Yu Yang Soon\textsuperscript{1}, Desiree Chen\textsuperscript{1}, Desiree Chen\textsuperscript{1}, Jeremy Chee Seong Tey\textsuperscript{1}

\textsuperscript{1} Department of Radiation Oncology, National University Cancer Institute, Singapore

Quality of reporting of thoracic radiotherapy treatment in prospective lung cancer trials

Purpose
To assess the quality of reporting of thoracic (T) radiotherapy (RT) for curative intent treatment in prospective lung cancer trials.

Methods
We searched MEDLINE for eligible lung cancer trials published from 1996 to 2016. We assessed the initial trial reports on whether they reported the ten criteria adequately: RT dose prescription method; RT dose-planning procedures; organs at risk dose constraints; target volume definition, simulation and / or motion management procedures; treatment verification procedures; total RT dose; fractionation schedule; conduct of quality assurance as well as presence or absence of deviations in RT treatment planning and delivery. We performed multivariable logistic regression using SPSS to determine the factors that may influence the quality of reporting.

Results
We found 85 eligible trial reports. Target volume definition, total RT dose and fractionation schedule were reported adequately in more than 90% of the included trials. Only simulation procedure, verification procedure and presence or absence of deviations in RT treatment planning and delivery were reported adequately in less than 20% of the included trials. Twenty-three trials (27%) reported seven criteria or more adequately. Multivariable logistic regression showed that trials with RT focused research question were more likely to have adequate quality in reporting (judged as adequate reporting in seven criteria or more) than trials with non-RT focused question (odds ratio 6.67, 95% confidence interval 1.25 to 35.67, \( P \) value = 0.03). Other factors including study design, journals’ impact factor, publication in radiotherapy focused journals and year of publication did not predict for adequate quality of reporting.

Conclusions
There is significant variability in the quality of reporting on thoracic radiotherapy treatment in prospective lung cancer trials. The CONSORT statement needs to provide clearer
Surgical approach versus non-surgical approach in the curative treatment of resectable stage III non-small cell lung cancer (NSCLC): a systematic review and meta-analysis

Background
To determine if the surgical approach is the preferred curative treatment option over non-surgical approach for resectable stage III NSCLC

Methods
We searched MEDLINE for comparative studies comparing the effects of surgical and non-surgical approaches on progression-free survival (PFS), overall survival (OS) and treatment related mortality (TRM). We assessed the methodological quality of the included studies using the MERGE criteria. We estimated the pooled hazard ratios (HR), risk ratios (RR), confidence intervals (CI), P values (P) and I squared statistic (I2) with random effects model using Revman 5.3. We assessed the quality of the summarized randomized trials evidence using the GRADE approach.

Results
We found five randomized trials and one retrospective population based comparative study including 12,229 Stage III NSCLC patients. These studies have low to moderate risk of bias in their methodology. The randomized trials (n = 981) showed that surgery did not improve PFS (HR 0.93, 95% CI 0.74 to 1.17, P = 0.56, I2 = 0%, low quality), OS (HR 0.95, 95% CI 0.82 to 1.11, P = 0.53, I2 = 0%, moderate quality) and cause more TRM (RR 3.75, 95% CI 1.65 to 8.54, P = 0.002, I2 = 0%, moderate quality). Subgroup analyses showed that the effect on OS was no different between the trials that use concurrent chemoradiotherapy versus those that do not and trials that use PET/CT for staging versus those that do not. Although retrospective study favored surgical approach (OS: HR 0.64, 95% CI 0.53 to 0.77, P < 0.00001, I2 = 82%), this discrepancy in OS is likely due to selection bias.

Conclusions
Surgical approach did not delay disease progression or improve survival and may cause more treatment related deaths compared to non-surgical approach in the curative treatment of resectable stage III NSCLC. Future research should focus on optimizing the non-surgical approach using more effective systemic agents and advanced imaging and radiotherapy techniques.
Systemic therapy alone versus addition of cranial radiotherapy in HER2-positive breast cancer patients with brain metastasis: A systematic review and meta-analysis

Purpose
To determine the benefit of adding radiotherapy (RT) to systemic therapy for HER2-positive (HER2+) breast cancer patients with brain metastasis (BM)

Methods
We searched MEDLINE for studies reporting outcomes of BM specific to HER2+ patients. We assessed the methodological quality of the included studies using the MERGE criteria. Meta-analysis with random effects model was performed using Revman 5.3 to estimate the event rate, confidence intervals (CI), P values (P) and I squared statistic (I²). Outcomes of interests were overall response rate (ORR), 6-month, 1-year and 2-year overall survival (OS), 6-month and 1-year intracranial progression-free survival (PFS). GRADE approach was used to appraise the quality of evidence of included trials.

