The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 46, Sep 2024
ISSN No. 2078-2101

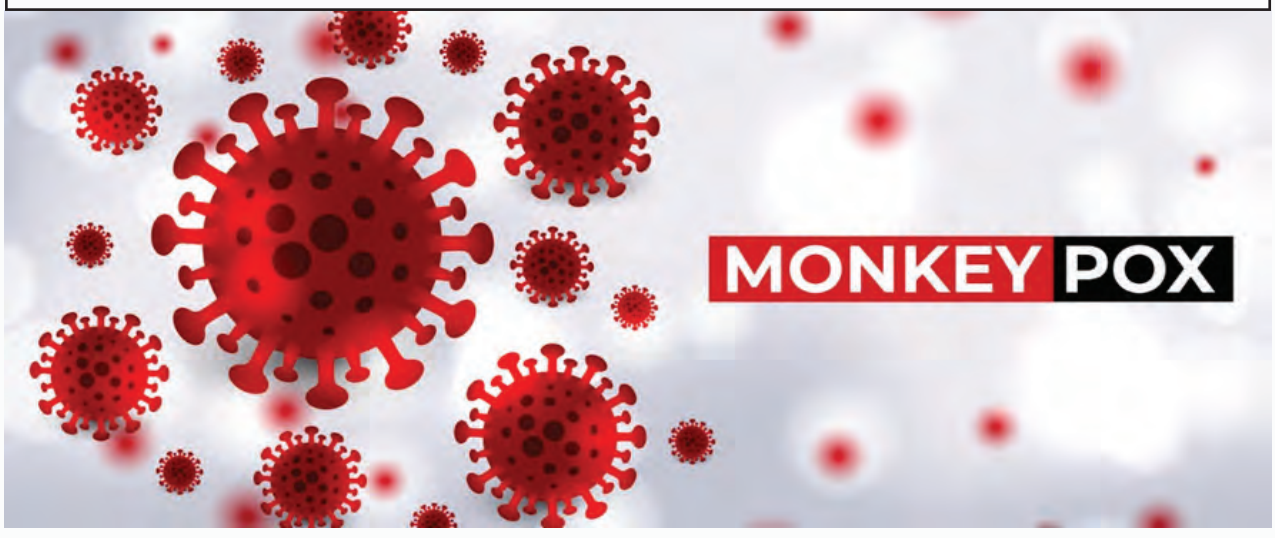


The International Tobacco Control Conference on

The Scourge of Smoking and Conflicts of Interest

October 27-28, 2024

STATE OF KUWAIT



The Official Journal of the Gulf Federation For Cancer Control

Table of Contents

Original Articles

Immunohistochemical Expression of Calretinin in Invasive Breast Carcinoma and its Correlation with Clinicopathological Parameters **07**
Gargi Madhukar Patil, Siddhi Gaurish Sinai Khandeparkar, Shital Subhash Gosavi, Chaitnya D. Khillare, Bageshri P. Gogate, Avinash R. Joshi, Ketki Ghanekar, Asmita S. Pawar

Immunohistochemical Study of Cyclin D1 and HER2/neu in Pre–neoplastic and Neoplastic Epithelial Lesions of Cervix **14**
Neha D. Newadkar, Siddhi Gaurish Sinai Khandeparkar, Bageshri P. Gogate, Aishawarya Gotekar, Priyanka Bhave, Rashmi Shinde, Aanchal Goyal

Survival Outcomes and Predictive Factors to Evaluate the Efficacy of Neoadjuvant Chemoradiation in Carcinoma Esophagus: An Institutional Experience from India **24**
Bhargav Shreeram Gundapuneedi, Vedamanasa Ikkurthi, Jagadesan Pandjatcharam, Y. Sree Sowmya, Raghuveer Reddy Janamolla

Open Nephron–Sparing Surgery for Renal Tumors is an Effective Surgical Option for Low HealthResource Settings in the Era of Laparoscopic Surgery **36**
Adil Ibrahim, Mohamed Mustafa, Imad Fadl Elmula

