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FULL PAPER

Comparative effectiveness of intensity modulated radiation therapy to 3-dimensional conformal radiation in locally advanced lung cancer: pathological and clinical outcomes

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Objective: Intensity-modulated radiotherapy (IMRT) has better normal-tissue sparing compared with 3-dimensional conformal radiation (3DCRT). We sought to assess the impact of radiation technique on pathological and clinical outcomes in locally advanced non-small cell lung cancer (LANSCLC) treated with a trimodality strategy.

Methods: Retrospective review of LANSCLC patients treated from August 2012 to August 2018 at Sheba Medical Center, Israel. The trimodality strategy consisted of concomitant chemoradiation to 60 Gray (Gy) followed by completion surgery. The planning target volume (PTV) was defined by co-registered PET/CT. Here we compare the pathological regression, surgical margin status, local control rates (LC), disease free (DFS) and overall survival (OS) between 3DCRT and IMRT.

Results: Our cohort consisted of 74 patients with mean age 62.9 years, male in 51/74 (69%), adenocarcinoma in 46/74 (62.1%), stage 3 in 59/74 (79.7%) and chemotherapy in 72/74 (97.3%). Radiation mean dose: 59.2 Gy (SD ± 3.8).

Radiation technique : 3DCRT in 51/74 (68.9%), IMRT in 23/74 (31%). Other variables were similar between groups. Major pathological response (including pathological complete response or less than 10% residual tumor cells) was similar: 32/51 (62.7%) in 3DCRT and 15/23 (65.2%) in IMRT, p=0.83. Pathological complete response (pCR) rates were similar: 17/51 (33.3%) in 3DCRT and 8/23 (34.8%) in IMRT, p=0.9. Surgical margins were negative in 46/51 (90.1%) in 3DCRT vs. 17/19 (89.4%) in IMRT (p=1.0). The 2-year LC rates were 81.6% (95% CI 69-89.4%); DFS 58.3% (95% CI 45.5-69%) and 3-year OS 70% (95% CI 57-80%). Comparing radiation techniques, there were no significant differences in LC (p=0.94), DFS (p=0.33) and OS (p=0.72).

Conclusion: When used to treat LANSCLC in the neoadjuvant setting, both IMRT and 3DCRT produce comparable pathological and clinical outcomes.

Advances in knowledge: This study validates the real-world effectiveness of IMRT compared to 3DCRT.

INTRODUCTION

Radiation therapy is frequently used in the treatment of stage III non-small cell lung cancer (NSCLC), using a range of radiation techniques. In three-dimensional conformal radiotherapy (3DCRT) several un-modulated fields (typically 3–4) are designed to deliver dose directed to the targets. With intensity-modulated radiotherapy (IMRT), optimized modulated radiation fields (typically 6–12) are designed to deliver the dose to the target. The shapes and intensities of each radiation field in IMRT are optimized by means of computer algorithms to conform the dose to the target and to spare the nearby critical structures. Volumetric modulated arc therapy (VMAT) delivers radiation by rotating the gantry while the radiation beam remains on, simultaneously changing rotation speed, shape of the radiation field, and rate of delivered dose. Both IMRT and VMAT planning techniques improve target coverage and reduce radiation exposure to adjacent critical organs compared to 3DCRT.[1,2]

Yet, with these advanced technologies, a great deal of concern has been expressed regarding the potential for interplay-effect between target motion and collimator motion that may lead to insufficient tumor irradiation during IMRT and VMAT delivery. Tumor movement due to respiration introduces another level of complexity to IMRT treatment planning and delivery, as each radiation field segment may only cover a portion of the target volume at any particular time.[3] Court et. al found that for most treatment techniques, these dose deviations averaged out after several fractions.[4] However, prospective, randomized trial results directly comparing the efficacy and toxicity of 3DCRT *vs* IMRT for lung cancer have not yet been published.[5]

We therefore performed a retrospective study, comparing 3DCRT *vs* IMRT. Primary endpoints included pathological response after chemoradiation and the margins of the resected surgical specimens; secondary endpoints were clinical outcomes including local control (LC) disease free survival (DFS) and overall survival (OS). We hypothesized that the two technologies produce the same rates of pathological response and similar clinical results.

