and Neck Tumor Control Probability: Radiation Dose-Volume Effects in Stereotactic Body Radiation Therapy for Locally Recurrent Previously-Irradiated Head and Neck Cancer: Report of the AAPM Working Group." Int J Radiat Oncol Biol Phys.

114. Veenhof, A. A., et al. (2009). "The relationship of histological tumor regression grade (TRG) and two different time intervals to surgery following radiation therapy for locally advanced rectal cancer." Int J Colorectal Dis 24(9): 1091-1096.

115. Verma, V., et al. (2017). "Influence of Fractionation Scheme and Tumor Location on Toxicities After Stereotactic Body Radiation Therapy for Large (>/=5 cm) Non-Small Cell Lung Cancer: A Multi-institutional Analysis." Int J Radiat Oncol Biol Phys 97(4): 778-785.

116. Vu, C. C., et al. (2013). "Prognostic value of metabolic tumor volume and total lesion glycolysis from (1) (8)F-FDG PET/CT in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer." Nucl Med Commun 34(10): 959-963.

117. Walker, G. V., et al. (2013). "Muddy water? Variation in reporting receipt of breast cancer radiation therapy by population-based tumor registries." Int J Radiat Oncol Biol Phys 86(4): 686-693.

118. Werner-Wasik, M., et al. (2008). "Increasing tumor volume is predictive of poor overall and progression-free survival: secondary analysis of the Radiation Therapy Oncology Group 93-11 phase I-II radiation dose-escalation study in patients with inoperable non-small-cell lung cancer." Int J Radiat Oncol Biol Phys 70(2): 385-390.

119. Westphalen, A. C., et al. (2011). "Prostate cancer: prediction of biochemical failure after external-beam radiation therapy--Kattan nomogram and endorectal MR imaging estimation of tumor volume." Radiology 261(2): 477-486.

120. Wheeler, J. A., et al. (1993). "Dedifferentiation of locally recurrent prostate cancer after radiation therapy. Evidence for tumor progression." Cancer 71(11): 3783-3787.

121. Wieder, H. A., et al. (2007). "Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival." Radiology 243(3): 744-751.

122. Wikipedia. The free encyclopedia. Cancer. https://en.wikipedia.org/wiki/Cancer. 2018.

123. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2018.

124. Wikipedia. The free encyclopedia. Stem cell. https://en.wikipedia.org/wiki/Stem_cell. 2018.

125. Witek, M., et al. (2014). "Tumor radiation therapy creates therapeutic vaccine responses to the colorectal cancer antigen GUCY2C." Int J Radiat Oncol Biol Phys 88(5): 1188-1195.

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