Brain metastasis: Types, methods of diagnosis and treatment in Nineveh province. **43**
Bassam Jasim1, Alya A Al Zobair, Ahmed Ali Albakr, Barrak F. Al Obeidy

Review Article

Relationship Between Social Support, Coping Strategies, Spirituality and Psychological Status among Breast Cancer Survivors **49**
Maryam Hasan, Leena Khonji, Gayathripriya Narayanan

Postoperative Radiotherapy in Resected Non–Small Cell Lung Cancer: Current Status and Enduring Challenges in 2024 ..... **54**
Fadila Kouhen, Hanaa El Gouach, Nadia Errafiy

Case Report

Synchronous Cutaneous and Brain Metastasis in a Treated Case of Squamous Carcinoma of Left Lower Alveolus: A rare Case report **61**
Prarabdh Singh, Sambit S Nanda, Ashutosh Mukherji

Lived Experiences of Pregnancy, Childbirth and Breastfeeding in Iranian Breast Cancer Survivors: a Qualitative Case Study **65**
Mohadeseh Pourzamani , Hadis Ashrafizadeh, Maryam Kiarsi, Marzieh Beigom Bigdeli Shamloo

Pembrolizumab in the Management of Chemorefractory Gestational Choriocarcinoma: Report of Two Cases. **74**
Fatma Al Zaabi, Ajit Venniyoor, Suad Al Kharusi

Extramedullary Hairy Cell Leukemia in Parotid Gland, Case Report and Review of the literature **79**
Mohammed Shafi Abdul Salam, Shaima Al Shammari, Dina Ismail Abd El Razik, Moustafa El–Kabany, Ramesh Pandita, Ahmad Alhuraiji

Conference Highlights/Scientific Contributions

- **News Notes** **83**
- **Advertisements** **85**
- **Scientific Activities** **87**

Review Article

Postoperative Radiotherapy in Resected Non–Small Cell Lung Cancer: Current Status and Enduring Challenges in 2024

Fadila Kouhen[1, 2], Hanaa El Gouach[1, 2], Nadia Errafiy[1,3]

[1] Mohammed VI University of Sciences and Health (UM6SS). Casablanca, Morocco. Department of Radiotherapy, International University Hospital Sheikh Khalifa.
[2]Neuro–Oncology, Onco–Genetics, and Precision Medicine Laboratory . Mohammed VI Center for Research & Innovation, Casablanca, Morocco
[3]Interdisciplinary laboratory of biosciences and health. Mohammed VI Center for Research & Innovation, Casablanca, Morocco

Abstract

Lung cancer remains a significant global health burden, with high incidence and mortality rates. Surgical resection followed by adjuvant systemic therapy is the standard of care for operable early–stage non–small cell lung cancer (NSCLC) and resectable stage IIIA disease. Adjuvant treatment regimens vary based on molecular and histological characteristics, with chemotherapy plus immunotherapy or targeted therapy being common approaches. The role of postoperative radiotherapy (PORT) in NSCLC management has been contentious, particularly following a meta–analysis suggesting potential harm, particularly in certain disease stages. However, recent evidence indicates improved survival outcomes in stage IIIA N2 NSCLC patients treated with modern PORT techniques, prompting further investigation into its role. This literature review aims to present updated efficacy and safety data regarding PORT in the adjuvant treatment of stage IIIA operable NSCLC, providing insights for clinical decision–making.

Keywords: guidelines, metaanalysis, clinical trials, lung cancer, postoperative radiotherapy

Introduction

Lung cancer remains a significant global health concern, maintaining its status as the most prevalent and deadliest cancer worldwide. With a staggering 2.1 million new cases and 1.8 million deaths annually, it overshadows other malignancies in both incidence and mortality rates followed by breast cancer, colorectal cancer and prostate cancer in terms of incidence, and by colorectal cancer, stomach cancer and liver cancer in terms of mortality[1].