METHODS AND MATERIALS

Retrospective, single institution, case review study. Electronic medical records were searched for patient and treatment characteristics, after Institutional Review Board approval.

Patients

Inclusion criteria: patients with Stage IIB to IIIB (American Joint Committee on Cancer seventh Edition) non-small cell lung cancer (NSCLC), who were treated at Sheba Academic Medical Center, Israel between August 2012 and August 2018 with concurrent chemotherapy and external beam radiotherapy (CCRT), followed by surgery. Exclusion criteria were small cell lung cancer, metastatic disease, and patients who did not undergo completion surgery. We did include one patient with solitary brain metastasis that was treated with stereotactic brain radiosurgery. Information on follow-up was reviewed up to January 2019.

Treatment

Our institutional trimodality approach, as well as chemotherapy protocols and radiation planning objectives have been previously described.[6] Briefly, positron emission tomography/CT (PET/CT) imaging for target delineation was used by image registration and fusion to the planning CT scan. Elective nodal irradiation was not used. Margins from gross tumor volume (GTV) to clinical target volume (CTV) was 0.5 cm, and from CTV to planning target volume (PTV) was 0.5–1 cm. Radiation dose was prescribed to 60 Gy except if limited by organ-at-risk doses, or stopped early due to patients' side-effects. Tissue heterogeneity corrections were included in the treatment planning system. Dose calculations were performed using the analytical anisotropic algorithm (AAA) in the Eclipse (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system. Radiation in both cohorts had a planned prescription goal of ≥95% of the treatment dose was prescribed volumetrically to >95% of the PTV.

Patients were categorized according to radiation treatment technique: 3DCRT *vs* IMRT. For the purpose of the analysis, IMRT and VMAT cases were combined together. Patients who were treated with a hybrid 3DCRT-IMRT plan were included in the IMRT cohort. Prior to 2016, our protocols included 3DCRT techniques except for tumors that were located close to the spine, in which case IMRT was preferred. Since the middle of 2016, IMRT has become the standard modality in our department for locally advanced lung cancer (LANSCLC) patients.

Daily image guided radiation therapy (IGRT) using daily kilovoltage imaging (kV/kV) or cone-beam CT (CBCT) was systematically applied to all lung cancer patients in our cohort. The choice of IGRT was according to physician guidance. For any patient, if more than 50% of images used were CBCT, it was listed in the CBCT group, and if less than 50% it was listed in the kV/kV group.

Chemotherapy was prescribed concurrently with the radiation, with platinum doublet, at the choice of the medical oncologist. Standard treatment regimens were:

- Cisplatin (CN) (37.5 milligram/meter square (mg/m^2) Day1, Day8, Day22, Day38) and vinorelbine (12.5 mg/m^2 Day1, Day8, Day22, Day38)
- Carboplatin (CT) at area-under curve (AUC) two with paclitaxel at 45 mg/m^2 both given every week or carboplatin at AUC 5 with paclitaxel 175 mg/m^2 every 3 weeks q3w
- Etoposide (EP) at 100 mg/m^2 Day1-3 with cisplatin at 75 mg/m^2 q3w or etoposide 50 mg/m^2 Day1-5 with cisplatin 50 mg/m^2 Day1,Day8 q4w

Surgery: A complete anatomical resection with hilar and mediastinal lymph node dissection was performed 6-to-8 weeks following completion of CCRT. The preferred surgical approach was a muscle-sparing lateral thoracotomy.

Pathological analysis

Pathological endpoints were tumor-regression and the surgical-margin status.

Pathological response was evaluated on the specimens according to protocols recommended by the College of American Pathologists, based on the modified tumor regression grading, as suggested by Junker et al.[7] Response was recorded as a dichotomous variable with 'favorable' or 'unfavorable' groups. Favorable pathological response included major tumor regression (MTR), defined as residual viable tumor estimated to be less than 10% of suspected area, or complete pathological response (pCR) if there were no viable tumor cells identified. Unfavorable pathological response was recorded if there was residual tumor of more than 10%, or no response.