Results
We found 3 phase II and 5 retrospective studies reporting the outcomes of HER2+ breast cancer patient with BM. ORR for systemic therapy alone is 47.57% (95%CI 31.9 to 63.5 and I² = 56%) and addition of cranial RT did not significantly improve ORR (ORR 49.9%, 95%CI 9.6 to 90.3, P = 0.95, I² = 95%). After systemic therapy alone, 6-month, 1-year and 2-year OS were 96.7%, 84.6% and 58.9% respectively compared to 76.4%, 50.5% and 20.0% when cranial RT is added. This is likely due to poor quality evidence. The prospective trials were judged to have low to moderate risk of bias while the other included studies had moderate to high risk of bias in their methodology. The 6-month and 1-year intracranial PFS are 31.1% and 4.4% respectively, but not reported for patient who received additional cranial RT.

Conclusion
As most of the included studies have methodological limitations, there is no clear evidence to conclude on the effect on ORR, OS and PFS when RT is added to systemic treatment for HER2+ breast cancer patients with BM. Future research with high quality randomized trials is warranted to determine the role of RT and at the same time investigate the difference in toxicity profiles for this group of patients.
Chemoradiotherapy versus chemotherapy for unresectable pancreatic cancer: A systematic review and meta-analysis

Purpose
To determine the benefit of adding radiotherapy (RT) to chemotherapy for patients with unresectable pancreatic cancer.

Methods and Materials
We searched MEDLINE for comparative studies comparing chemoradiotherapy with chemotherapy for patients with unresectable pancreatic cancer. We assessed the methodological quality of the included studies using the MERGE criteria. We performed the meta-analysis with random effects model using Revman 5.3 to estimate the pooled hazard ratios (HR), confidence intervals (CI), P values (P) and I squared statistic (I2). The primary outcome was overall survival (OS); secondary outcomes include progression-free survival (PFS) and adverse events (AE). We used the GRADE approach to appraise the quality of evidence from randomized trials.

Results
We found five randomised and three retrospective comparative studies including 830 patients. Only two randomized trials were judged to have low to moderate risk of bias while the other included studies had moderate to high risk of bias in their methodology. For the randomised trials, the addition of radiotherapy did not improve PFS (HR 0.90, 95% CI 0.74 to 1.10, P = 0.30, I2 = 11%, moderate quality evidence) or OS (HR 0.87, 95% CI 0.63 to 1.21, P = 0.41, I2 = 67%, very low quality evidence) and was associated with more frequent grade 3 or 4 gastrointestinal AE. Retrospective studies showed an improvement in PFS (HR 0.58, 95% CI 0.37 to 0.92, P = 0.02, I2 = 32%) and OS (HR 0.48, 95% CI 0.35 to 0.60, P < 0.0001, I2 = 6%), which was likely due to a result of imbalance in tumour characteristics between the two groups.

Conclusion
As most of the published studies have methodological limitations, there is no clear evidence of an effect on progression free and overall survival for adding RT to chemotherapy for patients with unresectable pancreatic cancer. Future research with high quality randomized trials is warranted to determine the role of RT for this group of patients.
Re-irradiation for recurrent Glioblastoma Multiforme (GBM): systematic review and metaanalysis

Purpose
The role of re-irradiation in patients with recurrent GBM is unclear. We sought to determine the efficacy and toxicity of re-irradiation for this group of patients.

Methods
We searched MEDLINE and various conference proceedings for eligible studies where patients were treated with re-irradiation for recurrent GBM. Outcomes of interest were 6 and 12-month overall survival (OS-6, OS-12), 6 and 12-month freedom from progression (FFP-6, FFP-12) and Grade 3 or 4 adverse events (AE). We used random effects model to pool outcomes across studies and compared pre-defined subgroups using interaction test.

