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The use of self-reflective learning and interactive technology to support interprofessional education

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Background: Communication between members of the interprofessional cancer healthcare team and patients who are living with cancer is an important, but often overlooked, issue. Comprehensive cancer care requires the effective communication of clinical information among members of the cancer management team, and with the patient and his/her loved ones. Good communication can expand the supportive role of the specialist and team members at crucial times for the patient. This can not only influence treatment selection, but also encourage patient empowerment, and positively shape patient outcomes.

Learning Gap

More than 75% of oncologists think that their communication skills are adequate, but they actually have difficulties discussing end-of-life issues, giving hope, and dealing with hostile patients. The areas of most perceived difficulty include intervening with patients
that are angry or in denial, as well as having to announce bad news. Furthermore, only 29% of residents in oncology understand the meaning of the term *shared decision making*, a process that helps ensure the patient maximal quality of life throughout the illness. Consequently, only 40%-50% of Canadians with a diagnosis of cancer indicate that their information and communication needs are met.

Purpose: CHAT (Cancer HealthcAre Team) is an interactive, case-based simulation CME program intended for interprofessional members of the cancer healthcare team designed to improve communication skills with patients. An interprofessional scientific committee comprised of 5 physicians (2 urologists, 1 radiation oncologist, 1 general practitioner in oncology, and 1 surgeon), 1 palliative care nurse, and 1 psychologist in oncology developed the program. Each member of this team possesses unique skills that enabled them to address specific areas of interest, such as communication skills and cancer treatment strategies. The Web site for CHAT was launched in April 2012.

Overall Program Objectives

By the end of this program, participants will be able to

□œ implement motivational interviewing techniques and empathetic communication strategies to empower patients;

□œ direct patients to reliable sources of medical information dealing with a cancer diagnosis or treatment;

□œ provide tools and resources to help address patient needs;

□œ ensure that treatment options were proposed to patients and that patients understand their responsibility in treatment decisions.

Methods: Using videos to demonstrate clinical practice scenarios, participants are encouraged to comment on what constitutes effective communication between healthcare professionals and patients living with cancer. This format actively engages the participant. An innovative, *Twitter-like* interface encourages participants to make comments, review comments from other participants, and reflect on the material presented.

Practice tools and resources will also be discussed. This program focuses on breaking bad news, eliciting information/giving information, and screening for distress, focusing on issues specific to prostate and colorectal cancer. A stand-alone *toolbox* is provided for the members of the cancer healthcare team.

The toolbox includes information on:

□œ Breaking bad news

□œ Screening for distress
□œ Effective communication
□œ Resources for patients

The toolbox provides access to useful tools and resources that are downloadable, so that participants can implement them in their practice and share them with peers.

Results: This program was launched in April 2012; therefore, participant data is not yet available. In the next phase of this program, we will measure that the use of instructive videos, self-reflection, and interactive questions may help participants to acquire an understanding of effective communication skills, and more readily assess the needs of patients living with cancer. This understanding may translate into an overall improvement in healthcare practice.

Discussion:

Case simulation activities for interprofessional education are powerful tools that give participants the means to

□œ understand how their interactions with patients can positively influence cancer treatment;
□œ improve their knowledge, communication skills, and confidence when helping patients living with cancer.

A 1991 Toronto meeting of healthcare professionals concluded that doctor-patient communication problems are common and can adversely affect patient care. Skills workshops and practice sessions have been conducted to remedy this problem.

Methods commonly used to improve communication skills include:

□œ Watching teachers
□œ Watching videos
□œ Role play

Watching videos has proven to be a powerful tool for learners to improve communication skills, and correct mistakes in their behaviour. In a systematic review of CME activities, The Johns Hopkins Evidence-Based Practice Center for Healthcare Research and Quality concluded that multimedia, multiple instructional techniques, and multiple exposures to subject matter should be incorporated into CME/CHE. Participating in CME activities that do not have multiple methods of learning will have minimal impact. Case-based learning is associated with improvements in knowledge.

Conclusions: This program will measure how instructive videos, self-reflection, and interactive questions help participants acquire an understanding of effective communication skills, and more readily assess the needs of patients living with cancer.

This innovative program is Web-based and iPad compatible, very flexible, and adaptable to the needs of participants. It is unique and engaging, and participants can immediately see how they influence feedback from others. This program allows users to know their deficiencies and knowledge gaps right away, which is a feature many others lack.

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Health indicators in the radiotherapy workplace

Authors : Genevieve Coulombe, Dominique Lefebvre, Daniel Payette, Michèle De Guise, Danielle Daunais, Amélie Ouellette, Jean-Pierre Guay, David Roberge

Purpose: In the context of a health promotion initiative, a questionnaire "together towards health" was developed. The questions assess physical and psychological health and the test is designed to identify areas which can be targeted for intervention.

Materials and methods: After review by administrators, the 40 item questionnaire was filled out by radiotherapy staff on a voluntary basis. Anonymized demographics were collected as well as information on lifestyle (exercise, sleeping habits, nutrition, alcohol use and smoking), stress (Perceived Stress Questionnaire) and workplace well-being. Respondents were asked to identify areas they would like to work on in individual or group settings. Bonferroni test was use for multiple comparisons.

Results: The response rate was approximately 55% (87 respondents — including 16 radiation oncologists, 12 physicists and 24 therapists). Median age was 37.7 years, 60.5% women.

Detailed results will be presented but, of note, were stress levels which were similar across professions and in keeping with population averages. Smoking prevalence was low (2.3%) as was reported daily exercise (8%). Residents reported less sleep (6.1 hours) than physicists ($p=0.046$). Therapist and physicists reported fewer opportunities for on the job learning than physicians and residents ($p \leq 0.007$).

The 3 top objectives cited for group activities were: exercise (43%), workplace wellbeing (24%) and stress management (21%). Top cited for individual improvement activities were: stress management (53%), physical activity (23%) and nutrition (14%).

Conclusions: Health indicators and workplace well-being indicators in a radiotherapy department may vary from those in the general population and sometimes vary across types of radiotherapy professionals. We will use the information collected to design a 12 week action plan for our department.

3

Adherence to Long Term Androgen Blockade in Localised High Risk Prostate Cancer and Causes of Non Compliance

Authors: Abdenour Nabid, Nathalie Carrier, André-Guy Martin, Jean-Paul Bahary, Marie Duclos, François Vincent, Sylvie Vass, Boris Bahoric, Robert Archambault, Céline Lemaire

Objectives: Long term androgen blockade (AB) increases survival in high risk prostate cancer (HRPC) but is also a source of many side effects.

The purpose of the present analysis is to evaluate adherence to AB in a group of 630 patients treated in a multicentric prospective randomised phase III trial (PCS IV clinical trials, Gov. # NCT 00223171).

Methods: PCS IV evaluates the duration of AB in HRPC. Patients were randomised to one month of antiandrogen (bicalutamide 50 mg die) and 36 (36 m) vs 18 (18 m) months of LHRH analog (goserelin 10.8 mg q 3 months) plus radiotherapy (RT): pelvis 44Gy, prostate 70 Gy, 2 Gy / fraction. AB was given neo adjuvant, concomitant and adjuvant. RT started 4 months after the beginning of AB.

Results: From October 2000 to January 2008, 310 patients were randomised to 36 m and 320 to 18 m of AB, 628 patients were considered for the analysis (2 patients who did not receive AB after being randomised were excluded). There are no significant differences in pre-treatment characteristics between the 2 groups, median values (interquartile range): age 71 (66-74) vs 71 (65-74) years, initial PSA 16.6 (8.6-28.4) vs 15.2 (8.4-28.0) ng/ml, Gleason score 8 (7-8) vs 8 (7-8) and no differences in clinical stage distribution T1: 72 vs 81 patients, T2: 155 vs 166, T3: 82 vs 70,T4: 0 vs 4. The median follow-up time is 72 months. Strict adherence to one month of antiandrogen was 93% (584/628): 93.2% (36 m) vs 92.8% (18 m). For LHRH analog strict adherence was 71% (446/628): 53.1% (36 m) vs 88.4% (18 m); adherence according to age stratification (<60, 60-64, 65-69, 70-74, ≥75) was 46.6% to 57.9% (36 m) vs 85.6% to 95.7% (18 m) and adherence amongst centers varied between 46.1% to 75% (36 m) vs 70% to 100% (18 m). Non compliance to LHRH analog was 28.9% (182/628): 46.9% (145/309) for 36 m and 11.6% (37/319) for 18 m. Thirteen causes of non compliance were recorded, side effects represent 44.5% (81/182): 49.7% (36 m) vs 24.3% (18 m); patients who received plus or minus one dose of LHRH analog: 18.1% (33/182); refusal to continue AB: 10.4% (19/182); death 9.9% (18/182); lost to follow-up 3.3% (6/182); unknown 3.3% (6/182); resistance to AB 2.7% (5/182); intercurrent disease 2.2% (4/182); prostatectomy 1.6 % (3/182); patients on 18m who continue until 36m 1.6% (3/182); second neoplasia 1.1% (2/182); progressive disease 0.5% (1/182); withdrawal from study 0.5% (1/182).