Additionally, a continuous variable was assessed, based on the average percentage area of residual tumor cells that remained as a proportion of the treatment-affected region of the excised lung. A pathological regression score was based on information from the primary tumor and the excised lymph nodes combined. Pathologic specimen scoring, performed by two senior pathologists, was blinded to the techniques of radiation.

Clinical outcomes

Local control (LC) and disease free survival (DFS) were determined by radiological follow-up (CT or PET/CT). Patients who were lost to follow up were censored at the last date of follow up. Survival status was determined from the national health database. We recorded episodes of acute toxicity (up to 3 months post-treatment) from the chemoradiation, according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4), as well as acute complications following surgical resection (3 months post- surgery).

Statistical analysis

Outcomes in the 3DCRT and IMRT groups were compared using non-parametric tests. We used the two-tailed chi-squared or Fisher exact test, as needed for dichotomous variables. For continuous variables that were normally distributed, the T-test or one-way ANOVA were used. Mann-Whitney or Kruskal-Wallis tests were used for non-parametric variables. The threshold of statistical significance was $p<0.05$. Kaplan-Meier estimation and log-rank regression, using STATA V.13 (StataCorp LLC) was used for survival analysis.

RESULTS

Our cohort included 74 patients (Table 1). Mean age was 62.9 years (range 45–79.7); 69% were male. Smoking status was: current smokers in 64.8% and past smokers in 14.8%. Histology was adenocarcinoma in 62.1% and squamous cell carcinoma in 28.3%. Clinical stages were IIB, III and IV in 18.9%, 79.7% and 1.2% respectively. Chemotherapy comprised CN, CT, EP in 28.4%,58.1% and 9.5% respectively..

Radiation dose: mean 59.2 Gy; (SD ±3.8; range 46–72); 90.5% of all cases were treated to at least 54 Gy. The technique used for radiation treatment was 3DCRT in 68.9%, IMRT in 6.7% and VMAT in 24.3%. Surgery type included: lobectomy, lobectomy with chest wall resection and pneumonectomy in 70.3%, 12.1 and 17.6% respectively.

Pathological response: favorable pathological response including pCR was observed in 48/74 patients (64.9%); unfavorable pathological response was observed in 26/74 patients (35.1%).

The 3DCRT and the IMRT groups were comparable in all variables besides the IGRT (Table 1): in the 3DCRT group the IGRT was CBCT in 12/51 (23.5%) *vs* 14/23 (60.9%) in IMRT group ($p < 0.001$).

Tumor volumes and dosimetric parameters are presented in Table 2. The total tumor volume, the primary tumor (gross target volume, GTV) and the lymph node volumes were similar between the two groups. The dosimetric parameters including lung V20 (volume receiving above 20 Gy), mean lung dose and mean esophageal dose were similar between the treatment techniques. The lung V5 (volume receiving above 5 Gy) was higher in the IMRT compared to 3DCRT group (53% *vs* 43.2%, $p = 0.024$). The PTV covered by 95% of the prescribed dose was higher in IMRT *vs* 3DCRT (97% *vs* 93.7%, $p < 0.01$). The mean heart dose in IMRT and 3DCRT groups was 7.2 Gy and 10.2 Gy respectively ($p = 0.53$) and the volume of the heart receiving 45 Gy and above (heart V45) was smaller in IMRT compared to 3DCRT groups (2.1cc *vs* 7.5cc, $p =0.06$). The maximal dose to the spine was lower in IMRT vs 3DCRT (38.8Gy vs 42.89Gy p<0.005).

Pathological response and radiation technique (Figure 1)

Favorable pathological response was similar between radiation techniques: for 3DCRT 32/51 (62.7%) and for IMRT 15/23 (65.2%) ($p = 0.83$). The rate of pCR was also similar for 3DCRT (17/51,33.3%) and IMRT (8/23,34.8%) ($p = 0.9$). The average percentage area of residual tumor cells was also similar between the radiation techniques: for 3DCRT 16% (SD ±25.5) and for IMRT 22% (SD ±27.2) ($p = 0.36$).

