

Postoperative radiotherapy for lung cancer: Is it worth the controversy?

Supplementary material

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Table 1: Studies evaluating PORT in pN2 NSCLC patients

Trial	Year	Study type	Stage	Patient number	Inclusion period	Staging	Resection	Chemotherapy	% PORT	Reason PORT	Technique PORT	Dose	OS	PORT	Non-PORT	p-value	LR	PORT	Non-PORT	p-value
Studies with inclusion < 1995 : before use of Linac and CT for staging and treatment planning																				
Sawyer [24]	1997	R	III-N2	224	1987-1993	NA	R0	No	39%	doctor's decision	NA	50.4 (median)	4y	43%	22%	0.005	4y	17%	60%	<0.05
Studies with inclusion < 2006: before use of PET and standard pathological N2 confirmation for staging and treatment planning																				
Matsugama [25]	2008	R	IIIA-N2	91	1986-2003	NA	R0	Neo and/or adj (29.7%)	49.4%	doctor's decision	Linac. CT based from 1999	25.2-63.9	5y	53.2%	39.3%	0.63	%LR	11.1%	43.4%	0.0005
Scotti [29]	2010	R	III-N2	175	1988-2004	CT brain imaging bone scan PET > 2000	NA	Adj (12%)	68.0%	doctor's decision	Linac	46-66	% alive	14.3%	7.1%	0.13	%LR	18%	43% ²	0.009
Lally [20]	2006	R	III-N2 ¹	1987	1988-2002	NA	R0/1/2	NA	47.0%	doctor's decision	Linac	NA	5y	27%	20%	0.004	-	NA	NA	NA
Perry [35]	2007	P	IIIA-N2	37	1998-2000	CT N2 path (50%)	R0	Adj (100%)	51.4%	randomization	NA	50	1y	74%	72%	0.91	%LR	42%	35%	NA
Douillard (ANITA) [39]	2008	P	IIIA-N2 ¹	224	NA	CT bone scan	R0	Adj (48.4%)	27.6%	doctor's decision	Linac	45-60	5y ³	47.4%	34%	NA	5y	14.6%	25.7%	NA
Corso [36]	2014	R	IIIA-N2 ¹	6979	1998-2006	NA	R0	Neo or Adj (34.3%)	11.2%	doctor's decision	Linac. 3D or IMRT	54 (median)	5y	34.1%	27.8%	<0.001	-	NA	NA	NA
Zou [26]	2010	R	III-N2	183	1998-2005	N2 path	R0	Adj (100%)	56.8%	doctor's decision	Linac. 3D	48-54	5y	30.5%	22.2%	0.007	5y	26.8%	66.2%	0.027
Studies with PET. brain imaging and pathological N2 confirmation for staging and treatment planning																				
Decaluwe [30]	2009	R	IIIA-N2	92	1999-2006	PET brain imaging	R0/1/2	Neo (100%)	NA	ypN2 and/or	Linac	51-66	5y	33%	NA	NA	-	NA	NA	NA

						N2 path				R1/2										
Mayer [38]	2006	P	III-N2 ¹	49	NA	CT bone scan N2 path	R0	No	53.5%	randomization	Linac. 3D	50-56	2y	45.5%	40.6%	>0.05	2y	1.2%	9.7%	<0.05
Moretti [31]	2009	R	III-N2	83	1994-2004	CT PET N2 path	R0/1	Adj (14%)	47%	doctor's decision	Linac. 3D	50-60	2y	43%	21%	0.002	2y	23%	NA	NA
Lou [33]	2012	R	IIIA-N2	61	1998-2008	PET (57%) N2 path (43%)	NA	Neo (100%) and adj (24.6%)	100%	ypN2	NA	33-64.8	5y ²	16%	NA	NA	5y	11.4%	NA	NA
Billiet [56]	2016	R	III-N2	150	1998-2012	PET brain imaging N2 path	R0/1/2	neoadjuvant (100%)	46.6%	ypN2 and/or R1/2	Linac. 3D	50-66	5y	32%	41.5%	0.44	5y	37.4%	44.8%	0.60
Askoxyliakis [32]	2014	R	III-N2	71	2001-2008	N2 path	R0/1	Neo or adj (100%)	100%	ypN2	Linac. 3D	40-60	5y	35.5%	NA	NA	5y	12.6%	NA	NA
Dai [27]	2011	R	IIIA-N2	221	2003-2005	N2 path	NA	Adj (72.9%) Neo (21.2%) or adj (34.8%)	43.4%	doctor's decision	Linac. 3D	60	5y	36.6%	30.6%	0.046	5y	36.1%	53.3%	0.025
Mantovani [28]	2013	R	III-N2	66	2003-2008	NA	R0	Neo or adj (34.8%)	100%	ypN2	Linac. 3D	50-54	5y	37%	NA	NA	5y	27.9%	NA	NA
Robinson [37]	2015	R	IIIA-N2	4483	2006-2010	N2 path	R0	Adj (100%)	41.3%	doctor's decision	Linac. 3D	45-82.8	5y	39.3%	34.8%	0.014	-	NA	NA	NA

NA: information not available; PORT: postoperative radiotherapy; R: Retrospective study; P: Prospective study; R0: complete resection; R1: microscopic incomplete resection; R2: macroscopic incomplete resection; neo: neo-adjuvant chemotherapy; adj: adjuvant chemotherapy; Linac: linear accelerator; OS: overall survival; LR: local recurrence; CT:, thoracic, and upper abdomen CT scan; Path: pathological; PET: positron emission tomography.