Conclusions: In a phase III randomised trial of AB in HRPC, adherence to one month of antiandrogen was very high. Adherence to LHRH analog at 18 months was high for both groups 85.8% (36 m) vs 88.4% (18 m), then dropped to 53.1% for the group randomized to 36 months of AB. Adherence does not depend on age and does not depend on centers if more than 20 patients were randomized per arm. Side effects were the main cause of AB cessation.

Source of Funding: AstraZeneca Pharmaceuticals grant

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Diabetes and cardiovascular mortality in men with locally advanced prostate cancer: update analysis from RTOG-92-02

Authors: K.S. Mak, Y. Yan, M.R. Smith, G.E. Hanks, H.D. Brereton, G. Bauman, S.A. Rosenthal, K.L. Zeitzer, H.M. Sandler and J.A. Efstathiou

Purpose/Objective(s): When combined with radiation therapy (RT), androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) agonist leads to improved survival in locally advanced prostate cancer, but are associated with incident diabetes (DM) and cardiovascular (CV) disease. We provide longer-term follow-up on mortality outcomes from a large randomized trial assessing ADT duration in locally advanced prostate cancer.

Materials/Methods: From 1992-1995, 1,554 men with prostate cancer (T2c-4, PSA <150 ng/mL) received RT and either 4 or 28 months of ADT with goserelin on RTOG 92-02. Proportional hazard models were used to analyze the relationship between treatment arm and CV mortality, and between prevalent DM and mortality outcomes. Covariates included treatment arm, age, race, stage, Gleason score, PSA, prevalent CV disease, hypertension, prevalent DM, and weight.

Results: After median follow-up of 11.3 years for surviving patients, there were 826 deaths, 218 (26%) due to prostate cancer and 197 (24%) due to CV disease. There were 153 deaths due to CV disease when censoring at time of salvage ADT. On multivariate analysis (MVA), longer-term ADT was associated with decreased prostate cancer mortality (PCM) versus short-term ADT (adjusted hazard ratio [HR] = 0.67; 95% confidence interval [CI] 0.50-0.89; p = 0.006). In contrast, prevalent DM was associated with greater all-cause mortality and non-prostate cancer mortality (NPCM), but not PCM. While weight, a risk factor for DM, was associated with greater PCM on MVA in a previous analysis (HR = 1.77; 95% CI 1.22-2.55; p=0.002), this association was not statistically significant with longer follow-up (HRZ1.46; 95% CI 0.95-2.50; p=0.08). CV mortality for men who received longer-term versus short-term ADT was 12.3% versus 9.7% at 10 years (Gray's p = 0.06). On MVA with and without censoring, duration of ADT was not associated with increased CV mortality, while conventional cardiac risk factors including age, prevalent CV disease, and prevalent DM were associated with greater CV mortality (Table). Results were similar with alternative definitions of CV mortality.

Conclusions: With additional follow-up, longer-term GnRH agonist therapy continues to decrease PCM in locally advanced prostate cancer without increasing CV mortality, alleviating concerns about the safety of ADT. Neither prevalent DM nor weight was associated with greater PCM in men receiving combined RT and ADT.

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The prostate cancer risk stratification (ProCaRS) project: recursive partitioning risk stratification analysis

Authors: G. Rodrigues, S. Gonzalez-Maldonado, H. Lukka, P. Warde, M. Brundage, J. Crook, F. Cury, G. Mok, E. Vigneault and T. Pickles

Purpose/Objective(s): The Genitourinary Radiation Oncologists of Canada (GUROC) published a three-group risk stratification (RS) system to assist prostate cancer decision-making in 2001. The Prostate Cancer Risk ProCaRS database has been established by merging data from seven unique databases. The objective of this project is to use the ProCaRS database to statistically model the predictive accuracy of expanded RS schemes and to assess the clinical utility of a proposed new GUROC RS
schema.

Materials/Methods: The RS analyses utilized the ProCaRS database that consists of 7974 patients from four Canadian institutions. This database contains patients treated with external-beam radiation therapy and LDR/HDR brachytherapy technique with approximately one-third of patients receiving some form of hormonal therapy. Conditional inference trees (otherwise known as Unbiased Recursive Partitioning Analysis) were utilized as the optimal methodology to explore the substratification of groups defined by the existing GUROC scheme. ASTRO II biochemical failure-free survival receiver operator curves and the associated area under the curve at 5 years were used to compare the predictive accuracy of proposed RS systems. Ten-fold cross-validated C-Indices were also obtained and used for comparison between various existing and proposed schema. All analyses were carried out using the R statistical language.

Results: Existing GUROC risk stratification classification was low-risk in 52%, intermediate-risk in 35%, and high-risk in 13%. The recursive partitioning ProCaRS analysis has suggested that the existing GUROC classification system could be altered to accommodate as many as six separate and statistical unique groups based on differences in ASTRO II biochemical failure-free survival (10-fold C-index 0.67 and AUC 0.70). These new GUROC groups would define subgroups of the existing lowrisk, intermediate-risk, and high-risk classifications. GUROC low-risk patients would be divided into new favorable-low and low-risk groups based on PSA $\leq$ 6 and PSA > 6. GUROC intermediate-risk patients can be subclassified into low-intermediate and high-intermediate groups. GUROC high-intermediate risk is defined as existing GUROC intermediate-risk with PSA $\geq$ 10 AND either T2b/c disease or T1T2a disease with Gleason 7. GUROC high-risk patients would be subclassified into an additional extreme-risk group (GUROC high-risk AND PSA = 90% OR [PSA >30]). Based on future consensus discussion, various groups can be collapsed into new or existing unified groups (e.g., high-intermediate with high-risk or not splitting low-risk due to limited clinical benefit).

Conclusions: GUROC subcategories have been identified by a recursive partitioning analysis of the ProCaRS database.

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Interim analysis (IA) results of COU-AA-302, a randomized, phase III study of abiraterone acetate (AA) in chemotherapy-naive patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

Citation: J Clin Oncol 30, 2012 (suppl; abstr LBA4518)

Authors: Charles J. Ryan, Matthew Raymond Smith, Johann Sebastian De Bono, Arturo Molina, Christopher Logothetis, Paul L. De Souza, Karim Fizazi, Paul N. Mainwaring, Jose Maria Piulats Rodriguez, Siobhan Ng, Joan Carles, Peter Mulders, Thian San Kheoh, Thomas W. Griffin, Eric Jay Small, Howard I. Scher, Dana E. Rathkopf, on behalf of the COU-AA-302 Investigators.

Background: AA is an androgen biosynthesis inhibitor that inhibits CYP17 and improves overall survival (OS) in post-docetaxel mCRPC. The primary objective of COU-AA-302 was to compare clinical benefit of AA + prednisone (P) vs placebo (PL) + P in chemo-naive, asymptomatic/mildly symptomatic mCRPC pts.

Methods: 1088 pts (151 centers; 12 countries) were randomized 1:1 to AA (1 g) + P (5 mg BID) or PL + P. Co-primary endpoints: radiographic progression-free survival (rPFS) and OS. Median times estimated using K-M method including LR statistic for inference. The Lan-DeMets α-spending function was used for OS.

Results: The Independent Data Monitoring Committee concluded that the OS, rPFS and secondary endpoints (Table) all favored the AA arm and unanimously recommended unblinding the study and crossing pts from PL to AA at IA (43% of total events). Median follow up = 22.2 mos. Grade 3/4 AEs (AA + P, PL + P) (%): hypertension 3.9 vs 3.0; hypokalemia 2.4 vs 1.9; ALT↑ 5.4 vs 0.7; AST↑ 3.0 vs 0.9.

Conclusions: AA + P produced a statistically significant improvement in rPFS and a strong trend for increased OS at this IA. AA resulted in clinically and statistically significant effects on all secondary endpoints. IA results confirmed the acceptable tolerability/safety profile of AA. This is the first randomized trial to demonstrate both OS and rPFS benefits in chemo-naive mCRPC and that inhibition of persistent extragonadal androgen synthesis significantly delays initiation of cytotoxic chemo. While median OS (AA arm) has not been reached, median PL arm OS (27.2 mos) is the longest measured in any phase III mCRPC study.

	AA + P (median, mos)	**PL + P (median, mos)**	**HR (95% CI)**	**P**
rPFS*	NR	8.3	0.43 (0.35, 0.52)	<0.0001
OS†	NR	27.2	0.75 (0.61, 0.93)	0.0097
Time to opiate use (cancer-related pain)	NR	23.7	0.69 (0.57, 0.83)	0.0001
Time to chemotherapy initiation	25.2	16.8	0.58 (0.49, 0.69)	<0.0001
Time to ECOG-PS deterioration	12.3	10.9	0.82 (0.71, 0.94)	0.0053
Time to PSA progression	11.1	5.6	0.49 (0.42, 0.57)	<0.0001

Abbreviation: NR, not reached.

