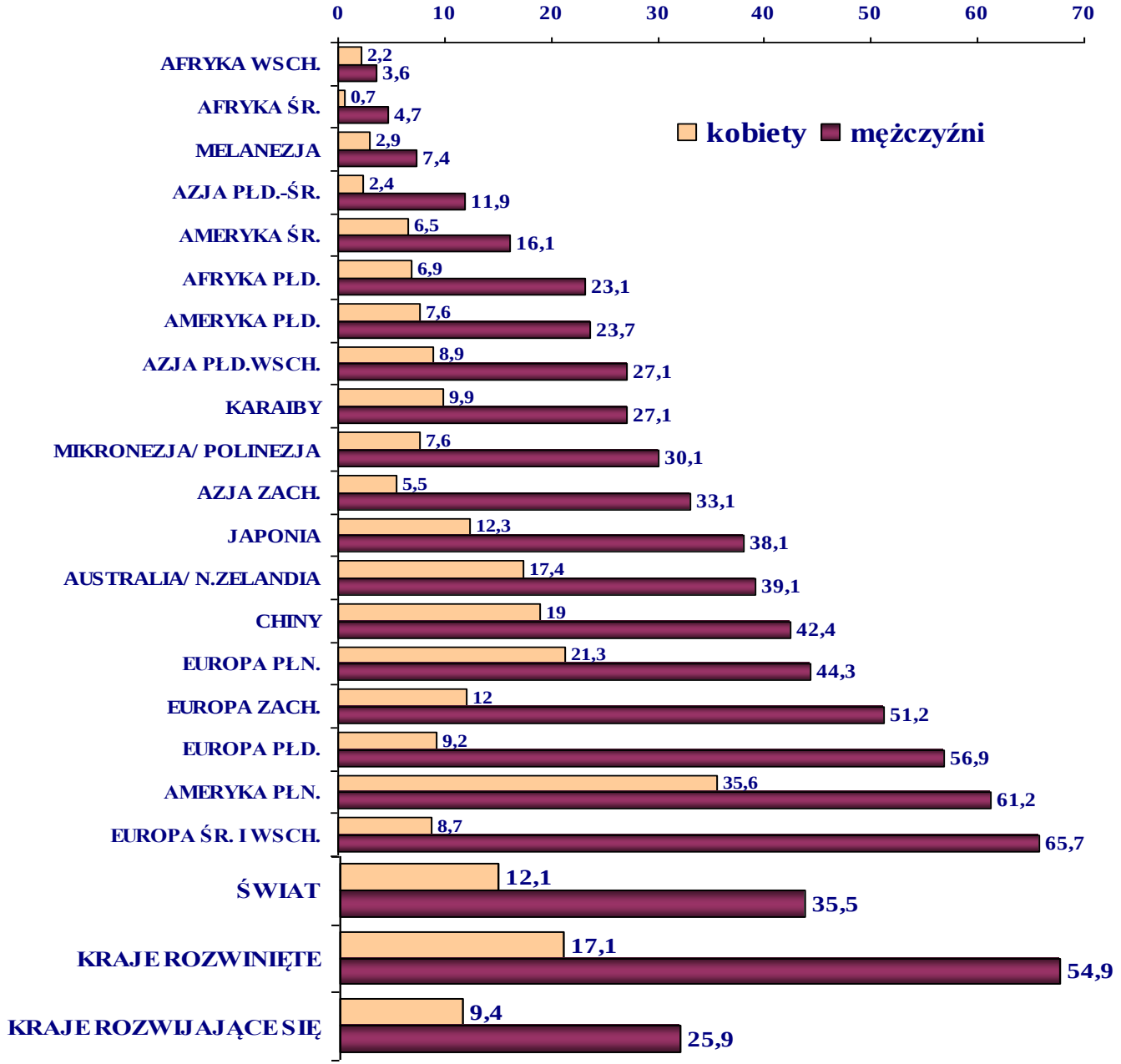
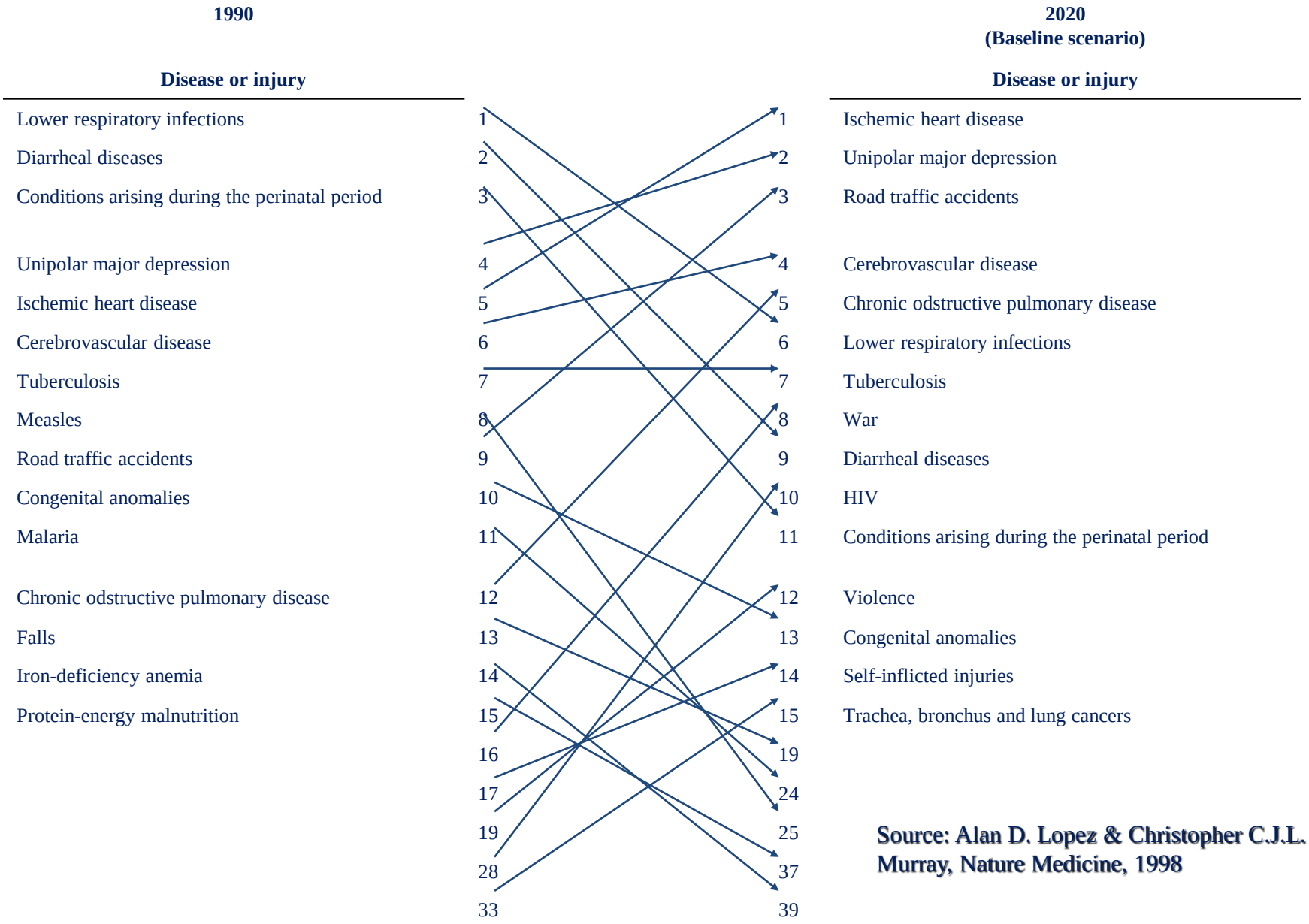
Postępy w leczeniu raka płuca w świetle medycyny opartej na faktach