Margins were negative in 90.1% (46/51) of patients treated with 3DCRT compared to 89.4% (17/19) with IMRT ($p = 1.0$).

Clinical outcome and radiation technique

At median follow-up of 3.6 years, the 2-year overall survival for 3DCRT was 82% (95% CI, 68–90%) and for IMRT was 85% (95% CI, 60–95%) ($p = 0.72$). 2-year overall LC rates were 81.6% (95% CI, 69–89.4%), DFS 58.3% (95% CI, 45.5–69%) and 3-year OS 70% (95% CI, 57–80%). Comparing radiation techniques, there were no significant differences in LC ($p = 0.94$), DFS ($p = 0.33$) or OS ($p = 0.72$). (Figure 2a,b,c).

DFS differed according to the pathological response. With 'favorable' pathological response, 2-year DFS was 71.9% (95% CI, 55–83%) compared to 35.3% (95% CI, 17.4–53.8%) in the 'unfavorable' pathological response group ($p = 0.01$); HR 2.45 (95% CI, 1.24–4.8) (Figure 2d).

OS at 2 years was also better if there was a favorable pathological response: 86.3% (95% CI, 72–93.6%) *vs* 74.8% (95% CI, 52–87.7%) with an unfavorable pathological response, but this difference did not reach statistical significance ($p = 0.29$). (Figure 2e).

Table 1. Patients' characteristics, disease and treatment details

Parameter	N (%) total 74	3DCRT total 51	IMRT total 23	p value
		N (%)	N (%)	
Age				
Mean years, (range)	62.9 (45–79.7)	63.2 (45–79.7)	62.2 (47.3–75.6)	NS ($p = 0.9$)
Gender				
Male	51 (69%)	38 (74.5%)	13 (56.5%)	NS ($p = 0.09$)
Female	23 (31%)	13 (25.5%)	10 (43.6%)	
Smoking status				
Current	48 (64.8%)	35 (68.6%)	13 (56.5%)	NS ($p = 0.40$)
Past	11 (14.8%)	8 (15.7%)	3 (13%)	
Never	13 (17.5%)	7 (13.7%)	6 (26.1%)	
Missing	2 (2.7%)	1 (1.9%)	1 (4.3%)	
Histology				
Squamous cell carcinoma	21 (28.3%)	17 (33.3%)	4 (17.4%)	NS ($p = 0.33$)
Adenocarcinoma	46 (62.1%)	30 (58.8%)	16 (69.5%)	
Other	7 (9.4%)	4 (7.8%)	3 (13%)	
Stage				
II	14 (18.9%)	10 (19.6%)	4 (17.4%)	NS($p = 0.79$)
III	59 (79.7%)	40 (78.4%)	19 (82.6%)	
IV	1 (1.2%)	1 (2%)	0 (0%)	
Chemotherapy				
CN	21 (28.4%)	19 (37.2%)	2 (8.7%)	$p = 0.15$
CT	43 (58.1%)	27 (53%)	16 (69.6%)	
EP	7 (9.5%)	3 (5.9%)	4 (17.4%)	
Other	2 (2.7)	1 (2%)	1 (4.3%)	
Not received	1 (1.4%)	1 (1.9%)	0 (0%)	
Surgery				
Lobectomy	52 (70.3%)	35 (68.6%)	17 (74%)	NS ($p = 0.82$)
Chest wall resection	9 (12.1%)	6 (11.7%)	3 (13%)	
Pneumonectomy	13 (17.6%)	10 (19.6%)	3 (13%)	
Pathological response				
Complete response	25 (33.8%)	17 (33.3%)	8 (32%)	NS ($p = 0.83$)
<10% residual	23 (31%)	16 (31.4%)	7 (30.5%)	
>10% residual	21 (28.3%)	14 (27.5%)	7 (33.4%)	
No response	5 (6.7%)	4 (7.8%)	1 (20%)	
Average percent of pathological residual tumor cells				
(mean ± SD)	17.8% (SD ± 26)	16% (SD ± 25.5)	22% (SD ± 27.2)	NS ($p = 0.36$)
Margin				
Negative	67 (90.5%)	46 (90.2%)	20 (87%)	NS ($p = 1$)
Positive	6 (8.1%)	5 (9.8%)	2 (8.7%)	
Missing	1 (1.4%)	0 (0%)	1 (4.3%)	