Results
We found 38 eligible non-comparative studies including 1358 patients with severe methodological limitations. Of these, thirteen studies used brachytherapy alone, 10 were of a prospective design and 6 employed concurrent systemic therapy. We found that re-irradiation was associated with a OS-6 rate of 75% (95% confidence interval (CI) 72 – 78%, I² = 44%), OS-12 rate of 39% (95% CI 34 – 43%, I² = 67%), FFP-6 rate of 39% (95% CI 30-49%, I² =85%), FFP-12 rate of 16% (95% CI 12-19%, I² = 27%), and Grade 3 or 4 AE rate of 5% (95% CI 2-9%, I² = 66%). Sub-group analysis showed that studies with prospective design had higher rates of OS-6 and OS-12 compared with studies of retrospective design (OS-6: 82% versus (vs) 73%, interaction P (IP) = 0.006; OS-12: 47% vs 37%, IP = 0.05) and studies which used concurrent systemic therapy had higher rates of OS-6 compared with studies that did not (83% vs 74%, IP = 0.02).

Conclusion
There is low quality evidence to suggest that re-irradiation, in selected patients, provides encouraging disease control and survival rates. High quality randomized trials are needed to establish the optimal management strategy for recurrent GBM.
CT based brachytherapy planning in cervical cancer- a study of long-term toxicity outcomes

Background/Objective
To report late rectal and bladder toxicity outcomes of a computed tomography (CT)-based image guided brachytherapy (IGBT) technique for treatment of cervical cancer. (M): Between 2008-2014, 95 women with FIGO stage IB to IVA cervical carcinoma treated with concurrent chemotherapy and external beam radiation therapy (EBRT) 50.4Gy in 28 fractions followed by planned prescription dose of 7Gy x 4 fractions of high-dose-rate (HDR) IGBT was retrospectively reviewed. Interstitial brachytherapy was not allowed. Toxicities were recorded on follow-up.

Outcomes
The median follow-up time was 29 months (range: 6-76). The 3-year cumulative incidences of local, locoregional and distant relapse free survival were 94.8% (SD±14.8), 87.4% (SD±15.5) and 76.8% (SD±15.3) respectively. The 3-year overall survival was 69.7% and the 3 year relapse free survival was 72.6% (SD±18.1). Twenty-two patients (23%) had Grade 2 proctitis and 10 patients (11%) had Grade 3 proctitis. This occurred more than 6 months post treatment. Six patients experienced radiation colitis which necessitated laser coagulation and 3 patients required transfusion for low haemoglobin levels. One patient had fecal incontinence and another with stage IVA cervical cancer who had undergone concurrent chemotherapy and radiation therapy continued to have radiation proctitis diarrhoea post procedure and required admission for intravenous fluids. Four patients (4%) had Grade 2 cystitis and 2 patients (2%) had Grade 3 cystitis. No patients had Grade 4 toxicities. There were 3 patients who developed recto-vaginal fistulae and one of these patients also developed a vesico-vaginal fistula. This was found to be due to tumour recurrence.

Conclusion
This study reports the excellent results of CT based image guided brachytherapy for local control and overall survival. Implementation of an interstitial IGBT program using the EMBRACE protocol may help to decrease late toxicity.
Adoption of prophylactic cranial irradiation for extensive stage small cell lung cancer: A population based outcomes study

Background
The survival benefit of prophylactic cranial irradiation (PCI) in extensive stage small cell lung cancer (ES-SCLC) is unclear. This study aimed to determine the use of PCI and the factors associated with its use as well as its impact on overall survival (OS) in the Singapore population.

Methods
We conducted a retrospective cohort study including patients diagnosed with ES-SCLC without brain metastases treated in the only two Singapore national cancer centres from 2003 to 2010. We identified the patients using the institutions’ pathology registries and linked the electronic medical records to the National Death Registry. We used multivariable logistic regression to identify factors associated with the use of PCI and its impact on OS. All analyses were performed using STATA version 11.0.

Results
We identified 224 eligible patients. 65 of 224 patients did not receive chemotherapy. 71 of 159 patients had at least stable disease (SD) after 1st line chemotherapy. 16 of these 71 patients received PCI. There was an increase in the use of PCI from the period 2007 to 2010 compared with 2003 to 2006 (13 patients versus 3 patients, chi-square P value = 0.01). The use of consolidation thoracic radiation therapy (TRT) was associated with use of PCI (odds ratio 18.3, 95% confidence interval (CI) 4.70 to 71.96, P value (P) < 0.001). PCI improved OS (adjusted hazard ratio 0.47, 95% CI 0.24 to 0.91, P = 0.02) compared to no PCI use among the 71 patients who had at least SD after 1st line chemotherapy. Consolidation TRT did not improve OS among this group of patients.

