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Pattern of Local Failure and its Risk Factors of Locally Advanced Non-small Cell Lung Cancer Treated With Concurrent Chemo-radiotherapy

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Abstract. *Background/Aim: The treatment outcome of locally advanced non-small cell lung cancer (LA-NSCLC) has been improved over the past years but local failure is still common for these patients. The purpose of this study is to analyze the pattern of local failure and its risk factor of concurrent chemo-radiotherapy (CCRT) for locally advanced LA-NSCLC. Patients and Methods: We evaluated 77 patients treated with CCRT for LA-NSCLC from July 2007 to December 2017 at our institution. Most of the patients were treated with 60 Gy in 30 fractions of radiotherapy and concurrent chemotherapy. The median follow-up time was 26 months. Results: Among the 77 patients, 50 developed progressive disease during follow-up, including 14 with only local recurrence (LR), 10 with only distant metastasis and 26 with both. Of the 14 patients with only LR, 12 had primary tumor recurrence and 2 had recurrence in lymph nodes. A primary tumor volume of 50 cm3 was identified as the optimal cut-off value that was significantly correlated with primary tumor recurrence and overall survival. Conclusion: Primary tumor recurrence without lymph node and distant metastasis was observed in 12 patients (16%). Primary tumor volume of 50 cm3 was the optimal cut-off value for the prediction of primary tumor recurrence.*

Lung cancer is a leading cause of cancer mortality worldwide (1, 2). Concurrent chemo-radiotherapy (CCRT), which combines platinum-based chemotherapy and radiotherapy is the standard treatment for locally advanced non-small cell lung cancer (LA-NSCLC) (3-7). However, the 5-year overall survival (OS) rate for patients with LA-NSCLC treated with CCRT is reportedly only at 15%-20% (4-6), with distant metastasis as the most common form of recurrence (7). Recently, consolidated blockade therapy using programmed cell death ligand 1 (PD-L1) inhibitor after concurrent chemo-radiotherapy for LA-NSCLC significantly improved progression-free survival and OS. Antonia *et al*. have reported that for LA-NSCLC patients treated with durvalumab after CCRT an 18-month OS and progression-free survival (PFS) was at 66.3% and 45.5%, respectively, both significantly longer compared to placebo-treated patients (8). Still, in cases where the PFS is significantly improved when consolidated PD-L1 blockade therapy involves durvalumab as maintenance therapy to prevent disease progression after CCRT, local recurrence (LR) remains high (7, 9). Although LR can be classified as a recurrence occurring in the primary tumor, lymph node or both primary tumor and lymph node, only few studies have analyzed LR with respect to the sites it develops. The patterns of local failure and its risk factors should be thoroughly investigated to consider what kind of countermeasure should be taken. Here, we analyzed patterns of local failure and its risk factors among 77 patients with LA-NSCLC who were treated with CCRT at our hospital between July 2007 and December 2017.

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Key Words: Local failure, locally advanced non-small cell lung cancer, concurrent chemo-radiotherapy.

Patients and Methods

We retrospectively analyzed patients with LA-NSCLC who underwent CCRT from July 2007 to December 2017 at our hospital. Most primary tumors were histologically diagnosed. However, a few patients could not undergo biopsies for medical reasons. For these patients, their tumors were diagnosed by our hospital's cancer board, based on laboratory and imaging findings. Tumors were clinically staged using i) contrast-enhanced computed tomography (CT), ii) gadolinium-enhanced head magnetic resonance imaging (MRI) and iii) fluorodeoxyglucose-positron emission tomography (FDG-PET) (10), and were classified according to the Union for International Cancer Control (8th edition) classification of malignant tumors (11). Radiotherapy was performed with the help of CT (LightSpeed RT 16, General Electric Company, Fairfield, CT, USA) image simulation, while the tumor respiratory