*rPFS analysis: Clinical cut off date (CCO) 12/20/2010. Other analyses: CCO 12/20/2011.

†Prespecified alpha level 0.0008.

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Intermittent (IAD) versus continuous androgen deprivation (CAD) in hormone sensitive metastatic prostate cancer (HSM1PC) patients (pts): Results of SWOG 9346 (INT-0162), an international phase III trial.

Citation: J Clin Oncol 30, 2012 (suppl; abstr 4)

Authors: Maha Hussain, Catherine M. Tangen, Celestia S. Higano, E. David Crawford, Glenn Liu, George Wilding, Stephen Prescott, Atif Akdas, Eric Jay Small, Nancy Ann Dawson, Bryan J Donnelly, Peter Venner, Ulka N. Vaishampayan, Paul F. Schellhammer, David I. Quinn, Derek Raghavan, Nicholas J. Vogelzang, Ian Murchie Thompson.

Background: Castration resistance occurs in the vast majority of HSM1PC pts treated with AD, with a median survival of 2.5 years (y). It is in part an adaptive process with activation of genes resulting in the production of autocrine/paracrine growth factors that contribute to maintaining the viability of PC cells. Replacing androgens before castration resistance is hypothesized to maintain PC androgen-dependence. Preclinically IAD prolonged time to castration resistance and early clinical data indicated feasibility and potential for better quality of life.

Methods: HSM1PC pts with performance status (PS) 0-2, PSA ≥ 5 ng/ml were treated with 7 months (m) of goserelin + bicalutamide. Pts achieving PSA ≤4 ng/ml on m 6 and 7 were stratified by prior neoadjuvant AD/finasteride, PS and disease extent (minimal, extensive) and randomized to CAD or IAD. Primary objective: To assess if overall survival (OS) with IAD is noninferior to CAD using a one-sided test with an upper bound hazard ratio=1.20, adjusting for stratification factors. Sample size: 756 pts/arm, type I and II error rates of 0.05 and 0.10.

Results: 3,040 pts were accrued by SWOG, CALGB, ECOG, NCIC, and EORTC (5/95-9/08). After 7 m of CAD, 1535 eligible pts achieved PSA ≤4.0 (median age 70 yrs, 4% PS 2, 48% extensive disease, 12% prior neoadjuvant AD) and were randomized to CAD (759 pts) or IAD (770 pts). Grade 3/4 related adverse events: IAD 30.3%, CAD 32.6%. Median follow-up was 9.2 yrs. Median and 10 yr OS: All eligible pts from study entry: 3.6 yrs, 17%; from randomization CAD: 5.8 yrs, 29%; IAD: 5.1 yrs, 23%, HR (IAD/CAD) = 1.09 (95% CI 0.95, 1.24). No interaction with therapy was significant (p>0.25) except suggestion with disease extent (p=0.08): extensive disease HR=0.96 (95% CI 0.79, 1.15, p=0.64); minimal disease: HR=1.23 (95% CI 1.02, 1.48, p=0.035). PC was cause of death in 56% of CAD and 64% IAD pts. OSby race was not different (p=0.44).

Conclusions: In HSM1PC, IAD is not proven to be non inferior to CAD. For extensive disease pts IAD was non inferior; however, IAD was statistically inferior in minimal disease pts suggesting that CAD is the preferred treatment in this group.

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Long-term survival after radiation therapy for early stage endometrial carcinoma: the Oslo study revisited

Authors: K. Lindemann, M. Onsrud, C.G. Tropé, G.B. Kristensen

Introduction: The benefit of radiation in patients with early stage endometrial carcinoma is still debatable. Data on long time risk conferred by radiation is scarce.

Aim: To study long-term survival and the risk of secondary cancer based on a previously published randomized study (Aalders J. et al., Obstet Gynecol 1980; 56: 419-27).

Patients and methods: Between 1968 and 1974, we included 568 patients with endometrial cancer FIGO stage I. After primary treatment with abdominal hysterectomy and bilateral salpingo-oophorectomy patients were randomized to receive either vaginal radium brachytherapy followed by external pelvic radiation 40 Gy (N=288) or brachytherapy alone (N=280). Data on survival and incident secondary cancers were obtained by linkage to the Registry of Statistics Norway and Cancer Registry of Norway. We used Cox proportional hazards model to estimate hazard ratios (HR) with 95% confidence intervals (95% CI). We also conducted analyses stratified by age groups.

Results: After median 21 (range 0-43.4) years of follow-up there was no significant difference in overall survival or relapse free survival between treatment arms with HR of 1.12 (95% CI: 0.95-1.33) and HR 0.88 (95% CI: 0.55-1.40), respectively. Patients treated with external radiation had significantly lower risk of developing locoregional relapse ($p< 0.001$). However, women younger than 60 years had a significant poorer survival after external radiation (HR 1.36; 95% Cl: 1.06-1.76). In this patient group the risk of secondary cancer was significantly increased (HR 1.9; 95% CI: 1.23-3.03).

Conclusions: We observed no survival benefit of external pelvic radiation in early stage endometrial carcinoma. In women younger than 60 years, pelvic radiation decreased survival, probably due to increased risk of subsequent second neoplasms. Adjuvant external radiotherapy cannot be recommended to this patient group. Those who have received such treatment might eventually benefit from prolonged post treatment surveillance with respect to secondary cancer.

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Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study

Authors: D. Miller, V. Filiaci, G. Fleming, R. Mannel, D. Cohn, T. Matsumoto, K. Tewari, P. DiSilvestro, M. Pearl, R. Zaino

Objective: To determine if the combination of carboplatin and paclitaxel (TC) chemotherapy is clinically inferior to the combination of doxorubicin, cisplatin, and paclitaxel (TAP) chemotherapy with regard to survival. To assess differences in toxicity profile, specifically neurotoxicity and infection between TAP and TC.

Method: Eligible, consenting patients received random allocation to doxorubicin 45 mg/m2 and cisplatin 50 mg/m2 (day 1), followed by paclitaxel 160 mg/m2 (day 2) with growth factor support (TAP) or paclitaxel 175 mg/m2 and carboplatin AUC 6 (day 1) (TC) repeated every 21 days for 7 cycles. In 2008 initial doses of TC were reduced (135 mg/m2, AUC 5) for those with a history of pelvic/spine irradiation.

Results: From 2003 to 2009, 1381 women (69 ineligible) were enrolled. After all patients completed therapy, the Data Monitoring Committee approved early release of data from a second planned interim analysis (based on 551 deaths); the results are reported herein. Treatment was hematologically well tolerated, with only 7% of patients receiving TAP and 6% on TC experiencing neutropenic fever. Neurologic toxicity for those receiving TAP was 26% grade N1 sensory neuropathy compared with 19% in those receiving TC (pb.01). Common grade N2 toxicities more often (pb.01) reported with TAP included: Thrombocytopenia (23% v 12%), other hematologic (30% v 22%), vomiting (7% v 4%), diarrhea (6% v 2%), and metabolic (14% v 8%); whereas neutropenia (52% v 79%) was more often reported with TC. Study treatment was discontinued due to toxicity in 18% on TAP and 12% on TC. The 7 planned cycles were completed in 62% of those on TAP and 69% on TC (p=.01). The interim analysis adjusted 90% upper confidence limit for the death hazard ratio (HR) of TC relative to TAP was 1.16 and excludes the inferiority region bounded at 1.2. PFS (median TC v TAP, 14 v 14 months; HR=1.03) and OS (median TC v TAP, 32 v 38 months; HR=1.01) results for TC were not inferior to TAP. A homogeneity test suggests consistent treatment effects across strata defined by measurable/recurrent v primary disease and pelvic irradiation history (pN.1).

Conclusion: TC is not inferior to TAP in terms of PFS and OS based on interim analysis results. Overall, the toxicity profile favors TC. Thus, TC as prescribed in this study is an acceptable backbone for further trials in combination with “targeted” therapies.

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CT and MRI-based Image Guided Brachytherapy for Cervical Cancer: A Multi-institutional Report

Authors: D. Simpson, C.M. Yashar, N. Kannan, K. Zakeri, R. McMurtrie, J. Einck, L. Mell, H. Kim, D. Scanderbeg, and S. Beriwal

Purpose/Objective(s): A multi-institutional report of clinical outcomes of women undergoing 3D planning for image guided brachytherapy (IGBT) for cervical cancer with at least 1 MRI.