Conclusion
The use of PCI remained low in the Singapore population between 2003 to 2010 despite an increase in its use since 2007. Patients who had at least SD after first line chemotherapy or had consolidation thoracic radiation therapy were more likely to receive PCI. Among patients who had at least SD after 1st line chemotherapy, the use of PCI was associated with an improved survival outcome.
Quality of reporting of radiotherapy in randomised controlled trials in prostate cancer

Purpose
To assess the quality of prostate radiotherapy (RT) treatment reporting in randomised controlled trials (RCTs) in prostate cancer.

Methods
We searched MEDLINE for RCTs of prostate cancer, published from 1996 to 2016 and included prostate RT as one of the intervention arms. We assessed the initial report of the included RCTs on whether they reported the ten criteria adequately: RT dose prescription method; RT dose-planning procedures; organs at risk (OAR) dose constraints; target volume definition, simulation procedures; treatment verification procedures; total RT dose; fractionation schedule; conduct of quality assurance (QA) as well as presence or absence of deviations in RT treatment planning and delivery. We performed multivariate analysis to determine the factors that may influence the quality of reporting.

Results
We found 59 eligible trial reports. There was significant variability in the quality of reporting. Target volume definition, total RT dose and fractionation schedule were reported adequately in 97% of included trials. OAR constraints, simulation procedures and presence or absence of deviations in RT treatment planning and delivery were reported adequately in 30% of included trials. 24 trials (40%) reported seven criteria or more adequately. Multivariate analysis showed that trials that published their quality assurance results were more likely to have adequate quality in reporting (judged as adequate reporting in seven criteria or more) compared to trials which did not (odds ratio 11.38, 95% confidence interval 1.67 to 78, P value =0.01).

Conclusions
There is significant variability in the quality of reporting on prostate radiotherapy treatment in RCTs of prostate cancer. We need to have consensus guidelines to standardise the reporting of radiotherapy treatment in RCTs.
Patient reported outcomes following Palliative gastric Radiotherapy for symptomatic advanced Gastric cancer (PROG): Results from a Phase 2 trial

Purpose
To determine the effect of gastric radiotherapy (RT) on patient reported outcomes (PROs; secondary endpoint) in the PROG trial.

Methods
Patients with symptomatic locally advanced or metastatic gastric carcinoma with at least one index symptom of bleeding, pain or obstruction were treated with palliative gastric radiotherapy to a dose of 36Gy in 12 fractions (at 3Gy daily fractions). PROs were assessed using the EORTC-C30 and stomach module STO22. Assessments were performed at baseline, 12th fractions and one month post RT. Paired T test was used to compare the mean scores from baseline, and at 12 fractions and one month post completion of RT

Results
Questionnaires were available from 49 of 50 patients at baseline, 36 of 45 patients at 12 fractions and 16 of 38 patients at one-month post RT. At 12 fractions, 50%, 28% and 44% of patients achieved a significant improvement in fatigue, nausea/vomiting and pain subscales in the C30 respectively. 42% and 28% of patients achieved a significant improvement in dysphagia and pain subscale in the STO22. The observed mean difference was 11 points and 4 points for pain subscale in the C30 and STO22 (P<0.02). At one-month post RT, 63%, 31% and 50% of patients achieved a significant improvement in fatigue, nausea/vomiting and pain subscales in the C30 respectively. 44% and 19% of patients achieved a significant improvement in dysphagia and pain subscale in the STO22. There were no significant differences in the mean scores in the subscales of interest.

Conclusions
Palliative gastric radiotherapy resulted in improvements in fatigue, dysphagia and pain at 12 fractions and at 1-month post radiotherapy in a significant proportion of patients. A phase III trial comparing the effects of different fractionation regimens on PROs is warranted
Lung surgery versus thoracic radiotherapy for curative treatment of Stage I non-small cell lung cancer (NSCLC): a systematic review and meta-analysis

Purpose
To determine if lung surgery (Sx) is the preferred curative treatment option over thoracic radiotherapy (TRT) for Stage I NSCLC

Methods
We searched MEDLINE for eligible studies comparing the effects of Sx and TRT on progression-free survival (PFS), overall survival (OS) and treatment related mortality (TRM). We assessed the methodological quality of the included studies using the MERGE criteria. We estimated the pooled hazard ratios (HR), risk ratios (RR), confidence intervals (CI), P values (P) and I squared statistic (I²) with random effects model using Revman 5.3. We assessed the quality of the summarized randomized trials evidence using the GRADE approach.