(Continued)

Table 1 (Continued)

IGRT				
kV/kV	47 (63.5%)	39 (76.5%)	8 (34.8%)	*p* < 0.001
CBCT	26 (35.1%)	12 (23.5%)	14 (60.9%)	
Missing	1 (1.4%)	0 (0%)	1 (4.3%)	

3DCRT. 3 dimensional conformal radiation; IMRT, intensity modulated radiation therapy; SD, standard deviation; NS, not significant; CN, cisplatin-vinorelbine; CT, carboplatin-paclitaxel; EP, etoposide-cisplatin; IGRT, image guided radiation therapy; Kv/Kv, kilovoltage imaging; CBCT, cone beam CT.

Toxicities and complications

Grade 2 acute esophageal toxicity from radiation was lower with IMRT (32% compared to 37% with 3DCRT, *p* = 0.66). Grade 4 esophagitis was recorded in 4% in 3DCRT *vs* 0% in IMRT (*p* = 0.53). Respiratory side-effects were recorded in 8% 3DCRT and 5% IMRT (*p* = 0.6) (Supplementary Table 1).
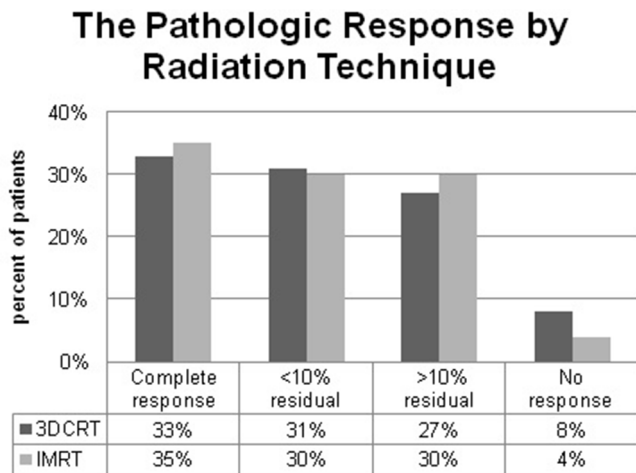
Acute complications from surgery were: respiratory 36% in both modalities. Chest wall necrosis occurred in three cases and broncho-pleural fistula in five cases (all in the 3DCRT group). Grade 5 surgical complications occurred in two patients in the 3DCRT group (2.7% of total 74 patients). Both of them underwent right pneumonectomy (Supplementary Table 1).

Table 2. Comparison of Tumor Volumes and Dosimetric parameters between 3DCRT and IMRT

		Mean ± SD (Median, range)	*P* value
Total tumor volume (cc)	3DCRT	169.6 ± 124.7 (152, 16–168)	0.14
	IMRT	133 ± 122.2 (77–432)	
Gross tumor volume GTV (cc)	3DCRT	135.2 ± 134.8 (99, 0–685)	0.26
	IMRT	99.8 ± 115.5 (40, 2–418)	
Lymph node volume (cc)	3DCRT	34.3 ± 42 (25, 0-182)	0.6
	IMRT	33.2 ± 34.7 (24.5, 0–145)	
Prescribed dose (Gy)	3DCRT	58.9 ± 3.4 (60,48–66)	*p* = 0.31
	IMRT	60 ± 4.7 (60, 46.2–72)	
PTV D95 (%)	3DCRT	93.7 ± 4 (95, 78–99)	<0.01
	IMRT	97 ± 3.4 (98.6, 88.5–100)	
Lung V20 (%)	3DCRT	23.4 ± 6.7 (24, 4–37)	0.75
	IMRT	24 ± 5.2 (24.4, 6.6–32.5)	
Mean lung dose (Gy)	3DCRT	13.7 ± 3.70 (14, 3-28)	0.613
	IMRT	14.17 ± 2.88 (14, 4–17.4)	
Lung V5 (%)	3DCRT	43.4 ± 17 (38, 10-81)	0.02
	IMRT	53.5 ± 11.5 (56.2, 13–66)	
Heart 45 (cc)	3DCRT	7.5 ± 11.1 (2.3, 0–47)	0.06
	IMRT	2.1 ± 3.6 (0.5, 0–12.6)	
Mean heart dose (Gy)	3DCRT	10.24 ± 10.18 (6.15, 0–34)	0.53
	IMRT	7.2.18 (5.5, 0–19.5)	
Mean esophageal dose (Gy)	3DCRT	19.96 ± 9.63 (20, 0-47)	0.86
	IMRT	20.15 ± 5.95 (20.9, 8.4–29.7)	
Spine max dose (Gy)	3DCRT	42.89 ± 10.36 (47.6, 4.4–54)	0.005
	IMRT	38.8 ± 8.10 (40.5,21–49.3)	