Materials/Methods: Women with FIGO IB-IVA cervical carcinoma diagnosed between 2007 and 2011 were treated with IGBT at 2 collaborating academic centers. Patients were treated with definitive external beam radiation therapy (EBRT) with concurrent chemotherapy followed by high-dose-rate (HDR) IGBT. All patients underwent planning computed tomography (CT) simulation at the time of each implant. All patients had at least 1 pelvic MRI at the beginning of IGBT for target delineation or planning. The dose was prescribed to the high-risk CTV (HRCTV) according to the GEC-ESTRO guidelines. Toxicity was graded according to the RTOG criteria. Follow-up time was measured from the date of last treatment. Time to local regional failure (LRF) was defined as time to first radiographic or pathologic evidence of disease recurrence anywhere in the pelvis and was estimated using the cumulative incidence function. Disease-free survival (DFS) time was defined as time to first evidence of LRF, distant metastasis, or death from any cause. Patients not experiencing any of these events were censored at last known medical encounter. The DFS and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: One hundred ten patients were evaluated. Mean and median follow-up times were 10.6 and 8 months, respectively, with a range of 0-42.8 months. Twenty-nine percent of patients were stage I-IIA and 71% were stage IIB-IVA. IMRT and 3D conformal RT were used in 69% and 31% of patients, respectively. Median EBRT dose was 45 Gy with 65% of patients receiving a boost to involved nodes or parametria. The median dose to the HRCTV was 2750 cGy (range, 2550 to 3000) in 5 (range, 3-5) fractions. The median combined IMRT/IGBT EQD2 sum D90 (dose to 90% volume) to the HRCTV was 84.2 Gy (range, 64.4-115.1). The median treatment course duration was 50 days. Two patients having persistent local disease and 1 found to have distant metastases during treatment were excluded from DFS analysis. One year LRF was 2.2%. One patient had an isolated pelvic recurrence at 9.6 months. One-year OS and DFS were 95.7% (95% CI: 91.0-100%) and 89% (95% CI, 77%, 100%), respectively. Forty-three patients (39%) experienced grade $\geq$ 2 acute toxicity, with 2 cases of acute grade 3 toxicity and no grade $\geq$ 4 toxicities. There was 1 late grade $\geq$ 3 toxicity observed.

Conclusions: This study is the first multi-institutional and largest report to date of CT/MRI based IGBT for treatment of cervical cancer in the United States. The results are promising with high local control and acceptable toxicity. Further investigation is needed to assess the long-term safety and efficacy of this treatment.

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The Prognostic Significance of Human Papilloma Virus and P16 in Patients With Vulvar Squamous Cell Carcinoma Treated With Radiation Therapy

Authors: M. Yap, J. Cuartero, G. Allo, M. Pintilie, K. Opfermann, A. Fyles, J. Murphy, S. Kamel-Reid, B. Clarke, and M. Milosevic

Purpose/Objective(s): Human papilloma virus (HPV) has been identified as an etiological agent in a subset of patients with vulvar squamous cell carcinoma (VSCC). The prognostic and predictive role of HPV status in women treated with radiation therapy (RT) in VSCC has not yet been determined. We investigated the associations between HPV, p16, and p53 status and clinical outcome in these women.

Materials/Methods: Patients treated with curative intent for VSCC at a single institution from 2000 to 2008 were retrospectively identified. Those who received definitive or adjuvant RT as part of the treatment regimen, and who had available pathological specimens, were included for analysis. HPV infection was detected using Roche Linear array hybridization and p16 and p53 immunohistochemistry performed on tissue microarray. Five year overall survival (OS) and disease-free survival (DFS) were analyzed using the Kaplan-Meier method. Log-rank tests were used for univariate analyses, and the Cox proportional hazards model for multivariate analysis. The risk of recurrence (RR) was estimated using cumulative incidence function and Gray's test, and the Fine and Gray model used for multivariate analysis.

Results: Forty-four patients were suitable for analysis, with a median age of 69 years. Thirty patients (70%) were staged as T1 (AJCC TNM 7.0), the remainder T2-3. Twenty-three patients (53%) had clinically and/or pathologically involved lymph nodes at diagnosis. Management regimens included: RT alone (n = 2); RT and chemotherapy (n = 5); RT and resection (n = 16); and RT, chemotherapy and resection (n = 21). Median RT dose was 50.0 Gy and median follow-up was 4.9 years. HPV was detected in 17/44 (39%) patients, HPV16 being the most common serotype (76%). Expression of p16 (p = 0.001) and loss of p53 (p = 0.03) were associated with HPV infection. For all patients, OS and DFS estimates at 5 years were 52% and 30% respectively. P16 positive patients (n = 13) had better DFS compared with p16 negative patients (n = 30), 66% versus 12% (p = 0.005). This result remained significant on multivariate analysis (HR = 0.22, CI 0.07-0.73, pZ0.01) when accounting for pathological tumor depth (p = 0.001). HPV positive patients had reduced RR compared to HPV negative patients, 23.5% versus 81.7% (p = 0.005) and this remained significant on multivariate analysis (HR = 0.2, CI 0.06-0.71, p = 0.01) when accounting for tumor depth (p = 0.001) and use of surgery (p = 0.008). Similarly, P16 expression was associated with reduced RR on multivariate analysis (HR = 0.2, CI 0.05-0.76, p = 0.02).

Conclusions: We have identified a favorable prognostic group in VSCC, with HPV and/or p16 positive patients demonstrating reduced recurrences. Identification of HPV and p16 status in VSCC patients prior to radiation therapy may improve risk stratification independent of clinical prognostic factors.

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Interim toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation (APBI) using 3D conformal external beam radiation therapy (3D CRT)

Background: Women with early stage breast cancer treated by breast conserving surgery (BCS) are increasingly offered APBI in the community despite limited evidence regarding efficacy and safety from randomized trials. Some phase II studies have reported increased toxicity from APBI using 3D CRT. We report the interim toxicity results of a multicenter randomized trial comparing 3D CRT APBI to standard whole breast irradiation (WBI).
Methods: Women > 40 years of age with invasive or non-invasive breast cancer < 3 cm treated by BCS were randomized to 3D CRT APBI (38.5 Gy in 10 fractions given twice daily) or WBI (50 Gy in 25 fractions or 42.5 Gy in 16 fractions given once daily ± boost irradiation). The primary outcome was ipsilateral breast tumour recurrence and important secondary outcomes were adverse cosmetic outcome (fair or poor on a global assessment using the EORTC Cosmetic Rating System for Breast Cancer) and toxicity using the NCI Common Terminology Criteria for Adverse Events 3.0. Cosmesis was assessed directly by a trained study nurse and the patient at baseline, 3 and 5 years post-randomization. Cosmesis was also assessed by a trained panel of radiation oncologists unaware of treatment allocation using digital photographs. Radiation toxicity was assessed by the study nurse during radiotherapy and in follow-up. The events required for the interim efficacy analysis have not been reached; however, the interim safety analysis based on the nurse-assessed adverse cosmesis was performed as planned after a median follow-up of 2.5 years. Upon review of the data, the Data Safety Monitoring Committee recommended release of the results.
Results: Between February 2006 and July 2011, 2135 women were randomized to 3D CRT APBI or WBI. There was an increased rate of adverse cosmesis at 3 years by nurse assessment in patients treated with APBI compared to WBI (see table, p<0.0001). Adverse cosmesis was also increased with APBI vs. WBI whether assessed by the patient (26.2% vs. 18.4%, p=0.004) or oncologist panel (35.1% vs. 16.6%, p<0.0001). In addition, grades I and II late radiation toxicities were increased in the APBI arm compared to the WBI arm; grades III and IV were rare in both treatment groups.
Conclusion: In patients who have undergone BCS, APBI delivered by 3D CRT was associated with worse cosmetic outcome and late radiation changes at 3 years compared to WBI. These results have implications for decision-making in patients considering 3D CRT APBI off-trial.

Nurse assessed Adverse Cosmesis

N of Subjects/Total Assessed (%) Time	APBI	WBI	P-value
Baseline	190/1007 (18.9%)	170/988 (17.2%)	0.35
At 3 years	139/442 (31.5%)	76/408 (18.6%)	< 0.0001

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Stereotactic Body Radiation Therapy With Ablative Dose on Liver Metastases: Radiation-induced Liver Disease (RILD) and Toxicity Assessment

Authors: S. Castiglioni, A. Tozzi, S. Arcangeli, P. Mancosu, G. Reggiori, P. Navarria, E. Clerici, A. Fogliata, L. Cozzi, and M. Scorsetti

Purpose/Objective(s): To assess the safety of high-dose stereotactic body radiation therapy (SBRT) with volumetric modulated arc therapy (VMAT) technique for the treatment of patients with unresectable liver metastases from solid tumors, with special regard on liver function.

Materials/Methods: Patients with 1 to 3 unresectable liver metastases with maximum individual tumor diameters less than 6 cm, a Karnofsky Performance Status of at least 70 and life expectancy more than 6 months were enrolled and treated by SBRT on a phase II clinical trial. Dose prescription to mean clinical target volume (CTV) was 75 Gy in 3 consecutive days, with planning target volume (PTV) covered by at least the isodose of 67%, and where possible, this limit on PTV was increased up to 95% of the prescription. When the dose constraints for normal tissues could not be fulfilled, dose reduction up to 30% was allowed. SBRT was administered using VMAT technique by RapidArc, with a flattening filterfree photon beam 10 MV (FFF) and maximum dose rate of 2400 MU/min.