Results
We found two randomized trials (pooled as a single report) and eight retrospective comparative studies (propensity matched) including 1620 patients. These studies have low to moderate risk of bias in their methodology. There was low quality evidence from randomized trials showing that there was no difference between Sx and TRT on PFS (HR 1.43, 95% CI 0.43 to 4.74, P = 0.56), OS (HR 7.17, 95% CI 0.86 to 59.55, P = 0.07) and TRM (RR 3.43, 95% CI 0.15 to 80.83, P = 0.44). Retrospective studies showed that surgical approach was associated with improvement in PFS (HR 0.32, 95% CI 0.17 to 0.59, P < 0.00001, I² = 0%) and possible increase in TRM (RR 3.12, 95% CI 0.53 to 18.40, P = 0.21, I² = 0%).

Conclusions
There was low quality evidence from randomized trials demonstrating that lung surgery is not superior to thoracic radiotherapy in the curative treatment of resectable NSCLC. The discrepancies between the randomized and retrospective studies were likely due to selection bias. Future research with high quality randomized trials are warranted to determine the optimal treatment approach for Stage I NSCLC.
Dosimetric comparison on the accuracy of dose calculation algorithms measured in inhomogeneous phantom in the case of lung SBRT

Background
Dose inaccuracies result in inhomogeneous regions due to loss of electronic equilibrium at tissue interfaces. Lung Stereotactic Body Radiotherapy (SBRT) is high dose in nature and requires a sharp dose fall-off from the planning target volume (PTV) to the organs at risk (OAR). This study evaluates the dosimetric comparison between treatment plans using Acuros XB (AXB) grid-based and X-ray Voxel Monte Carlo (XVMC) model based algorithms.

Methods
12 Intensity Modulated Radiation Therapy (IMRT) and 12 Volumetric Modulated Arc Therapy (VMAT) treatment plans were created on the 0.1cm CT study set slices of the inhomogeneous phantom targeting a 13.7cm³ PTV within the 598.1cm³ cedar insert (lung), 45Gy at 9Gy/fraction was prescribed with 5 coplanar 6MV IMRT beams or 2 dynamic conformal arcs. Plans were first optimized and calculated with AXB; thereafter with XVMC utilizing 0.3cm³ grid size. Dosimetric comparison was evaluated using independent software in terms of dose volume histogram (DVH) statistics related to the PTV coverage and OAR doses, homogeneity (HI) and conformity (CI) indices. Dosimetric validation was performed with ion chamber measurements.

Results
DVH results showed that AXB IMRT plans yielded a minimum 95.0% coverage and a global maximum of 113.0% for PTV; mean and maximum doses for lung at 20.8% and 114.0%; HI and CI at 0.123 and 1.017. XVMC IMRT treatment plans yielded a minimum 94.8% coverage and global maximum of 125.8% for PTV, mean and maximum doses for lung at 20.2% and 128.5%; HI and CI of 0.245 and 1.022. Dosimetric validation showed both algorithms agreed with measurements to within 3.0%.

Conclusion
Both AXB and XVMC treatment plans met our departmental requirements for treating lung SBRT cases. AXB IMRT calculated plans showed optimal plans with better PTV coverage with lesser dose gradients, lowest lung dose and better HI and CI. This study confirms that AXB algorithm adequately accounts for doses within tissue inhomogeneities.
Purpose
Multiple randomized trials (RCTs) reported that concurrent chemotherapy (CCT) with or without adjuvant chemotherapy (AC) improves survival in stage II-IVB nasopharyngeal carcinoma (NPC) compared to radiation therapy alone. However, it is unclear if similar benefits can be observed in routine practice as patients included in RCTs could be very different from patients in routine practice. The aim of this study is to compare the effects of CCT with or without AC as estimated from observational studies (OBS) with findings from RCTs.

Methods and Materials
We searched MEDLINE for eligible studies determining the effect of addition of CCT with or without AC in stage II-IVB NPC. Outcome of interest was overall survival (OS). We performed the meta-analysis with random effects model to estimate the pooled hazard ratios (HR), confidence intervals (CI), and I squared statistic (I²) for both RCTs and OBS and compared them using Altman interaction test.