3DCRT, 3 dimensional conformal radiation; IMRT, intensity modulated radiation therapy; Gy, radiation units in Gray; PTV. planning target volume; D95, volume covered by 95% of the dose; LungV20, volume receiving above 20 Gy; LungV5, volume receiving above 5 Gy; Heart 45, heart volume receiving dose above 45 Gy.

Figure 1. The pathological response by radiation treatment technique.

The Pathologic Response by Radiation Technique

	Complete response	<10% residual	>10% residual	No response
■3DCRT	33%	31%	27%	8%
▫IMRT	35%	30%	30%	4%

DISCUSSION

Compared to 3DCRT, IMRT offers improved target coverage and reduced doses to organ at-risk by using complex modulated radiation beams. However, in lung cancer therapy there has been concern regarding the 'interplay effect' that may potentially reduce the actual dose delivered to the tumor.

In this study we found that for NSCLC, 3DCRT and IMRT techniques resulted in similar pathologic response, negative margins, local control, disease free and overall survival. This data adds support to the effectiveness of IMRT compared to 3DCRT modalities in treating LANSCLC.

In a dosimetric study, Bortfeld et al found that for a typical treatment with 30 fractions, the standard deviation of the delivered dose is generally within 1% of the expected value for dose delivery if one assumes a typical motion amplitude of 5 mm (1 cm peak-to-peak) due to averaging of the dose in fractionated IMRT planning. This is the same as for treatments with conventional static beams.[8] Therefore, the final dose delivered to the target and normal tissue is expected to be similar to that for conventional radiotherapy delivered without intensity modulation, and the additional effects specific to the IMRT delivery technique seem to be relatively small.

To our knowledge this study is the first report of comparison between these techniques, using pathologic regression scoring after 60 Gy chemoradiation to LANSCLC, thus, further supporting the previously reported dosimetric studies.

In a study by Pataer et al, the percentage of residual viable tumor cells and surgical pathologic stage were associated with OS. Long-term OS and DFS were significantly prolonged in patients who had ≤10% viable tumor cells (favorable response) compared with patients with >10% viable tumor cells (unfavorable response); with 5-year OS 85% *vs* 40% ($p < 0.0001$) and 5-year DFS 78 *vs* 35% ($p < 0.001$), making this cut-point a clinically relevant endpoint to measure.[9] Our study also confirmed a statistically significant increase in DFS in the favorable pathologic response

group, with doubling of the 2-year DFS from 35.3 to 71.9% (HR 2.45 $p = 0.01$).