Results: Between February 2010 and August 2011, 57 patients with 77 lesions were enrolled in this trial. Among them, 21% had extrahepatic disease at the time of SBRT. Primary tumor sites were colon in 24, breast in 19, bilio-pancreatic in 6, uterus in 5, and others in the remaining 17. Seventyfour (74%) of patients had 1 lesion, 19% and 7% of patients had 2 and 3 lesions, respectively. Sixty-three lesions (82%) were treated with a full dose of 75 Gy. Dose reduction was provided in only 14 lesions to respect the dose constraints. Mean beam-on time was 2.9 1.5 min (range, 1.9-6.2 min). None of the patients experienced grade 3 or higher acute toxicity. Grade 2 acute toxicity, mainly gastrointestinal, occurred in 7 patients (14%). No radiation-induced liver disease (RILD) was detected. Given the short length of follow-up, no data on late toxicity are currently available.

Conclusions: Findings suggest that SBRT for unresectable liver metastases is associated with a low incidence of acute toxicity, and can be considered as a safe and noninvasive therapeutic option in this setting.

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Long-term Quality of Life in Patients Treated in TROG 01.04: A Randomized Trial Comparing Short Course and Long Course Preoperative Radiation Therapy for Rectal Cancer

Authors: S. Ngan, R. Fisher, B. Burmeister, J. Mackay, S. McLachlan, J. Beresford, B. McClure, D. Goldstein, D. Joseph, and M. Solomon

Purpose/Objective(s): To compare long-term quality of life (QOL) between short course (SC) and long course (LC) preoperative radiation therapy for rectal cancer.

Materials/Methods: This trial was performed under the auspices of TROG/AGITG/ CSSANZ/RANZCR. Three hundred twenty-six patients with T3 rectal cancer were randomized to short course (SC) and long course (LC) preoperative radiation therapy. Two hundred ninety-five patients were eligible for QOL analysis. SC consisted of radiation therapy 5 x 5 Gy in 1 week, early surgery and 6 courses of adjuvant chemotherapy. LC was 50.4 Gy, 1.8 Gy/fraction, in 5.5 weeks, with continuous infusion 5-FU 225 mg/m2/day, surgery in 4 to 6 weeks, and 4 courses of chemotherapy. QOL was measured using the EORTC QLQ-C30 and QLQ-CR38. Assessments were performed at baseline and 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months in patients who had not relapsed. Changes from baseline of nine QOL scales, pertaining to global QOL and pelvic functioning and symptoms, were nominated as major endpoints (the Hochberg procedure was used to adjust for multiple comparisons) and an area-undercurve (AUC) statistic (from 1 to 5 years) was used as the main criterion and analyzed using linear mixed models. Pointwise differences, especially at 5-years, were compared using an exact 2-sample permutation test at the 1% level of significance.

Results: The overall completion rate of QOL questionnaires at 5 years was 80%. There appeared little difference in long-term QOL between SC and LC. AUC analyses indicated there was little difference in global health status/QOL between arms (p Z 0.50) though there was a tendency for symptoms in the area of the gastrointestinal tract to be less prominent in SC patients (nominal p Z 0.044; adjusted p Z 0.31). There were no significant AUC differences for the other major endpoints (constipation, diarrhea, sexual functioning, sexual enjoyment, micturition, male sexual problems, and defecation). At five years (n Z 156), global health status/QOL between arms was not significant (p Z 0.64). Symptoms in the area of the gastrointestinal tract tended to favor SC (p Z 0.040). There were no differences at 5 years between arms in symptom scales for constipation, diarrhea, micturition, sexual functioning, sexual enjoyment, male sexual problems or defecation. Female sexual problems was not analyzed due to lack in response to this question (n Z 11). There were no significant differences between arms among physical functioning, role functioning, emotional functioning, cognitive functioning, or social functioning.

Conclusions: We found no clear difference in long-term QOL between SC and LC for global health status/QOL and pelvic functioning and symptoms.

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Prognostic Value of CA 19-9 in a Phase I/II Trial of Dose Escalated Intensity Modulated Radiation Therapy (IMRT) With Concurrent Full-dose Gemcitabine (G) in Unresectable Pancreatic Cancer

Authors: J.M. Vainshtein, M. Schipper, M. Zalupski, T.S. Lawrence, R. Abrams, I.R. Francis, W. Leslie, and E. Ben-Josef

Purpose/Objective(s): Although established in the post-resection setting, the prognostic value of CA19-9 in unresectable pancreatic cancer is less clear. We examined the prognostic utility of CA19-9 in unresectable pancreatic cancer pts treated on a prospective trial of IMRT dose-escalation + G.

Materials/Methods: Fifty pts with unresectable pancreatic cancer were treated on a multi-institutional phase I/II IMRT dose escalation trial with G at 1000 mg/m2. IMRT dose was escalated from 50-60 Gy in 2.5 Gy increments in 25 fractions. CA19-9 was obtained at baseline (b) and during routine follow-up. Non-secretors, defined by bCA19-9 <10 U/mL, were excluded. All CA19-9 analyses were based on log (CA19-9). Cox models were used to assess the effect of predictors on each time to event outcome. Stepwise forward regression was used to build multivariate (MV) predictive models.

Results: Thirty-eight pts were eligible for the present analysis. Median and mean bCA19-9 were 156 and 837 U/mL (range 11-5,028). Median survival (MS) was 15.2 mo (95% CI 12.6 - 22.2) and 2-yr OS was 26.6% (13.2 -42.0). Median progression free survival (PFS) was 9.2 mo (6.5 - 13.2), median freedom from local progression (FFLP) was 21.6 mo (15.42 - NR), and median freedom from distant progression (FFDP) was 10.6 mo (7.7-15.9). On MV models identified by stepwise regression modeling, independent predictors of OS were bCA19-9 (HR Z 1.37, p < 0.01), age (HR Z 1.05, p Z 0.030), and female sex (HR Z 0.40, p Z 0.034). For FFDP, CA19-9 at 3 mo (HRZ1.96, p < 0.01), female sex (HRZ0.13, p < 0.01), and GTV (HR Z 0.98, p < 0.01) were predictive. No MV models were identified for PFS or FFLP. For pts with bCA19-9 <90 vs. >90, median OS was 23.0 mo vs. 11.1 mo, (HR Z 2.88, p < 0.01), while PFS was 15.7 vs. 7.0 mo (HR Z 3.99, p < 0.01). As a time-dependent co-variate, rising CA19-9 over 100 was highly predictive of PFS (HRZ 3.29, p < 0.01) and OS (HR Z 3.47, p < 0.01). Univariate predictors for OS were bCA19-9 (HR Z 1.19, p Z 0.04) and age (HR Z 1.049, p Z 0.02), for PFS were bCA19-9 (HR Z 1.38, p < 0.01) and CA19-9 at 3 mo (HR Z 1.44, p < 0.01), for FFLP were bCA19-9 (HR Z 1.54, p < 0.01) and GTV (HR Z 1.015, p Z 0.04), and for FFDP were CA19-9 at 3 mo (HR Z 1.36, p Z 0.02) and female sex (HR Z 0.40, p Z 0.053).

Conclusions: In unresectable pancreatic cancer pts treated with dose escalated IMRT + G, baseline CA19-9 is an independent predictor of outcome even after controlling for established prognostic factors. Baseline CA19-9 should be used as a stratification factor in future trials in unresectable pancreatic cancer.

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Memantine for the Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy (WBRT): First Report of RTOG 0614, a Placebo-Controlled, Double-Blind, Randomized Trial

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Background: Radiotherapy (RT) is an effective therapy for patients with brain tumors. However there are concerns regarding cognitive deterioration after RT. Memantine, an N-Methyl-D-aspartate receptor antagonist, has been shown to be beneficial for vascular and Alzheimer's dementias. Therefore we conducted a phase III trial to evaluate the potential protective cognitive effects of memantine in patients receiving WBRT.

Methods: Eligible adult patients with brain metastases were stratified by Recursive Partitioning Analysis Class (I or II) and prior radiosurgery or surgical resection. Patients received WBRT (37.5Gy in 15 fractions) and were randomized to receive placebo or memantine, 20mg per day, within 3 days of initiating radiotherapy, for 24 weeks. Standardized tests of cognitive function were performed at baseline, 8, 16, 24, and 52 weeks. The primary endpoint, memory decline at 24 weeks as measured by the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR), required 442 patients to detect a mean difference of 0.87 between the treatment arms with 80% power and an alpha of 0.025. Secondary objectives included time to cognitive decline, overall survival (OS), and progression-free survival (PFS).