Results
We found nine RCTs and 19 OBS including 6523 patients. Eight RCTs and 14 OBS had at least 75% of its patients with stage III-IVB NPC while only one RCT and five OBS had at least 75% of its patients with stage II NPC. The survival benefit associated with chemotherapy was similar in both RCTs and OBS focusing on stage III-IVB NPC (RCTs HR 0.67, 95% CI 0.56 – 0.81, I² = 48% vs OBS HR 0.71 95% CI 0.62 – 0.82, I² = 4%, interaction P (IP) = 0.67). Similarly, there was no significant difference in OS for RCT and OBS focusing on stage II NPC (RCTs HR 0.34, 95% CI 0.17 to 0.66, I² = non-applicable due to single study vs OBS HR 0.61, 95% CI 0.37 to 1.02, I² = 0%, IP = 0.17).

Conclusion
Patients with stage II and stage III-IVB nasopharyngeal carcinoma treated in routine practice received similar survival benefits associated with concurrent chemotherapy with or without adjuvant chemotherapy as patients treated in randomized trials.
Neoadjuvant chemotherapy plus concomitant chemoradiation versus concomitant chemoradiation for locoregionally advanced nasopharyngeal carcinoma: A systematic review and meta-analysis of comparative studies

Purpose
To determine if adding neoadjuvant chemotherapy (NACT) to concomitant chemoradiation (CCRT) for patients with locoregionally advanced nasopharyngeal carcinoma (NPC) improves overall survival.

Methods and Materials
We searched MEDLINE for eligible studies comparing NACT plus CCRT versus (vs) CCRT alone for locoregionally advanced NPC. We assessed the methodological quality of studies using the MERGE criteria. Meta-analysis was performed with random effects model using Revman 5.3 to estimate the pooled hazard ratios (HR), confidence intervals (CI), P values (P) and I squared statistic (I^2). The primary outcome was overall survival (OS); secondary outcomes include progression-free survival (PFS) and adverse events (AE). We used the GRADE approach to appraise the quality of evidence from randomized trials.

Results
We found four randomized and five retrospective comparative studies including 2178 patients with low to moderate risk of bias in their methodologic quality. Pooled estimates from both randomized and retrospective studies demonstrated a benefit in PFS (HR 0.78, 95% CI 0.66-0.93, P=0.006, I^2=0%) and OS (HR 0.77, 95% CI 0.61-0.96, P=0.02, I^2=0%) with NACT. In the randomized trials, there was moderate quality evidence that NACT improved PFS significantly (HR 0.73, 95% CI 0.57-0.93, P=0.01, I^2=0%); trend towards OS benefit (HR 0.76, 95% CI 0.56-1.03, P=0.08, I^2=0%) and was associated with more frequent AE. There were no significant differences in the results between the randomized and retrospective comparative studies (PFS HR 0.73 vs 0.82, interaction P (IP) = 0.58; OS HR 0.76 vs 0.78, IP=0.93).

Conclusion
Neoadjuvant chemotherapy delays disease progression substantially and may improve survival for locoregionally advanced nasopharyngeal carcinoma. There were no divergent results between randomized and retrospective comparative studies. Future trials should test more effective and/or better tolerated agents during the neoadjuvant therapy phase.
Quality of reporting of cranial irradiation in randomised controlled trials in primary central nervous system tumours

Purpose
To assess the quality of reporting of cranial irradiation treatment in randomised controlled trials (RCTs) in primary central nervous system (CNS) tumours.

Methods
We searched MEDLINE for randomised trials of primary CNS neoplasms, published from 1996 to 2016 and included cranial irradiation as one of the intervention arms. We assessed the initial RCTs report on whether they reported the ten criteria adequately: target volume definition, total radiation dose, fractionation schedule, prescription point, description of dose planning procedures, organs at risk (OAR) dose constraints, simulation procedures, verification procedures, conduct of quality assurance (QA) as well as presence or absence of deviations in radiotherapy (RT) treatment planning and delivery. We performed multivariate logistic regression using SPSS v16 to determine the factors that may affect the quality of reporting.