The feasibility of NSCLC treatment with chemoradiation to high dose (60 Gy) in the neoadjuvant setting has been reported. The RTOG 0229 Phase II trial prescribed "full-dose" concurrent chemoradiation (*i.e.* 60 Gy) followed by resection. Mediastinal pathological clearance was observed in 63% of patients, similar to our finding of 64.8% major tumor regression. There was a 14% (5/37) incidence of grade 3 postoperative pulmonary complications and only one postoperative grade 5 adverse event (3%), comparable to our surgical complication rates. Similarly, they reported a 2-year OS of 75% for those who achieved nodal clearance *vs* 52% for those with residual nodal disease.[10]

In our study we observed lower rates of serious surgical complications in IMRT *vs* 3DCRT: grade 4 complications in 6% with 3DCRT compared to 0% in IMRT and grade 5 complications in 2 out of 51 patients (4%) in 3DCRT compared to 0% in IMRT. This may be explained by the improved conformity and homogeneity of the IMRT planning technique compared to 3DCRT but requires validation in a larger cohort.

Moreover, we found reduced rates of esophagitis as well as respiratory toxicity in the IMRT group. In a retrospective study by Yom et al, reduced grade ≥3 pneumonitis was seen in IMRT compared to 3DCRT (8% *vs* 32%).[11] The RTOG 0617, a prospective, randomized phase III trial, compared definitive chemoradiation to 60 Gy vs 74 Gy. They observed that the decline in quality-of-life was significantly reduced with the use of IMRT, suggesting that improved radiation technique may help enhance the therapeutic window for patients with lung cancer.[12] In a secondary analysis of this pivotal trial, 2-year OS, LC and PFS were compared between IMRT and 3DCRT, and, as concluded in this study, found to be similar between techniques. Furthermore, Chun et al also reported reduced pneumonitis with IMRT compared with 3DCRT (7.9% *vs* 3.5%, $p = 0.04$) and lower heart doses ($p < 0.05$). In fact, their study suggested that the volume of heart receiving high-dose was associated with OS ($p < 0.05$), further supporting routine use of IMRT for locally advanced NSCLC.[13] In our analysis the volume of the heart receiving high-dose was also lower in IMRT than in 3DCRT ($p = 0.06$).

Two population-based studies have shown IMRT to be associated with significantly decreased incidence of pulmonary toxicity, reduced esophagitis rate and fewer placements of percutaneous gastric feeding tubes.[14,15] Reduced incidence of esophagitis may also be the result of dose de-escalation to the lymph nodes. According to Van de Bosch et al, lymph node control may be achieved at lower radiation doses than needed for the primary tumor.[16]

Comparative effectiveness between 3DCRT and IMRT for stage III NSCLC has been assessed in population-based studies, with the two techniques found to be similar in local control and survival in the definitive setting (without completion surgery). Shirvani et al found that based on the SEER-Medicare database, IMRT was associated with similar oncologic outcomes to those