motion was evaluated using four-dimensional CT (Advantage 4D, General Electric Company). Conventional three-dimensional conformal radiotherapy (3D-CRT) was used for all the patients. The prescribed dose was 60 Gy in 30 fractions for most of the patients but an adjusted dose, such as 54 Gy in 27 fractions, 64 Gy in 32 fractions and 66 Gy in 33 fractions were used for few patients by clinicians. The X-ray energy was 10-MV generated by our linear accelerator (CLINAC iX, Varian Medical Systems, CA, USA). GTV in expiratory- and inspiratory-phase CT images were delineated and defined as the internal target volume (ITV). Clinical target volume (CTV) was defined as the ITV + 5-mm margin with an additional prophylactic lymph node area at mediastinum. Planning target volume (PTV) was defined as the CTV + 5-mm margin. Treatment plan was created and calculated using commercially available software (Xio, Elekta, Stockholm, Sweden). The following chemotherapeutic regimens were chosen according to physician's judgment: i) S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) at a dose of 80 mg/m^2 administered orally twice daily for 14 days plus cisplatin (Nippon Kayaku Co., Ltd, Tokyo, Japan) at a dose of 60 mg/m^2 administered on day 1, ii) cisplatin at a dose of 40 mg/m^2 plus docetaxel (Sanofi K.K., Paris, France) at 40 mg/m^2 on days 1, 8, 29, and 36, iii) paclitaxel (Bristol-Myers Squibb, New York, NY, USA) at 40 mg/m^2 plus carboplatin (Nippon Kayaku Co.) at a dose of AUC2 for 6 weeks), iv) carboplatin at a dose of AUC 2 plus docetaxel at a dose of 40 mg/m^2 on days 1, 8, 29, and 36), v) low-dose carboplatin at a dose of 30 mg/m^2 per day 5 days a week for 20 days. These regimens were concurrently administered with thoracic radiation of 60 Gy.

Data collection, definitions of terms and patients' consent. To evaluate treatment efficacy and adverse events, patients were required to visit our hospital every 2-3 months for the first year and every 3-6 months thereafter. Diagnostic imaging, such as CT, MRI, or FDG-PET was performed every 2-3 months for the first 2 years and every 3-6 months thereafter. Adverse events were classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (12). We defined OS as the time between starting the treatment and the last follow-up date or death. Local control (LC) of the tumor was defined as the absence of recurrence at the originally irradiated site. Local recurrence was classified as the recurrence of the primary tumor and/or the one in the associated nearby lymph node. Primary tumor control was defined as being free from primary tumor recurrence. PFS was defined as the duration of freedom from local and distant recurrence or death. This study was approved by our hospital's institutional review board (approval number: 18095). An opt-out consent was obtained from all patients by giving information regarding this study on posters around the hospital and in the website of the hospital.

Statistical analyses. We calculated LC, PFS, OS, and primary tumor control rates using the Kaplan–Meier method. Factors considered to affect primary tumor recurrence were compared to one another using the log-rank test. Receiver operating characteristic (ROC) curves were calculated to find the optimal cut-off values for predicting primary tumor recurrence. Values of $p<0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc., Armonk, NY, USA).

Results

A total of 77 patients received CCRT during July 2007 to December 2018. Their median follow-up period was 26 months (range=6-132 months). Patient and treatment characteristics are summarized in Table I. Two-year cumulative rates in this cohort were i) LC=52%, ii) PFS=39% and iii) OS=73%. Of the 77 patients, 50 developed progressive disease (PD) during their follow-up period, including 14 with only LR, 10 with only distant metastasis and 26 with both. Of the 14 patients with only LR, 12 had recurrent primary tumors and 2 had recurrence at lymph nodes (one in the hilar lymph nodes and one in the subcarinal lymph nodes) (Figure 1). Among the twelve patients (16%) that developed only primary tumor recurrence after CCRT, 11 patients received chemotherapy thereafter and 1 patient received best supportive care. At the last follow up, 6