Results
We screened 916 article, of which 50 were eligible. There was significant variability in the quality of reporting among the included studies. Total RT dose and fractionation schedule were reported adequately in >90% of included trials. OAR constraints, treatment verification procedures and presence or absence of deviations in RT treatment planning and delivery were reported adequately in <30% of included trials. Fourteen trials reported ≥7 criteria adequately. Multivariate analysis revealed trials which published their RT QA results as a separate report were six times more likely to have adequate quality in reporting compared to trials which did not (odds ratio 5.94, 95% confidence interval 1.05 to 33.50, P value = 0.04). Other factors including primary efficacy outcome, journals’ impact factor, and year of publication did not predict for adequate quality of reporting.

Conclusions
The quality of reporting on cranial irradiation in the treatment of primary CNS tumours is variable. Guidelines should be introduced to improve clarity and ensure consistency in reporting.
Develop a low dose PET/CT imaging protocol for early detection of lung cancer in high risk patients

Background
Lung cancer screening with low-dose computed tomography (CT) has been shown to be better than chest X-rays but has low specificity. Detection accuracy may be improved with positron emission tomography (PET) at a cost of additional radiation. We previously reported on simulated low-dose PET imaging and demonstrated 10×10^6 net true counts as sufficient for quality diagnostic images. We now hypothesize that we can maintain image quality with a 92% reduction of fluorodeoxyglucose (FDG) tracer activity from 6 to 0.5 mCi and use machine learning to predict human response.

Methods
9 patients have completed two sequential PET/CT scans in a day. Scan is done with 0.5 mCi FDG using a low-dose protocol, followed by routine PET/CT (6 mCi). PET data from routine scan were manipulated to emulate various noise levels corresponding to 9 predefined true count levels ranging from 0.25×10^6 to 20×10^6 and matched to the low-dose scan to compare noise statistics. The data were reconstructed with independent noise realizations. 10 lesions in 7 patients were identified as having size and uptake consistent with those found in early disease. Detection performance was determined by machine learning, namely, convolution neural networks trained by 4 previous observer responses.

Results
Lesion detection accuracy was evaluated in 4458 total image sub-volumes. Regions containing both target lesions (2627 samples) and healthy lung background (1831 samples) were used to assess sensitivity and specificity at all noise levels. Results presented are stratified by true count/millions: <0.5, 0.5-1, 1-2, 2-5, 5-10, 10-20, >20. The mean sensitivities and specificities (%) across the 4 observer models were 0.35, 18.85, 62.35, 85.4, 95.73, 96.23, 96.42, and 6.64, 6.93, 20.43, 66.54, 93.55, 96.87, 98.25.

Conclusion
Low-dose PET can provide good lesion detection performance within the true count range of 5-10×10^6. Deep learning techniques are feasible for predicting human responses in this complex imaging task.
Radiation Response Assessment by Hybrid Positron Emission Tomography/Magnetic Resonance Imaging for Cervical Cancer Treatment

Background
Treatment response after radiation therapy (RT) in locally advanced cervical cancer is commonly assessed 3 months post treatment. This study aims to investigate the effectiveness of hybrid imaging that incorporates magnetic resonance imaging (MRI) and positron emission tomography (PET) to evaluate treatment response and tumour visualization during and post – RT.

Methods
Six patients with histo-pathologically confirmed cervical cancer and undergoing RT as part of their treatment plan were enrolled. As standard care, all patients received 5-6 weeks of daily external beam radiotherapy (EBRT) and 4-5 sessions of localized brachytherapy. Subjects underwent a total of four multi-parametric PET/MRI scans at baseline, before the first and third brachytherapy insertions and three months post-treatment. The scans used two different 18F-FDG dosages, 6 mCi for the first & fourth scans and 3 mCi for the second & third scans. Each scan was evaluated for multi-modality changes in metabolic target volume (MTV), MR volume, mean SUV and mean ADC values.

Results
Five patients attained complete radiological treatment response on the PET/MRI scans, with observations reflecting largest reductions in MTV and MR volume between the baseline and second scan (post external RT). For four out of six patients, the ADCMean increased after EBRT. Significant reductions in SUVMean was observed post-EBRT and for some patients there was a mid-treatment rise in SUVMean. The increase in SUVMean at the 3 months post-treatment scan could be attributed to the close proximity between the tumour and the bladder that might result in ROI mapping errors between anatomical and functional images.