Figure 2. Kaplan Meier survival estimates of (a) Local Control (b) Disease Free Survival and (c) Overall Survival according to treatment technique, and disease free survival (d) and overall survival (e) according to pathological regression. 3DCRT, three dimensional conformal radiation therapy; IMRT intensity modulated radiation therapy.
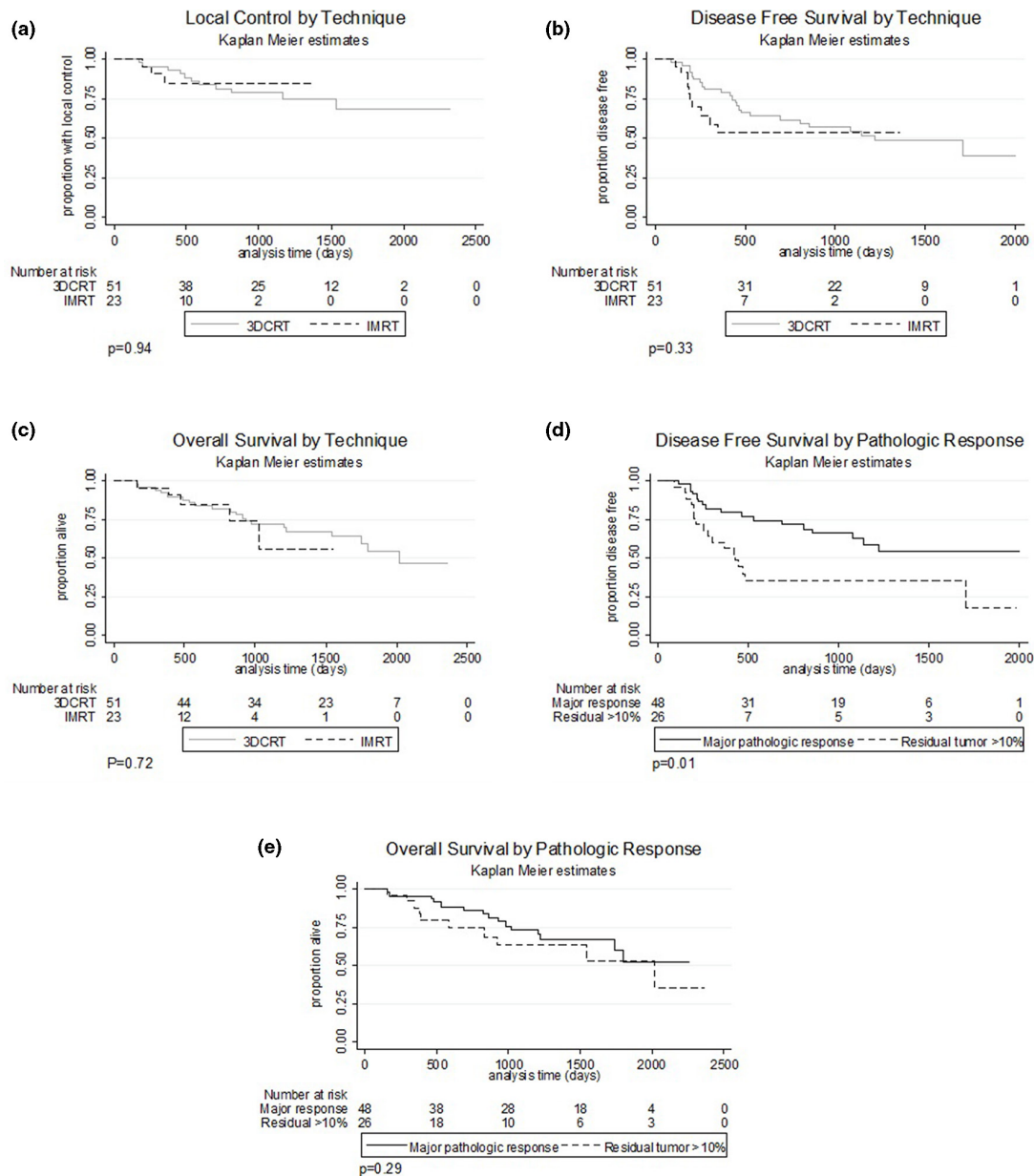
of 3DCRT[15] and even improved overall survival compared to 3DCRT in cases of large tumors.[14]

In our study the IGRT was correlated to the technique: daily CBCT was performed in 14/22 (63.6%) of the IMRT group compared to only 23.5% with 3DCRT. Volumetric imaging, in particular, CBCT offers more precise localization of soft tissue targets and critical organs which reduces setup uncertainty and permits the use of smaller volumes and complex planning. This has real implications for radiotherapy's therapeutic ratio. Bissonnette et al showed that using IGRT, high geometric accuracy is achievable for NSCLC patients, potentially leading to reduced PTV margins.[17] Furthermore, in a retrospective trial, Kilburn

et al demonstrated a substantial local control increase of 16% for patients treated with IGRT using daily kV/kV or CBCT compared to weekly MV portal imaging.[18]

Limitations of this study include the retrospective design and single-center cohort, making generalization of the results to other cancer centers limited. However, the use of uniform methods of radiotherapy planning and blinded pathologic reporting strengthen our findings.

Since prospective randomized trials comparing these techniques are unlikely to be conducted, this study adds evidence for the comparative effectiveness of IMRT in lung radiation therapy

based on NSCLC pathological specimens that were excised after 60 Gy chemoradiation.

In conclusion, for the first time we have demonstrated the comparative effectiveness of IMRT and 3DCRT for LANSCLC,

according to pathological specimens, in the trimodality treatment strategy.

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