Cigarette smoking stands as the paramount risk factor for lung cancer. Alongside smoking, exposure to secondhand smoke, as well as occupational hazards like asbestos and specific metals such as chromium, cadmium, and arsenic, further compound the risk profile for this deadly disease.

Non–small cell lung cancer (NSCLC) represents the majority, comprising over 85% of all lung cancer cases. The most common forms of NSCLC are adenocarcinoma and squamous cell carcinoma.

Most patients present with locally advanced or advanced disease which were associated with poor survival; 5–year survival is less than 18%. Despite this grim backdrop, over the last decade, significant advancements have occurred in screening, diagnostic techniques, and biomarkers testing . These breakthroughs have revolutionized treatment paradigms, enabling personalized therapeutic interventions finely tuned to the unique characteristics of each patient.

For early–stage non–small–cell lung cancer (NSCLC) deemed functionally operable and stage IIIA disease that is surgically resectable, complete surgical resection stands as the primary treatment modality of choice[2].

Corresponding author: Kouhen Fadila (MD). Mohammed VI University of Health Sciences (UM6SS). Casablanca, Morocco. Department of Radiotherapy, International University Hospital Sheikh Khalifa. Postal address: 10101. Email: fadila10m@hotmail.com. Phone : +212671030061

Nevertheless, patients with pathologically involved mediastinal nodes (pN2) or positive surgical margins (R1/R2) face alarming rates of local–regional recurrence with rates ranging between 40–60%. Adjuvant treatments such as chemotherapy (CT) and radiotherapy (RT) have therefore been evaluated in order to improve the prognosis of NSCLC disease.

The benefit of adjuvant chemotherapy has been recently confirmed by 2 meta–analyses and several trials notably the International Adjuvant Lung Cancer Trial (IALT), encompassing over 1800 randomized patients across stages I, II, and III[3,4]. Despite this, the role of postoperative radiotherapy (PORT) remain controversial.

Our objective is to comprehensively review the body of research surrounding postoperative radiotherapy (PORT), encompassing its historical evolution, investigations into its effectiveness, and analyses of its associated risks and adverse effects. Additionally, we aim to provide insights into emerging research concerning PORT within the landscape of lung cancer management, thereby enhancing our understanding of its contemporary relevance and clinical implications.

Is Postoperative radiotherapy helpful or harmful for NSCLC ?

Several meta–analyses based on individual patient data of both published and unpublished trial addressed the issue of postoperative radiotherapy on the outcome of completely resected NSCLC.

Analyzing individual data from 2128 patients across nine randomized trials, the PORT group compared postoperative radiation therapy to surgery alone for curative purposes[5]. With a median follow–up of 3.9 years for surviving patients, the meta–analysis revealed a significant adverse effect of PORT on survival outcomes.

Among the entire patient cohort, 707 deaths occurred among 1056 patients assigned to the postoperative radiotherapy arm, while 661 deaths were recorded among 1072 patients in the surgery alone arm. This translated to a 21% relative increase in the risk of death or a 7% absolute decrease in survival at 2 years, reducing overall survival from 55% to 48% (mortality hazard ratio, 1.21; 95% confidence interval [CI], 1.08–1.34; p = 0.001).

Subset analyses indicated that postoperative radiotherapy (PORT) might have a detrimental impact on overall survival, particularly among patients who underwent complete resection and had no mediastinal involvement (either pN0 or pN1).

The adverse effects of postoperative radiotherapy (PORT) have been attributed to a heightened occurrence of cardiac and respiratory complications, due to the use of outdated two–dimensional radiation techniques that are no longer prevalent in modern treatment approaches. Supporting this theory, several recent high–quality cohort studies have shown that PORT did not elevate mortality rates in patients with pIIIA–N2 NSCLC when employing contemporary treatment modalities (table1).