Table I. *Patient and treatment characteristics (N=77).*

Characteristic	N (%)
Age, years*	70 (39-88)
Gender	
Male	65 (84)
Female	12 (16)
Histopathological type	
Adenocarcinoma	37 (48)
Squamous cell carcinoma	33 (43)
Others	5 (6)
Not identified	2 (3)
Chemotherapy regimen	
CDDP+DTX	28 (37)
CBDCA+PTX	27 (35)
CBDCA+DTX	15 (19)
Daily low-dose CBDCA	5 (6)
CBDCA+nabPTX	1 (1)
CDDP+VNR	1 (1)
T classification	
T1b	2 (3)
T1c	9 (12)
T2a	11 (14)
T2b	14 (18)
T3	18 (23)
T4	23 (30)
N classification	
N0	3 (4)
N1	17 (22)
N2	42 (55)
N3	15 (19)
Clinical stage	
IIA	1 (1)
IIB	10 (13)
IIIA	29 (38)
IIIB	30 (39)
IIIC	7 (9)
Gross primary tumor volume, cm^3*	60 (1.5-780)
Radiation dose	
54 Gy in 27 fractions	1 (1)
60 Gy in 30 fractions	69 (90)
64 Gy in 32fractions	3 (4)
66 Gy in 3 fractions	4 (5)

*Shown as median (range). CBDCA: Carboplatin; CDDP: cisplatin; DTX: docetaxel; nabPTX: nab-paclitaxel; PTX: paclitaxel; VNR: vinorelbine; N: number.

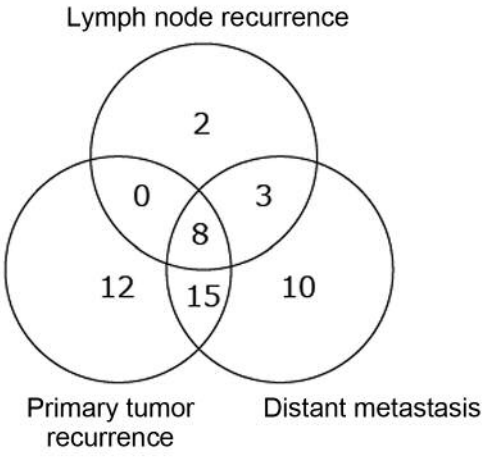

Figure 1. *Pattern of failure including lymph node recurrence, primary tumor recurrence and distant metastasis. Among 77 patients, 50 developed progressive disease during follow-up, including 14 with only local recurrence (LR), 10 with only distant metastasis and 26 with both. Of the 14 patients with only LR, 12 had recurrent primary tumors only and 2 had recurrence at lymph nodes only.*

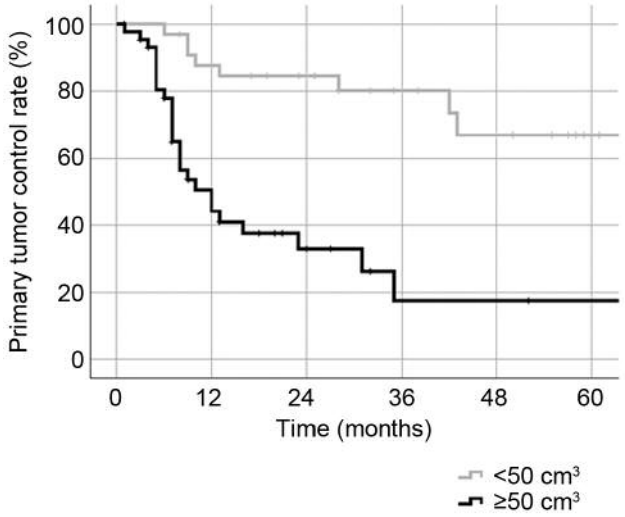

Figure 2. *Cumulative primary tumor control rates. A 2-year cumulative primary tumor control rate was approximately at 35% for primary tumors ≥50 cm^3.*

patients with only primary tumor recurrence had died of the disease. Primary tumor recurrence was observed in 35 of the 77 patients (45%). In the univariate analysis, only primary tumor volume was significantly correlated with primary tumor recurrence. In the ROC analysis, primary tumor volume of 50 cm^3 was the optimal cut-off value that could predict primary tumor recurrence; patients with smaller tumors (<50 cm^3) had a 2-year cumulative primary tumor control rate of 84.5%, compared to 32.9% for patients with larger tumors (≥50 cm^3) (Figure 2). Lymph node recurrence was observed in 13 patients (17%). There were no significant factors for lymph node recurrence in the univariate analysis. Only the primary tumor volume was significantly correlated with overall survival. These results are summarized in Table II.