Results: 554 patients were accrued between March 2008 and July 2010 of which 508 were eligible. Patient and treatment characteristics were well-balanced between arms. Grade 3 or 4 toxicities and study compliance were similar between arms with only 32% of patients completing drug therapy per protocol mainly due to death and patient refusal to continue treatment. Median follow-up for censored patients was 12.4 months. No differences in OS or PFS were seen between the arms. The memantine arm had significantly longer time to cognitive decline (HR 0.78; 95% CI, 0.62 to 0.99; p=0.02); the probability of cognitive decline free survival at 24 weeks was 30.6% in the memantine and 19.7% in the placebo arm. There was less decline on the HVLT-R DR in the memantine arm (median decline of 0) compared to the placebo arm (median decline of 0.90) at 24 weeks (p=0.059). There was less decline on the HVLT-R Delayed Recognition in the memantine arm at 24 weeks (p=0.0149) and the Mini Mental State Exam (MMSE) (p=0.0093). Fewer patients receiving memantine experienced decline on Controlled Oral Word Association (COWA) at 8 weeks (2% deterioration vs. 13% deterioration; p=0.0015). Linear regression models for the complete case date, revealed significant differences favoring the memantine arm for COWA at 8 weeks (p=0.008) and 16 weeks (p=0.0041) and for Trail Making Test Part A and MMSE (p=0.0137 and 0.0038, respectively) at 24 weeks. Using the imputed data, a significant difference was found for COWA scores at 8 weeks (p=0.0103) favoring the memantine arm.

Conclusions: Memantine was well tolerated with toxicity profile very similar to placebo. Patients treated with memantine had better cognitive function over time; specifically memantine delays time to cognitive decline and reduces the rate of decline in memory, executive function and processing speed in patients receiving WBRT. The primary endpoint did not quite meet statistical significance, likely because of a much lower than expected compliance with cognitive assessments. (Funded by the National Cancer Institute and Forest Pharmaceuticals, RTOG 0614 ClinicalTrials.gov number, NCT00566852.)

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Patient Beliefs About Palliative Radiation Therapy (RT) in Incurable Lung Cancer

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Purpose/Objective(s): Prior studies suggest that providers and patients may be overly optimistic when predicting prognosis for incurable cancers. This may lead to unnecessarily aggressive therapies near the end of life, such as lengthy courses of palliative RT. We investigated patient beliefs and understanding about the goals of palliative RT for incurable lung cancers.

Materials/Methods: The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) study, a population- and health system-based prospective cohort study, enrolled 5,013 patients with newly diagnosed lung cancer in 5 geographic regions, 10 Veterans Administration sites, and 5 large health maintenance organizations from 2003-2005.We identified patients _ age 21 with stage IIIB (wet) or IV lung cancer who completed or were scheduled to have RTand completed the baseline interview approximately 4 months after diagnosis. We analyzed patient/surrogate responses to the question: "After talking with your doctors about radiation therapy, how likely did you think it was that radiation would."

Results: Among 832 patients with stage IIIB or IV lung cancer at diagnosis who had received or were scheduled to have RT, 384 (46%) completed surveys on their beliefs about RT. Median survival in this cohort was 11.5 months. 78% of patients believed that RT was very or somewhat likely to help them live longer, and 43% believed that RT was very or somewhat likely to cure their cancer. With respect to symptoms, 67% believed that RT was very or somewhat likely help them with problems they were having because of lung cancer, and 66% believed that RT was very or somewhat likely to have side effects or complications. Full results are shown in the Table.

Conclusions: A majority of patients with incurable lung cancer who receive palliative radiation believe that it is likely to prolong life, and a significant proportion believes that it is likely to cure their disease. This suggests an opportunity to improve care delivery by improving patient communication and understanding of the goals of palliative RT.

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A Phase II Study of Accelerated Hypofractionated 3-dimensional Conformal Radiation Therapy for Inoperable T1-3 N0 M0 Non-small Cell Lung Cancer: NCIC CTG BR.25

Authors: P. Cheung, S. Faria, S. Ahmed, P. Chabot, J. Greenland, E. Kurien, I. Mohamed, J. Wright, K. Ding, and C. O'Callaghan

Purpose/Objective(s): Radiation therapy is a curative treatment option for early stage non-small cell lung cancer (NSCLC). Based on promising retrospective data using accelerated hypofractionated schedules, a prospective multi-institutional phase II trial was performed. This was done in an era when the majority of centers did not have stereotactic body radiation therapy capability.

Materials/Methods: From 2006-2008, 80 patients with peripherally located T1-3 N0 M0 NSCLC were enrolled from 17 institutions across Canada. All patients had biopsy confirmation of NSCLC. Maximum allowable tumor size was 5 cm. Eligible patients received a dose of 60 Gy in 15 fractions using a 3-dimensional conformal technique without inhomogeneity correction. The gross tumor volume (GTV) was the primary tumor only, with no expansion for the clinical target volume (CTV). The planning target volume (PTV) margin was 1.5 cm in all directions. The PTV margin could be decreased to 1.0 cm in the transverse plane to spare critical structures. An assessment for breathing induced tumor motion (fluoroscopy or 4D CT) was required to ensure that the tumor was adequately covered by the PTV. Daily image guidance was not mandated during treatment. All radiation therapy plans were centrally reviewed. Patients were evaluated weekly during treatment and every 4 months afterwards until 2 years. From years 2 to 5, the follow-up decreased to every 6 months. The primary endpoint was the 2 year local control rate of the primary tumor using a modified RECIST criteria. Toxicities were measured using the CTCAE v3.0.

Results: Five patients were found to be ineligible and 2 had major protocol violations. Median follow-up of the patients was 49 months (range 21-63 months). Median age of the patients was 75.9 years. 80% of patients were ECOG 0-1 at baseline. The actuarial rate of local control at 2 years was 88%. Overall survival was 69% at 2 years. The actuarial rates of developing regional and distant relapse at 2 years were 9% and 24%, respectively. Distant relapse included the development of a solitary tumor anywhere in the lung separate from the treated primary tumor. Tumor size >3 cm was associated with a statistically significant increase in distant relapse (p Z 0.03). The most common grade > Z 3 toxicities were fatigue (6.3%), cough (7.5%), dyspnea (13.8%), and pneumonitis (10%). One patient died of massive hemoptysis over 2 years after radiation therapy that was scored as possibly related to the protocol treatment.

Conclusions: Conformal radiation therapy to a dose of 60 Gy in 15 fractions resulted in favorable local control and overall survival rates in patients with medically inoperable T1-3 N0 M0 NSCLC. Severe toxicities were uncommon in this prospective study of a relatively simple treatment technique.

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Involved-field (IF) Versus Extended-field (EF) Radiation Therapy (RT) for Patients in Early Unfavorable Stages of Hodgkin Lymphoma: 10-year Update of the HD8 Trial of the German Hodgkin Study Group (GHSG)

Authors: H.T. Eich, J. Kriz, B. Klimm, S. Sasse, H. Go¨rgen, V. Diehl, P. Borchmann, R. Mueller, and A. Engert

Purpose/Objective(s): Combined modality treatment consisting of chemotherapy followed by RT has shown better results in respect to overall survival (OS), progression free survival (PFS) and freedom from treatment failure (FFTF) compared to RT alone for patients in early unfavorable stages of HL. The HD8 trial was designed to test whether IF-RT is as effective as EF-RT. The main aim was to reduce treatment related toxicity. The present analysis shows the 10-year follow-up data.

Materials/Methods: The HD8 study was a two arm randomized trial. Patients with de novo HL in clinical stages I and II having one or more risk factors (1) large mediastinal mass, (2) extranodal disease, (3) massive spleen involvement, (4) elevated ESR or (5) _3 involved lymph node areas), IIB having risk factor (4) or (5) and patients in clinical stages IIIA without risk factors received two cycles of COPP/ABVD followed by RT. RT consisted of either 30 Gy EF-RT (arm A) + 10 Gy to initial bulky disease or 30 Gy IF-RT (arm B) + 10 Gy to initial bulky disease.

Results: From 1993 to 1998, a total of 1,204 patients were randomized. Five hundred thirty-two patients in each treatment arm were eligible. The 10-year follow-up analysis revealed no arm differences with respect to FFTF (79.8% vs. 79.7%), PFS (79.8% vs. 80%) and OS (86.4% vs. 87.3%), respectively. Non-inferiority of IF-RT was demonstrated for the primary endpoint FFTF (95% CI for HR Z 0.72-1.25). Older patients showed a poorer outcome when treated with EF-RT. Fifteen percent of patients in arm A and 12.2% patients in arm B died due to secondary malignancies (5.3% vs. 3.4%) or HL (3.2% vs. 3.4%). Patients treated with EF-RT developed more often secondary malignancies (n = 58 vs. n = 45), especially AMLs (n = 11 vs. n = 4).

Conclusions: Reduction of RT-size and RT-volume from EF to IF does not result in poorer long-term outcome and is associated with less long-term toxicity for patients in early unfavorable stages of HL.

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LBA2 N09C6 (Alliance) - A Phase III, Randomized Double-Blind Study of Doxepin Rinse versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Head and Neck Radiotherapy with or without Chemotherapy

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Purpose/Objective(s): Oral mucositis (OM) remains a significant toxicity in patients receiving radiotherapy (RT) for malignancies of the head and neck (H&N). Previous pilot research (J Pain Symptom Manage, 2007. 33(2): 111-4.) has suggested that doxepin, a tricyclic antidepressant, reduces RT induced OM when used as a mouth rinse.