Is there a place for postoperative radiotherapy (PORT) in the management of completely resected pIIIA–N2 non–small cell lung cancer (NSCLC)?

Stage pIIIA–N2 NSCLC represents a diverse spectrum of diseases, characterized by considerable heterogeneity. Recent studies have identified numerous clinicopathological factors linked to prognosis, including the number of N2 metastases, involvement of N2 stations, tumor size, histological type, age, and gender[6].

Surveillance, Epidemiology, and End Results (SEER) analyses and the Adjuvant Navelbine International Trialist Association (ANITA) retrospective analysis suggest that PORT using modern radiation therapy techniques may be safely delivered with a potential OS benefit for stage IIIA (N2) disease[7,8].

Retrospective analysis from the Surveillance, Epidemiology, and End Results (SEER) database and the Adjuvant Navelbine International Trialist Association (ANITA) suggest that postoperative radiotherapy (PORT) using modern radiation therapy techniques may be safely administered with the potential for overall survival (OS) benefit in stage IIIA (N2) disease[7,8].

A population–based study using the National Cancer Database investigated the impact of PORT, employing modern radiation therapy techniques, on overall survival (OS) in 3340 patients with N2 NSCLC who underwent surgery and adjuvant chemotherapy between 1998 and 2006[9]. The study found that compared to no PORT, the use of PORT was associated with a statistically significant reduction in 5–year OS in patients with pN0–pN1 disease. However, in patients with pN2 disease, PORT was linked to a statistically significant improvement of 6.3% in 5–year OS. The beneficial effect of PORT on OS in pN2 disease was found to be dependent on radiation dose, with patients receiving doses between 45–54Gy demonstrating better outcomes than those treated with doses exceeding 54Gy. Notably, for patients treated with doses exceeding 54Gy, OS was similar to those not receiving PORT.

More recently, an updated meta–analysis published in 2018 focused on patients with resectable non–small cell lung cancer (NSCLC) and pN2 disease. This analysis included data from 8 randomized controlled trials and 8 retrospective series published between 1996 and 2015. The findings revealed that with modern techniques, postoperative radiotherapy (PORT) significantly enhances local control and improves survival[10].

First author /year	Number of patients	Type of surgery	Study design	Radiotherapy technique	Radiotherapy dose	Disease free survival DFS	p	Overall Survival 5–years	p
Douillard, 2006[7]	840	LOBECTOMY / PNEUMECTOMY	OBSERVATION+/–PORT VS CHEMOTHERAPY+/–PORT	NR	45 TO 60 GY (2 GY/FC)	20·7 MONTHS 36·3 MONTHS	P=0·002;	40 % VS 56 % 31% VS 43 %	
Scotti, 2010[20]	175	LOBECTOMY: 58.9% PNEUMECTOMY: 41.1%	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	2D BEFORE 2000 3D AFTER 2000	46–66 GY (2 GY/FC)	32,1% 15,1 %	0,015		NS
Kim, 2014[21]	219	LOBECTOMY / PNEUMECTOMY	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	2D BEFORE 2005 3D AFTER 2005	50–56 GY	38,4% 31 %	P 0.292	49.9% 58.2%	NS P = 0.466
Billiet, 2014[22]	2387	LOBECTOMY / PNEUMECTOMY	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	2D 3D		HR = 0,31	0,01	HR = 0,76	0,02
Feng, 2015[23]	357	LOBECTOMY / PNEUMECTOMY	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	3D	50.4 GY (1.8 GY/FR)	8,1 % 33,6 %	<0,001	57,5 % 35,1 %	0,003
Mikell ,2015[24]	2115	NR	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	3D		NR		39.8% 34.7%	P = 0.048
Fei Ga,2020[25]	357	LOBECTOMY/ SLEEVE LOBECTOMY	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	3D	60,2 GY (1,8 GY/FC)	26.8% 16.4%	0.04	57.5% 35.1%	P = 0.003
Cécile Le Pechoux 2022 [12]	501	NR	CHEMOTHERAPY+PORT VS CHEMOTHERAPY	NR	54 GY IN 27–30 FRACTIONS	47.1% 43.8%	0.85	3 YER OS: 78,3% 68.5%	NS
Zhouguang Hui, 2021[13]	364		CHEMOTHERAPY+PORT VS CHEMOTHERAPY	3D /IMRT	50GY IN 25 FRACTIONS	40,5% 32,7%	0.2	3 YER OS: 66.5% 82.8%	0;93