Discussion

We analyzed the pattern of local failure and its risk factors in LA-NSCLC patients treated with CCRT. Among the 77 patients who received CCRT, 14 patients (18%) developed only local recurrence, 12 (16%) had recurrent primary tumors and 2 (2%) had recurrence at the lymph nodes. The 2-year effect rates were i) LC: 52%, ii) PFS: 39% and iii) OS: 73%, which are consistent with reported results for CCRT-treated LA-NSCLC patients (3-6, 13).

Differences in LC, PFS and OS between regimens of chemotherapy, such as cisplatin + docetaxel *vs*. others, carboplatin + paclitaxel *vs*. others, and carboplatin + docetaxel *vs*. others were not observed in this study. It would, however, be difficult to interpret differences in local control between regimens of chemotherapy in our results due to the small number of patients. In addition, in the literature, the differences in PFS and OS between regimens of chemotherapy appear controversial (14, 15). During follow-up, 50 of the 77 patients (68%) we treated experienced PD, including 14 with only LR, 10 with only distant metastasis and 26 with both. The most frequent recurrence pattern involved both LR and distant metastasis. Systemic chemotherapy and concomitant PD-L1 blockade therapy has been shown to address both LR and distant metastasis simultaneously (8).

When possible, salvage surgery should be considered for primary tumor recurrence (16); however, its application is limited due to the poor performance status of the patients or other medical reasons. At the last follow up, 6 of 12 patients with only primary tumor recurrence died from the disease, possibly due to the fact that local recurrence is difficult to salvage.

An increased radiation dose to the primary tumor may represent a measure towards saving patients from primary tumor recurrence and improving their overall survival. However, it must be noted that intense local treatment using dose-escalated radiotherapy was associated with a worse overall survival in the RTOG0617 study, due to the increased levels of toxicity (17). If the high radiation doses would be focused only on the exact location of the primary tumor using intensity-modulated or stereotactic ablative radiotherapy (SABR) with image guidance, the extra dosing to organs at risk, such as the heart or mediastinum, could be minimized. For example, Alexander *et al*. have reported the feasibility of definitive image-guided intensity modulated radiotherapy (IMRT) combined with SABR in LA-NSCLC patients to increase the dose to the primary tumor (18). In their report, 40-50 Gy in 4 fractions of SABR were delivered to the primary tumor and 63 Gy in 35 fractions of IMRT were delivered to

Table II. *Univariate analysis of primary tumor control rate, lymph node control rate and overall survival rate.*

	No. of patients	Two-year primary tumor control rate (%)	*p*-Value	Two-year lymph node control rate (%)	*p*-Value	Two-year overall survival rate (%)	*p*-Value
Age			0.602		0.428		0.599
<70 years	32	45		86		70	
≥70 years	45	58		84		75	
Gender			0.366		0.726		0.738
Male	65	50		90		82	
Female	12	63		84		71	
Histology			0.285		0.327		0.913
Squamous cell carcinoma	33	50		77		68	
Others	44	65		90		70	
T classification			0.057		0.297		0.866
T1-2	36	64		90		74	
T3-4	41	41		80		71	
N classification			0.853		0.812		0.634
N0-1	20	50		90		78	
N2-3	57	53		83		71	
Stage			0.734		0.447		0.825
Stage II	11	50		100		81	
Stage III	66	53		82		71	
Tumor volume			<0.001		0.128		0.007
<50 cm^3	34	85		91		85	
≥50 cm^3	43	33		79		60	
Radiation dose			0.29		0.779		0.408
≤60 Gy	70	50		85		72	
>60 Gy	7	71		86		83	

lymph node target volume. The 2-year local, regional, and distant control was 60%, 62%, and 38%, respectively and no local failure was observed in patients following SABR+IMRT, while 23% of patients failed locally following IMRT alone.