¹ subgroup analysis

² value from graph

³ in chemotherapy group

Table 2: Studies evaluating toxicity after PORT in NSCLC patients

Trial	Year	Study type	Stage	Patient number	Inclusion period	Resection	Chemotherapy	% PORT	Reason PORT	Technique PORT	Dose	Toxicity	PORT	non-PORT	p-value
Kepka [49]	2011	P	pN1-N2	291	2003-2007	R0	Neo or adj (43%)	58.8%	ypN2	Linac, 3D	50-60	Intercurrent death	5%	5%	NS
Lally [50]	2007	R	N1-N2	6148	1983-1993	R0/1/2	NA	58%	doctor's decision	NA	NA	Cardiac death	6%	6%	0,97
Dai [27]	2011	R	IIIA-N2	221	2003-2005	NA	Adj (72,9%) neoadjuvant (100%)	43.4%	doctor's decision ypN2 and/or R1/2	Linac, 3D or 2D	60	Intercurrent death	7%	8%	0,497
Billiet [56]	2016	R	III-N2	150	1998-2012	R0/1/2		46.6%		linac, 3D	50-66	Intercurrent death	5%	9.3%	0.29
												TOTAL	6% (233/3903)	6% (178/2907)	0.80
Machtay [47]	2001	R	II-III	202	NA	R0/1/2	No	100%	NA	Linac	55 Gy (mean)	Intercurrent death	14%	NA	NA
Mantovani [28]	2013	R	III-N2	66	2003-2008	R0	Neo (21,2%) or adj (34,8%) Neo (100%) and adj (24,6%)	100%	ypN2	Linac, 3D	50-54	Intercurrent death	5%	NA	NA
Lou [33]	2012	R	IIIA-N2	61	1998-2008	NA	Adj (50,4%)	100%	ypN2	NA	33-64.8	Intercurrent death	21%	NA	NA
Wakelee [48]	2004	P	II-IIIA	488	1991-1997	R0	Adj (50,4%)	100%	randomization ypN2 and/or R1/2	NA	50.4	Intercurrent death	13%	NA	NA
Decaluwe [30]	2009	R	IIIA-N2	92	1999-2006	R0/1/2	Neo (100%)	NA	doctor's decision	Linac	51-66	Intercurrent death (in all patients)	5%	NA	NA
Taylor[62]	2003	R	IIB-IIIA	98	1990-2000	R0/1/2	Neo (100%)	44.9%	doctor's decision	2D	27-70	Intercurrent death (in all patients)	13%	NA	NA
TOTAL	4906 PORT patients											MEAN	7.3% (358/4906)		

NA: information not available; PORT: postoperative radiotherapy; R: Retrospective study; P: Prospective study; R0: complete resection; R1: microscopic incomplete resection; R2: macroscopic incomplete resection; neo: neo-adjuvant chemotherapy; adj: adjuvant chemotherapy; Linac: linear accelerator

Table 3: Studies evaluating LR in pN2 NSCLC patients with or without PORT

	WITHOUT PORT					WITH PORT				
	Study	Stage	Patient group	Chemotherapy	# patients with LR first site	Study	Stage	Patient group	Chemotherapy	# patients with LR first site
LOW-RISK PATIENTS (R0, ypN0/1)	Amini 2013 [13]	III-N2	R0, ypN0/1	Neo (100%) and adj (14.4%)	47/153	No data available				
	Billiet 2016 [56]	III-N2	R0, ypN0/1	Neo(100%)	25/64					
	TOTAL % 95% CI				72/217 33.1% (0.27-0.39)					
HIGH-RISK PATIENTS (R1/2, ypN2)	No data available					Zou 2010 [26]	III-N2	R0	Adj (100%)	28/104
						Billiet 2016 [56]	III-N2	R0/1/2	Neo (100%)	20/70
						Lou 2012 [33]	IIIa-N2	NA	Neo (100%) and adj (24,6%)	7/61
						Askoxylakis 2014 [32]	III-N2	R0/1	Neo or adj (100%)	5/53
						TOTAL % 95% CI				60/288 20.9% (0.16-0.24)

CT: chemotherapy; S: surgery; PORT: postoperative radiotherapy; R0: complete resection; R1: microscopic incomplete resection; R2: macroscopic incomplete resection; neo: neo-adjuvant chemotherapy; adj: adjuvant chemotherapy; LR: local recurrence