Conclusion
Significant treatment response to RT can be detected early using PET/MRI, typically by the end of EBRT. Hybrid PET/MRI allows fusion of soft tissue morphological imaging with functional imaging to provide a multi-parametric imaging, potentially allowing a personalized treatment.
Establishment of 3D Expansion of Cervical Circulating Tumor Cells as a Prognostic Tool for Chemoradiotherapy Response

Background
Circulating Tumour Cells (CTCs) are rare cells shed from tumours into the bloodstream (Pantel et al. 2007). Current CTC enrichment techniques are limited in sensitivity, and present an underestimate of total CTCs. In vitro expansion of CTCs allows a more complete characterization of cancer as compared to tumour biopsies. This study aims to develop a procedure for the label-free expansion of CTC clusters from serial blood samples of the same patient.

Methods
The CTC Cluster Assay, a novel microfluidic assay for CTC expansion (Khoo et al. 2016) which mimics tumour microenvironment in vitro was utilised. Clusters are co-cultures of CTCs and blood-derived tumour associated cells which maintain and promote cluster formation; flat-based cylindrical microwells do not achieve cluster formation. This assay is a single-step procedure that does not require pre-enrichment, minimizing loss of cells and viability. Efficiency of cluster formation has been demonstrated previously in patients with breast cancer (>70% in pre-treatment samples) (Khoo et al. 2016, Khoo et al. 2015).

Results
Cluster phenotype correlates with patient prognosis. Here, we demonstrate the assay’s applicability to samples from patients with Stage 2-4 cervical cancer undergoing chemoradiation or palliative chemotherapy. 7.5-10 ml of blood samples were obtained at four timepoints (baseline, week 3, week 5 and 3-month post treatment). Samples were processed for device optimisation or culture. For samples cultured, 28.6% were positive with clusters. CD45- putative CTC population varies from 10-50%. For one positive sample, ~40% of the putative CTC population was EpCAM+.

Conclusion
Liquid biopsy allows personalized evaluation of cancer-immune cell interactions on a routine basis throughout treatment. These translate to high applicability in cases where the primary or metastatic tumor cannot be biopsied, and allow us to utilise the cultures for biomarker discoveries.
Impact of intensity modulated radiotherapy (IMRT) on benefit of concurrent chemotherapy with or without adjuvant chemotherapy in localized nasopharyngeal carcinoma versus radiation therapy alone: meta-analysis of results from non-IMRT and IMRT studies

Background
Many randomized trials (RCTs) using non-IMRT techniques reported that concurrent chemoradiation (CCRT) improved survival but increased radiation-related toxicity in localized nasopharyngeal carcinoma (NPC) compared to radiation therapy (RT) alone. However, it is unclear if similar survival benefits and toxicity outcomes can be observed using IMRT. The aim of this study was to compare treatment effects in studies involving non-IMRT with those using IMRT.

Methods
We searched MEDLINE for eligible RCTs and observational studies (OBS) determining the effect of CCRT in localized NPC. Overall survival (OS), and toxicity (G3-4 acute mucositis, late hearing loss) outcomes were examined. We performed the meta-analysis with random effects model to estimate the pooled hazard ratios (HR), risk ratios (RR), confidence intervals (CI), p values (P) and I-squared statistic (I2) for RCTs and OBS.

Results
All 10 RCTs found used non-IMRT, and 13 OBS identified, used the IMRT technique. 6,098 patients were included in this meta-analysis. The survival benefit was similar between RCTs versus OBS IMRT [HR 0.67, 95% CI 0.56 – 0.80, P < 0.0001, I2 = 51% vs HR 0.72, 95% CI 0.60 – 0.87, P = 0.007, I2 = 0%]. CCRT was associated with a statistically significant increased risk of G3-4 acute mucositis in RCTs (RR 1.45, 95% CI 1.28 to 1.64, P < 0.0001, I2 = 0%) but not in OBS IMRT (RR 1.23, 95% CI 0.93 to 1.62, P = 0.15, I2 = 52%). Similarly, CCRT resulted in a statistically significant increased risk of Grade 3-4 late hearing loss in RCTs (RR 1.53, 95% CI 1.07 to 2.19, P = 0.02, I2 = 0%) but not in OBS IMRT (RR 1.02 95% CI 0.53 to 1.99, P = 0.94, I2 = 0%).

Conclusion
Significant survival benefit with CCRT for localized NPC seen in RCTs persisted in observational studies in the IMRT era. The addition of concurrent chemotherapy worsened acute G3-4 mucositis and late hearing loss in earlier studies with non-IMRT technique, not detected in later observational studies using IMRT.