Since the primary tumor volume (≥50 cm^3) was the only significant factor for primary tumor recurrence such patients with a high risk of recurrence might be good candidates for intense local treatment.

This study has some limitations. First, it is a single-institution retrospective study, which may bias patient selection. Second, if the primary tumor volume correlated with lymph node recurrence, an intense local therapy only on the primary tumor may not lead to an improved outcome. However, in this study the primary tumor volume did not correlate significantly with lymph node recurrence, which might support our idea to intensify local treatment only on the primary tumor. Third, the additional effect of PD-L1/PD-1 blockade therapy on local control is uncertain. The Pacific trial has shown greater PFS with PD-L1/PD-1 blockade therapy after CCRT for LA-NSCLC (8). However, whether the improvement in PFS resulted from an improved control of either the primary tumors, lymph nodes, distant metastasis, or all three, is unclear. If PD-L1/PD-1 blockade therapy significantly suppresses the LR of the primary tumor, the dose-escalation would be unnecessary. Further studies are needed to clarify whether consolidated PD-L1/PD-1 blockade therapy decreases the local control of the primary tumor or not.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

TA collected data and wrote the manuscript. NK, MI, RH and YK collected data. TA, YR, SS, YM, KK, HK, SN and SK performed treatment and evaluated patients. All Authors read and approved the manuscript.

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References

1 Alberg AJ, Brock MV, Ford JG, Samet JM and Spivack SD: Epidemiology of lung cancer. Chest *143(5 Suppl)*: e1S-e29S, 2013. PMID: 23649439. DOI: 10.1378/chest.12-2345

2 Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C and Reid ME: The international epidemiology of lung cancer: Latest trends, disparities, and tumor characteristics. J Thorac Oncol *11(10)*: 1653-1671, 2016. PMID: 27364315. DOI: 10.1016/j.jtho.2016.05.021

3 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, D'Amico TA, DeCamp MM, Dilling TJ, Dobelbower M, Doebele RC, Govindan R, Gubens MA, Hennon M, Horn L, Komaki R, Lackner RP, Lanuti M, Leal TA, Leisch LJ, Lilenbaum R, Lin J, Loo BW Jr., Martins R, Otterson GA, Reckamp K, Riely GJ, Schild SE, Shapiro TA, Stevenson J, Swanson SJ, Tauer K, Yang SC, Gregory K and Hughes M: Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw *15(4)*: 504-535, 2017. PMID: 28404761. DOI: 10.6004/jnccn.2017.0050

4 Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S and Pignon JP: Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol *28(13)*: 2181-2190, 2010. PMID: 20351327. DOI: 10.1200/JCO.2009.26.2543

5 Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, Chen M, Kim DW, Kim HK, Min YJ, Kang JH, Choi JH, Kim SW, Zhu G, Wu YL, Kim SR, Lee KH, Song HS, Choi YL, Sun JM, Jung SH, Ahn MJ and Park K: Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. J Clin Oncol *33(24)*: 2660-2666, 2015. PMID: 26150444. DOI: 10.1200/JCO.2014.60.0130

6 Yamamoto N, Nakagawa K, Nishimura Y, Tsujino K, Satouchi M, Kudo S, Hida T, Kawahara M, Takeda K, Katakami N, Sawa T, Yokota S, Seto T, Imamura F, Saka H, Iwamoto Y, Semba H, Chiba Y, Uejima H and Fukuoka M: Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol *28(23)*: 3739-3745, 2010. PMID: 20625120. DOI: 10.1200/JCO.2009.24.5050

7 Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N and Ariyoshi Y: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol *17(9)*: 2692-2699, 1999. PMID: 10561343. DOI: 10.1200/JCO.1999.17.9.2692