Materials/Methods: A multi-institution, randomized, double-blind, placebo-controlled, phase III trial with a cross-over phase and subsequent optional continued active agent usage, was designed to assess the efficacy of doxepin oral rinse and spit (25 mg in 5 ml water) versus placebo for the treatment of RT related OM and conducted through the Alliance for Clinical Trials in Oncology (NCCTG/CALGB/ACOSOG). Patients undergoing definitive H&N RT (> 50.0 Gy) including > 1/3 of the oral cavity, with OM pain rated > 4 using a patient reported numerical analog pain questionnaire (scale 0 to 10) were eligible. Patients received a single blinded dose of doxepin or placebo on day 1 and then crossed over to the opposite study arm on a subsequent day. To assess OM related pain after doxepin/placebo rinse, a pain questionnaire was administered at baseline and at 5, 15, 30, 60, 120, and 240 minutes. After completing the study, patients were given the option to continue doxepin. The study's primary endpoint was total OM pain reduction as measured by the area under the curve (AUC) of the pain scale over time using data from day 1. The baseline-adjusted AUC between two treatment arms was compared using the Wilcoxon rank-sum test. At the 5% significance level, there was an 80% power to detect a clinically meaningful standardized effect size of 0.5 with 128 patients (64 patients for each arm) based on the two-sample t-test with equal-variance assumption.

Results: 155 patients (140 eligible for the primary endpoint) were enrolled in the study between 12/17/2010 and 5/17/2012. Baseline factors were evenly distributed across arms. Analysis of the primary endpoint revealed that the pain reduction AUC was greater for doxepin (-9.1) vs. placebo (-4.7), p=0.0003. Analysis of the crossover data revealed similar findings: doxepin (-7.9) vs. placebo (-5.6), p=0.009. Doxepin was well tolerated, but had more rinse stinging/burning and unpleasant taste and caused greater drowsiness, compared to the placebo. 64% of patients elected to continue doxepin (p=0.002) in the optional continuation phase.

Conclusion: OM pain was significantly less following doxepin rinse than placebo. The majority of patients elected to continue doxepin during RT for OM pain, after the double-blind, cross-over portion of the study. This study sets a new standard of care for the treatment of oral pain due to radiation-related OM.

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Low-risk Breast Ductal Carcinoma In Situ (DCIS): Results From the Radiation Therapy Oncology Group 9804 Phase 3 Trial

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Purpose/Objective(s): The quest to identify women with DCIS, who receive no significant benefit from radiation (RT), continues despite several phase III trials demonstrating RT reduces the risk of local failure (LF).RTOG 9804 identified "good risk" patients based on the best pathology knowledge of the time (mammographic detection, <2.5 cm size, margins 3 mm and low-intermediate nuclear grade). Women were randomized to RT or observation (OBS). Tamoxifen (Tam) for 5 years was optional in both arms. **Materials/Methods:** Ipsilateral local failure (LF) was the primary end point; LF and contralateral failure (CF) were estimated using cumulative incidence and overall (OS) and disease-free (DFS) survival were estimated using Kaplan-Meier method. Treatment arms were compared by the log-rank test. With 1,790 patients, 80% power and using a 2-sided log-rank test at 0.05, 9,804 was designed to detect a reduction in 5 yearLRfrom6.0%to 3.5%withRT.Dose in the RT arm was 50Gy in 25-28 or 42Gy in 16 fractions, with no boost allowed.

Results: Due to lower than projected accrual, the study closed early in 2006 with 636 patients, and 585 eligible patients are included in this analysis. Median follow-up time was 7.17 years, with Tam used in 62%; mean age was 59.At 7 years, LF in the RT arm was 0.9%(95%CI: 0.0-2.2) versus 6.4%in the OBS arm (95%CI: 3.2-9.6), pZ0.0005. In the OBS arm, 12 of 18 LF occurred in the same quadrant. The 2 LF in the RT arm were in distant quadrants. No failures involving skin were observed in either arm. With limited events: age, grade, margin status, and size did not correlate with LF. Rate of grade (G) 1-2 worst acute toxicit was 30%versus 76%; G3-4 toxicities were 4.0%and 4.2%, respectively in the OBS and RT arms. The rate of worst late RT toxicity was: G1 30%, G2 4.6%, and G3 0.7%. OS and DFS were excellent in both arms.

Conclusions: In this "good risk" subset of DCIS, the LF rate was decreased significantly with the addition of RT. Longer follow-up is planned, as late failures continue to occur.

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Improved Survival With Adjuvant Radiation in Elderly Women With Early-stage Breast Cancer

Authors: R.J. Cohen, L. Li, W. Citron, M. Oh, C. Drogula, S. Cheston, C. Bui, and S.J. Feigenberg

Purpose/Objective(s): The Cancer and Leukemia Group B (CALGB) studied the addition of radiation to lumpectomy and tamoxifen in women age 70 and older with clinical stage I, estrogen receptor positive (ER+) breast cancer. At a median follow-up of 10.5 years, there was an absolute reduction of 6% in ipsilateral breast tumor recurrence with the use of radiation, but there was no improvement in overall survival (OS) or cause specific survival (CSS). The purpose of this study was to evaluate survival outcomes of elderly women with ER+, early stage breast cancer treated with lumpectomy and radiation versus lumpectomy alone using a large, population-based database.

Materials/Methods: The Surveillance, Epidemiology, and End Results (SEER) database was utilized to obtain data for all women ages 70 to 84 years old diagnosed with T1 N0 M0, ER+, breast cancer between 1990 and 2008 who underwent lumpectomy with or without adjuvant radiation therapy. The Kaplan-Meier method was used to calculate OS and CSS.

Results: Twenty-nine thousand, one hundred twenty-seven women who survived at least one year following initial breast cancer diagnosis were identified. Median follow-up was 10 years. Fifty percent of patients received adjuvant radiation. With increasing age, the use of adjuvant radiation decreased with 55% of women age 70-74, 50% of women 75-79, and 40% of women 80-84 years old receiving external beam radiation. At 5 years, CSS was 97.6% (95% confidence interval [CI]: 97.3%-97.8%) for surgery alone versus 98.3% (95%CI: 94.9%-95.8%) for adjuvant radiation. The improvement in CSS with the addition of radiation persisted at 10 years: 94.3% (95% CI: 93.8%-94.8%) versus 95.4% (95% CI: 94.9%-95.8%), ($p < 0.05$). The median survival was 11.1 years for patients receiving surgery alone and 13.1 years for surgery and radiation. The OS was significantly better at all time points for women receiving radiation. At 5, 10, and 15 years, the OS was 83.0%, 56.1%, and 30.2% for those treated with surgery alone compared to 89.5%, 66.8%, and 40.8% treated with surgery and radiation ($p < 0.05$).

Conclusions: Elderly women with early stage breast cancer treated with surgery and adjuvant radiation have improved outcomes compared to those treated with surgery alone, likely related to an improvement in locoregional control. The patients selected for radiation were likely healthier with longer anticipated life expectancy. However, even in the surgery alone patients, median survival was 11.1 years. Although information regarding hormonal therapy usage is not available, the improvement in CSS with the addition of radiation suggests that in healthy, elderly women, adjuvant radiation should be strongly considered as part of their breast cancer treatment.

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Should Ductal Carcinoma In Situ (DCIS) be Removed From the ASTRO Cautionary Group for Off-protocol Use of Accelerated Partial Breast Irradiation (APBI)? A Pooled Analysis of Outcomes for 300 Patients With DCIS treated With APBI

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Purpose/Objective(s): Limited data have been published regarding the validity of the ASTRO Consensus Panel (CP) guidelines and ductal carcinoma in situ (DCIS). The purpose of this study was to analyze patients with DCIS treated with APBI within a pooled set of patients treated on the American Society of Breast Surgeons (ASBrS) MammoSite Registry Trial.

Materials/Methods: A total of 300 women with DCIS underwent APBI between April 1993 to November 2010 as part of the ASBrS Registry Trial (n = 192) or at WBH (n = 108). Patients with pure DCIS $\leq$ 3 cm (n = 125) were assigned to the cautionary risk group per ASTRO CP guidelines and analyzed compared to the pooled invasive suitable (n = 653) group and pooled invasive suitable/cautionary (n = 1,298) group with regards to ipsilateral breast tumor recurrence (IBTR), regional recurrence (RR), distant metastases (DM), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS).