Table 1: Recent studies evaluating the role of PORT for completely resected pIIIA–N2 non–small cell lung cancer patients

Furthermore, Tingting Liu et al. conducted the first meta–analysis to assess the role of PORT in completely resected pIIIA–N2 NSCLC based on clinicopathological features. Their analysis incorporated data from one randomized trial and 12 retrospective studies that met the eligibility criteria.

This study reaffirmed that postoperative radiotherapy (PORT), utilizing modern radiation therapy techniques, significantly improved both overall survival (OS) (HR = 0.85; 95% confidence interval [CI]: 0.79–0.92) and disease–free survival (DFS) (HR = 0.57; 95% CI: 0.38–0.85) compared to non–PORT treatment in patients with N2 NSCLC who underwent surgery and adjuvant chemotherapy between 1998 and 2006[9]. The analysis revealed that while the use of PORT was associated with a statistically significant reduction in 5–year OS in patients with pN0–pN1 disease, it led to a significant improvement of 6.3% in 5–year OS among patients with pN2 disease. Moreover, the OS benefit of PORT in pN2 disease was contingent upon radiation dose, with patients receiving 45–54Gy demonstrating superior outcomes compared to those treated with doses exceeding 54Gy. Notably, for patients treated with doses exceeding 54Gy, OS was comparable to those not receiving PORT.

Based on these data, ASTRO guideline recommends PORT in the setting of gross primary/nodal residual disease or positive margins[11].

Nevertheless, the findings from a recent large multi–institutional randomized trial, Lung ART (NCT00410683), unveiled during the European Society for Medical Oncology (ESMO) Virtual Congress 2020 and published in the Lancet Journal in 2022[12], have challenged the current established guidelines. Lung ART, a phase 3, open–label, randomized superiority trial, compared mediastinal postoperative radiotherapy (PORT) to no PORT in NSCLC patients with complete resection and proven N2 involvement through nodal exploration and cytological or histological confirmation.

The primary objective of the trial was to assess disease–free survival (DFS) at 3 years from enrollment, with secondary objectives focusing on safety, tolerability, and overall survival (OS). Initially aiming to enroll 700 patients from 64 hospitals and cancer centers across five countries, the trial faced recruitment challenges, leading to a revised target of 500 patients and adjusted improvement expectations in 3–year DFS to 12%. Ultimately, between August 2007 and July 2018, 501 patients were included in the study, randomized to either the control arm or the PORT arm, receiving 54 Gy over 5 weeks.

The median age of patients was 61, with a male predominance of approximately 66%, and adenocarcinoma being the most common histology (73%). A majority of patients received chemotherapy, with 77% receiving it postoperatively and 18% receiving it preoperatively.

Following a median follow–up period of 4.8 years, the results revealed that the 3–year DFS rates were 47% for the PORT group and 44% for the non–PORT group. Additionally, median DFS times were 30.5 months for the PORT group and 22.8 months for the control group (p=0•18). The 3–year OS was 66.5% with PORT vs 68.5% with no PORT. Notably, PORT was associated with higher rates of early and late grade 3 or 4 toxicities.

In light of these findings, the authors concluded that conformal PORT should not be recommended as the standard of care for patients with stage IIIAN2 NSCLC. Similarly, the Phase 3 PORT–C Randomized Clinical Trial corroborated that PORT did not improve DFS[13]. However, it is noteworthy that the Lung ART trial revealed a significantly lower rate of mediastinal relapse in the PORT arm compared to the control arm, emphasizing the potential benefit of PORT in preventing mediastinal relapse despite its lack of significant impact on overall survival or DFS.