8 Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Faivre-Finn C, Reck M, Vansteenkiste J, Spigel DR, Wadsworth C, Melillo G, Taboada M, Dennis PA and Özgüroğlu M; PACIFIC Investigators: Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med *379(24)*: 2342-2350, 2018. PMID: 30280658. DOI: 10.1056/NEJMoa1809697

9 Offin M, Shaverdian N, Rimner A, Lobaugh S, Shepherd AF, Simone CB 2nd, Gelblum DY, Wu AJ, Lee N, Kris MG, Rudin CM, Zhang Z, Hellmann MD, Chaft JE and Gomez DR: Clinical outcomes, local-regional control and the role for metastasis-directed therapies in stage III non-small cell lung cancers treated with chemoradiation and durvalumab. Radiother Oncol, 2020. PMID: 32361014. DOI: 10.1016/j.radonc.2020.04.047

10 Baxa J, Matouskova T, Ludvik J, Sedlmair M, Flohr T, Schmidt B, Bejcek J, Pesek M and Ferda J: Single-source Dual-energy CT as a Part of 18F-FDG PET/CT: Direct comparison of iodine-related and metabolic parameters in non-small cell lung cancer. Anticancer Res *38(7)*: 4131-4137, 2018. PMID: 29970540. DOI: 10.21873/anticanres.12704

11 Brierley J, Gospodarowicz MK and Wittekind C: TNM classification of malignant tumours. Eighth ed. Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc, 2017.

12. National Cancer Institute: National Cancer Institute Common Terminology Criteria for Adverse Events v4.0: June *14*: 1-80, 2010 Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [Last accessed on 8th May 2020]

13 Tokito T, Azuma K, Yamada K, Naito Y, Matsuo N, Ishii H, Natori H, Kinoshita T and Hoshino T: Prognostic value of serum tumor markers in patients with stage III NSCLC treated with chemoradiotherapy. In Vivo *33(3)*: 889-895, 2019. PMID: 31028213. DOI: 10.21873/invivo.11555

14 Tingting Liu, Zheng He, Jun Dang and Guang Li: Comparative efficacy and safety for different chemotherapy regimens used concurrently with thoracic radiation for locally advanced non-small cell lung cancer: a systematic review and network meta-analysis. Radiat Oncol *14(1)*: 55, 2019. PMID: 30925881. DOI: 10.1186/s13014-019-1239-7

15 Steuer CE, Behera M, Ernani V, Higgins KA, Saba NF, Shin DM, Pakkala S, Pillai RN, Owonikoko TK, Curran WJ, Belani CP, Khuri FR and Ramalingam SS: Comparison of concurrent use of thoracic radiation with either carboplatin-paclitaxel or cisplatin-etoposide for patients with stage III non-small-cell lung cancer: A systematic review. JAMA Oncol *3(8)*: 1120-1129, 2017. PMID: 27978552. DOI: 10.1001/jamaoncol.2016.4280

16 Dickhoff C, Otten RHJ, Heymans MW and Dahele M: Salvage surgery for recurrent or persistent tumour after radical (chemo)radiotherapy for locally advanced non-small cell lung cancer: a systematic review. Ther Adv Med Oncol *10*: 1758835918804150, 2018. PMID: 30305851. DOI: 10.1177/1758835918804150

17 Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces YI, Narayan S, Iyengar P, Robinson C, Wynn RB, Koprowski C, Meng J, Beitler J, Gaur R, Curran W Jr and Choy H: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol *16(2)*: 187-199, 2015. PMID: 25601342. DOI: 10.1016/S1470-2045(14)71207-0

18 Chi A, Wen S, Monga M, Almubarak M, He X, Rojanasakul Y, Tse W and Remick SC: Definitive upfront stereotactic ablative radiotherapy combined with image-guided, intensity modulated radiotherapy (IG-IMRT) or IG-IMRT alone for locally advanced non-small cell lung cancer. PLoS One *11(9)*: e0162453, 2016. PMID: 27611833. DOI: 10.1371/journal.pone.0162453

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