Results: Median age was 62 years (range: 50-83 years) and median tumor size was 6.0mm (range: 0.0-28.0 mm). DCIS patients were younger, with higher grade but smaller tumors, and were more likely to have close margins compared with the pooled suitable and suitable/cautionary groups. The rate of IBTR for all DCIS patients was 1.6% at five years with no RR or DM noted while CSS was 100% and OS was 95.8%. No differences in IBTR (1.6% vs. 2.4%, p = 0.68), RR (0% vs. 0.4%, p = 0.47), DM (0% vs. 0.8%, p = 0.32), DFS (100% vs. 96.3%, p = 0.14), or CSS (100% vs.98.6%, p = 0.22) were noted between DCIS patients and pooled invasive suitable patients. OS, however, was improved in DCIS patients (95.8% vs. 90.9%, p = 0.03). Similar findings were seen for DCIS versus invasive suitable/cautionary patients including no differences in IBTR (1.6% vs. 3.1%, p = 0.46), RR (0% vs. 0.6%, p = 0.40), DM (0% vs. 2.5%, p = 0.11), or CSS (100% vs. 98.3%, p = 0.16) but improved DFS (100% vs. 94.4%, p = 0.04) and OS (95.8% vs. 90.8%, p = 0.03) were seen in DCIS patients. Findings were similar for DCIS patients 60 years and older (n = 74), except that OS was not significantly different.

Conclusions: Excellent clinical outcomes were seen for both patients with invasive breast cancer within the suitable group as well as those with DCIS within the cautionary subgroup (98.4% local control at 5-years) despite more aggressive clinical-pathologic features in the DCIS cohort. This analysis of the largest published data of patients with DCIS treated with APBI supports consideration for removal of DCIS from the cautionary risk group as outcomes are similar (and excellent) in a large pooled analysis.

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Postmenopausal Women With Luminal A Subtype May Not Require Breast Radiation Therapy – Results From a Randomized Clinical Trial of Tamoxifen ± Radiation

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Purpose/Objective(s): To determine the value for molecular subtyping, using a six biomarker panel, in predicting ipsilateral breast tumor recurrence (IBR) for women age 50 and older with T1 and T2 node negative breast cancer enrolled in a randomized trial of tamoxifen (Tam) +/- whole breast radiation (WBRT).

Materials/Methods: Between December 1992 and June 2000, 769 women were randomized to WBRT and Tam, (n = 386) for 5 years, or Tam alone (n = 383). Median age was 68 years; 639 (83%) had pT1 tumors. Intrinsic molecular subtyping was determined using semi-quantitative analysis of immunohistochemical staining for ER, PR, Ki-67, HER2, EGFR and cytokeratin (CK) 5/6 on tissue microarrays constructed from the formalin fixed paraffin-embedded tumor blocks of 304 of the 345 available samples. Tumors were categorized as luminal A (ER or PR positive, HER2 negative, Ki-67 <14%), luminal B (ER or PR positive, HER2 negative, Ki67 >14%), luminal-HER2 (ER or PR positive, HER2 positive), HER2 enriched (ER and PR negative, HER2 positive), and basal-like (ER and PR negative, HER2 negative and CK5/6 or EGFR positive). Median follow-up was 10 years (range 0.1-16 yrs).

Results: IBTR at 10 years was 13.8% with Tam compared to 5.0% with Tam/WBRT ($p < 0.0001$). Luminal A tumors (n = 133) had the lowest rate of IBTR: 8% at 10 years with Tam alone and 4.6% with Tam/WBRT ($p = 0.27$). IBR for luminal A Grade I/II was 4.9% with Tam alone and 5.5% with Tam/WBRT (n = 114, $p = 0.85$). In contrast, luminal B (n = 82) had an IBR of 16.1% with Tam alone and 3.9% with Tam/WBRT ($p = 0.058$). Luminal HER2 (n = 11), HER2-enriched (n = 11), and basal (n = 16) demonstrated the highest risk of IBR (40.0% with Tam alone and 9.9% with Tam/WBRT ($p = 0.029$).

Conclusions: A six marker IHC molecular subtype appears to be predictive for radiation response in women over 50 with T1/2 node negative breast cancer. Luminal A subtype demonstrated a low risk of breast relapse with Tam alone, particularly in those with Grade I/II tumors. These results require validation in additional specimens and clinical trials, but this subgroup represents a significant proportion of women in this trial (114/253 or 45%), who may be spared the inconvenience and side effects of breast radiation. In contrast, breast RT is beneficial in women with higher risk subtypes (Luminal B, Lum/HER2, HER2-enriched, basal).

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Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of national surgical adjuvant breast and bowel project B-18 and B-

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Purpose: The limited information on predictors of locoregional recurrence (LRR) after neoadjuvant chemotherapy (NC) has resulted in controversy about the optimal use of adjuvant radiotherapy and the timing of sentinel lymph node biopsy. PATIENTS AND **Methods:** We examined patterns and predictors of LRR as first event in combined analysis of two National Surgical Adjuvant Breast and Bowel Project (NSABP) neoadjuvant trials. NC was either doxorubicin/cyclophosphamide (AC) alone or AC followed by neoadjuvant/adjuvant docetaxel. Lumpectomy patients received breast radiotherapy alone; mastectomy patients received no radiotherapy. Pathologic complete response was defined as the absence of invasive tumor in the breast. Multivariate analyses were used to identify independent predictors of LRR. The primary end point was time to LRR as first event. **Results**: In 3,088 patients, 335 LRR events had occurred after 10 years of follow-up. The 10-year cumulative incidence of LRR was 12.3% for mastectomy patients (8.9% local; 3.4% regional) and 10.3% for lumpectomy plus breast radiotherapy patients (8.1% local; 2.2% regional). Independent predictors of LRR in lumpectomy patients were age, clinical nodal status (before NC), and pathologic nodal status/breast tumor response; in mastectomy patients, they were clinical tumor size (before NC), clinical nodal status (before NC), and pathologic nodal status/breast tumor response. By using these independent predictors, groups at low, intermediate, and high risk of LRR could be identified. Nomograms that incorporate these independent predictors were created.

Conclusion: In patients treated with NC, age, clinical tumor characteristics before NC, and pathologic nodal status/breast tumor response after NC can be used to predict risk for LRR and to optimize the use of adjuvant radiotherapy.

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Traitement locaux ablatifs de la maladie oligométastatique: les progrès technologiques modifient les profils évolutifs cliniques

Authors: J. Thariat, S. Vignot, R.-J. Bensadoun, F. Mornexe
Les traitements systémiques permettent rarement un contrôle durable de la maladie au stade métastatique mais il convient de distinguer différents profils évolutifs métastatiques allant d'une présentation oligométastique à des métastases disséminées. Nous avons évalué les pistes physiopathogéniques et les pratiques de traitement des oligométastases. Une revue de la littérature a été réalisée pour évaluer les pratiques de traitement local ablatif des oligométastases. L'amélioration des traitements locaux permet d'envisager des traitements ablatifs avec des taux de contrôle local des sites traités dépassant 70 % et des survies prolongées avec une qualité de vie acceptable. L'évolution des traitements locaux ablatifs a modifié la prise en charge de la maladie oligométastatique, s'intégrant dans une chronicisation de la maladie métastatique, permettant dans quelques cas une rémission prolongée du cancer, sous réserve d'une bonne sélection des indications, selon des critères et scores qui restent cependant à optimiser.

Maladie oligométastatique, un nouveau concept: irradiation en conditions stéréotaxiques de métastases pulmonaires. Revue de la littérature

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La maladie pulmonaire métastatique a longtemps été prise en charge par des traitements systémiques, les traitements locaux n'étaient considérés que dans un but purement palliatif. Plusieurs études cependant ont permis d'objectiver un bénéfice à traiter localement les métastases, particulièrement les oligométastases. La chirurgie a pris alors une place importante dans ce cas, mais le développement des techniques de radiothérapie en conditions stéréotaxiques d'une part, et les cas de refus ou contre-indication à la chirurgie. D'autre part, ont poussé les auteurs à mener des études pour évaluer l'efficacité de la radiothérapie en conditions stéréotaxiques dans le traitement de ces métastases. Cette revue de la littérature décrit la réalisation de cette technique de radiothérapie pour le traitement des oligométastases pulmonaires et les critères de sélection de patients pouvant en bénéficier. Elle compare les résultats de différentes études menées dans ce sens, ce qui a permis d'objectiver l'efficacité de cette technique en termes de contrôle local, de survie globale et de tolérance. La radiothérapie en conditions stéréotaxiques a donc émergé comme une alternative de choix, efficace et bien tolérée, avec un taux de contrôle local comparable à celui obtenu par chirurgie (74 à 100 %). La qualité de vie après radiothérapie en conditions stéréotaxiques sera surement, à l'avenir, un paramètre permettant de conforter ce choix thérapeutique et devra être étudiée finement.

Oligométastases : prise en charge thérapeutique a visée curative? Radiofrequence pulmonaire?

Authors: J. Palussiere., E. Descat , F. Cornelis
L'ablation tumorale percutanée consiste à détruire une tumeur par des modifications de température. Ce que permettent ces techniques peu invasives c'est de traiter efficacement des tumeurs tout en épargnant le parenchyme non tumoral. La faible morbidité est un atout essentiel pour la prise en charge des patients métastatiques dont la maladie est lentement évolutive, et qui nécessiteront souvent plusieurs temps de traitement local. La taille de la tumeur et son emplacement peuvent être des limites à la réalisation de ces traitements.