An important limitation of both the PORT–C and Lung ART studies lies in the absence of patient–specific genetic mutation analysis, which is crucial given the substantial proportion of patients with non–squamous NSCLC, predominantly adenocarcinoma, within both trials (83.8% in PORT–C and 78.4% in Lung ART).

Ongoing and future analyses are planned in Lung ART to identify patients for whom PORT could be recommended. Further studies assessing the feasibility of stereotactic radiotherapy for micro or macro residual of disease are also warranted[14].

What are the benefits of postoperative thoracic radiotherapy for NSCLC with positive margins?

Regarding the management of positive margins in patients undergoing lobectomy or pneumonectomy for stage II or III non–small cell lung cancer (NSCLC), there is limited evidence regarding the use of postoperative radiotherapy (PORT)[15].

Wang et al. Investigate the National Cancer Database (NCDB) to assess the survival outcomes of patients with positive margins who underwent PORT[16].

Their findings indicated that PORT was associated with improved overall survival (OS) for all patients with pN0–pN2 disease, with a hazard ratio of 0.80. This suggests that positive margin status serves as a strong indication for the administration of PORT in these patients.

However, it is crucial to note that the evidence supporting this recommendation stems from retrospective analyses, and there remains a need for randomized

prospective trials to further validate these findings and provide more robust evidence.

What timing sequence is optimal for postoperative radiotherapy and chemotherapy in locally advanced or incompletely resected NSCLC?

The most common cause of mortality in patients with locally advanced NSCLC is distant recurrent disease. This is why we associate chemo and radiation therapy to have both a better regional and systemic control of disease. Moreover, chemoradiation could be delivered in a concurrent (cCRT) way or in a sequential (sCRT) way. Several randomized studies have shown that concurrent chemoradiotherapy (CRT) offers a survival advantage over sequential regimens in the unresectable disease, making CRT the standard of care in patients with unresectable disease[17]. However, the preferred sequencing of chemotherapy and PORT in the adjuvant treatment of patients with resected lung cancer remain controversial. In the Journal of Clinical Oncology, investigated the optimal sequencing of postoperative radiotherapy and chemotherapy for locally advanced or incompletely resected NSCLC[18]. The authors selected two cohorts of patients with nonmetastatic NSCLC who had received at least a lobectomy followed by multiagent chemotherapy and radiotherapy, by using the National Cancer Database; cohort one included patients with R0 resection and pN2 disease, whereas cohort two included patients with R1–2 resection regardless of nodal status. A total of 747 patients in cohort one and 277 patients in cohort two were included, with a median follow up of 32.8 and 27.9 months, respectively. The median OS was 58.8 months for patients who received chemotherapy before PORT versus 40.4 months for patients who received CRT in cohort one (P , .001). For cohort two, the median OS was 42.6 months for patients who received chemotherapy before PORT versus 38.5 months for patients who received CRT (P = .42). Nevertheless, this study was criticized for several reasons in particular, its retrospective nature not including all factors which may impact survival, and is lacking information on toxicity, local recurrence, and cause of death. Unfortunately, there is no arm available to compare sequential with concurrent chemotherapy at the phase III European Organisation for Research and Treatment of Cancer trial ,LungART[12]. Although the optimal sequence is not etabliched, National Comprehensive Cancer Network (NCCN)[19] recommended to administer PORT after postoperative chemotherapy and concurrently with chemotherapy for positive resection margins.

Conclusion:

For over two decades, there has been ongoing debate regarding the administration of radiotherapy to patients with mediastinal lymph node involvement post–surgery. Although there is a strong consensus to offer postoperative radiotherapy (PORT) in cases of incomplete resection, the absence of randomized evidence has left uncertainty. Despite this, randomized controlled trials have failed to demonstrate that the benefits of PORT outweigh its risks. Consequently, conformal PORT should not be routinely administered to patients with NSCLC and completely resected N2 involvement. Future studies are needed to better identify patients at high risk of disease recurrence, potentially through the analysis of circulating tumor DNA and detection of postsurgical minimal residual disease. Additionally, exploring the synergistic effects of adjuvant radiotherapy and immunotherapy could provide valuable insights.

Acknowledgement:

Pr. Fadila Kouhen, Dr. Hanaa El Gouach, and Pr Nadia Errafiy provided essential expertise and support for this study.

Funding and Conflict of Interest:

The authors declare no funding sources or conflicts of interest.

References :

1. Freddie Bray, BSc, Jacques Ferlay, Isabelle Soerjomataram, and al.: Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018, 68:394–424. 10.3322/caac.21492. Epub 2018 Sep 12
2. Paul E.Van Schil ,BramBalduyck ,Michèle De Waele ,Jeroen M.Hendriks and al .: Surgical treatment of earlystage non–small–cell lung cancer. EJC Suppl. 2013, 11:110–122. 10.1016/j.ejcsup.2013.07.021
3. The International Adjuvant Lung Cancer Trial Collaborative Group: Cisplatin–Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small–Cell Lung Cancer . N Engl J Med. 2004, 350:351–360. 10.1056/NEJMoa031644
4. Pignon JP, Tribodet H, Scagliotti GV, et al.: Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008, 20:3552–9. 10.1200/JCO.2007.13.9030. Epub 2008 May 27
5. Postoperative radiotherapy in non–small–cell lung cancer: systematic review and meta–analysis of individual patient data from nine randomised controlled trials. PORT Meta–analysis Trialists Group. Lancet. 1998, 25:257–63. 10.1016/s0140–6736(98)00048–8
6. Tingting Liu, Yanshu Mu, Jun Dang, and Guang Li: The role of postoperative radiotherapy for completely resected pIIIA–N2 non–small cell lung cancer patients with different clinicopathological features: a systemic review and meta–analysis. J Cancer. 2019, 10:3941–3949. 10.7150/jca.28680

7. Douillard JY, Rosell R, De Lena M, et al.: Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non–small–cell lung cancer treated with adjuvant chemotherapy: The Adjuvant Navelbine International Trialist Association (ANITA) randomized trial. Int J Radiat Oncol Biol Phys. 72:695–701. 10.1016/j.ijrobp.2008.01.044

8. Lally BE, Zelterman D, Colasanto JM, et al.: Postoperative radiotherapy for stage II or III nonsmall–cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol. 2006, 1:2998–3006. 10.1200/JCO.2005.04.6110. Epub 2006 Jun 12

9. Corso CD, Rutter CE, Wilson LD, Kim AW, Decker RH, Husain ZA: Re–evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non–small cell lung cancer using the National Cancer Database. J Thorac Oncol. 2015, 10:148–55. 10.1097/JTO.0000000000000406

10. Sakib N, Li N, Zhu X, et al.: Effect of postoperative radiotherapy on outcome in resectable stage IIIA–N2 non–small–cell lung cancer: an updated meta–analysis. Nucl Med Commun. 2018, 39:51–9. 10.1097/MNM.0000000000000764

11. Rodrigues G, Choy H, Bradley J, et al.: Adjuvant radiation therapy in locally advanced non–small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence–based clinical practice guideline. Pract Radiat Oncol. May–Jun. 2015, 149–155. 10.1016/j.prro.2015.02.013

12. Le Péchoux C, Pourel N, Barlesi F, et al.: Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non–small–cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): an open–label, randomised, phase 3 trial.. The Lancet oncology. 2022, 23:104–114. 10.1016/S1470–2045(21)00606–9

13. Zhouguang Hui, Yu Men, Chen Hu, et al.: Effect of Postoperative Radiotherapy for Patients With pIIIAN2Non–SmallCell Lung Cancer After Complete Resection and Adjuvant Chemotherapy The Phase 3 PORT–C Randomized Clinical Trial. JAMA Oncol. 2021, 7:1178–1185. 10.1001/jamaoncol.2021.1910

14. Emanuela Olmetto , Marco Perna? Cecilia Cerbai, and al: A narrative review of postoperative adjuvant radiotherapy for non–small cell lung cancer. Mediastinum. 2022, 6:4. 10.21037/med–21–31

15. Antonin Levy; Olaf Mercier, and Cécile Le Péchoux: Indications and Parameters Around Postoperative Radiation Therapy for Lung Cancer. Journal of Clinical Oncoogy . 2022, Feb 20;40(6):556–566. 10.1200/JCO.21.01774

16. Wang W, Men Y, Wang J , et al.: Postoperative radiotherapy is effective in improving survival of patients with stage pIII–N2 non–small–cell lung Cancer after pneumonectomy. BMC Cancer 19. 478:

17. Mark R. Waddle, Stephen Ko1, Margaret M. Johnson and al: Post–operative radiation therapy in locally advanced non–small cell lung cancer and the impact of sequential versus concurrent chemotherapy. Transl Lung Cancer Res. 2018, 7:171–175. 10.21037/tlcr.2018.03.21

18. Francis S, Orton A, Stoddard G, et al.: Sequencing of Postoperative Radiotherapy and Chemotherapy for Locally Advanced or Incompletely Resected Non–Small– Cell Lung Cancer. J Clin Oncol. 2018, 1:333–341. 10.1200/JCO.2017.74.4771

19. Riely GJ, Wood DE, Ettinger DS, et al. Non–Small Cell Lung Cancer, Version 4.2024. J Natl Compr Canc Netw. 2024 May;22(4):249–274. doi: 10.6004/jnccn.2204.0023.

20. Vieri Scotti,Icro Meattini , Calogero Saieva and al .: Post–operative radiotherapy in N2 non–small cell lung cancer: A retrospective analysis of 175 patients. Radiother Oncol . 2010, Jul;96(1):84–8.10.1016/j.radonc.2010.05.010

21. Byoung Hyuck Kim , Hak Jae Kim , Hong–Gyun Wu and al: Role of postoperative radiotherapy after curative resection and adjuvant chemotherapy for patients with pathological stage N2 non–small–cell lung cancer: a propensity score matching analysis. Clin Lung Cancer. 2014, 15:356–64. 10.1016/j.cllc.2014.05.005. Epub2014 Jun 6

22. Charlotte Billiet , Herbert Decaluwé, Stephanie Peeters and al.: Modern post–operative radiotherapy for stage III non–small cell lung cancer may improve local control and survival: A meta–analysis. Radiother Oncol. 2014, 110:3–8. 10.1016/j.radonc.2013.08.011. Epub 2013 Oct 4

23. Feng W, Zhang Q, Fu XL, et al.: The emerging outcome of postoperative radiotherapy for stage IIIA(N2) non–small cell lung cancer patients: based on the three–dimensional conformal radiotherapy technique and institutional standard clinical target volume. BMC Cancer 15. 348:

24. John L Mikell , Theresa W Gillespie, William A Hall, Dana C Nickleach and al.: Postoperative radiotherapy is associated with better survival in non–small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol. 2015, 10:462–71. 10.1097/JTO.0000000000000411

25. Fei Gao, Nan Li, YongMei Xu, and GuoWang Yang: Evaluation of Postoperative Radiotherapy Effect on Survival of Resected Stage III–N2 Non–small Cell Lung Cancer Patients. Front Oncol. 2020, 10:1135.10.3389/fonc.2020.01135

26. Felip E, Altorki N, Zhou C, et al.: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IBIIIA non–small–cell lung cancer (IMpower010): a randomised, multicentre, open–label, phase 3 trial. Lancet.2021, 9:1344–1357. 10.1016/S0140–6736(21)02098–5.