Kazimierz Roszkowski- Śliż

Zachorowalność na raka płuca w regionach świata wg WHO (IARC). Współczynniki standaryzowane wg wieku na 100.000. 2014 r.



Change in the rank order of disease burden for 15 leading causes worldwide, 1990 – 2020 (as measured by DALYS)



Source: Alan D. Lopez & Christopher C.J.L. Murray, Nature Medicine, 1998

Lung Cancer (2005) 49, 25–33

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www.elsevier.com/locate/lungcan

Complete resection in lung cancer surgery: proposed definition

Ramón Rami-Porta[a,*], Christian Wittekind[b], Peter Goldstraw[c]

for the International Association for the Study of Lung Cancer (IASLC) Staging Committee[1]

Wyniki oceny patologicznej węzłów chłonnych bez klinicznych cech limfadenopatii śródpiersiowej

	c TNM				
	N0	N1	N2	Total	% of total (n = 103) studied
p TNM	47	7	0	54	52,43
N0					
N1	15	9	0	24	23,3
N2	19	5	1	25	24,27
Total	81	21	1	103	100
% of total (n – 103 studied)	78,64	20,39	0,97	100	
Probablity that cTNM	58	42	100	55,3	
= pTNM for nodal staging				(57/103x100)	

Źródło:Fernando H.C., Goldstraw P.: The accuracy of clinical evaluative intrathoracic staging in lung cancer as assessed by postsurgical pathologic staging. Cancer 1990; 65: 2503-2506.

Częstość patologicznie potwierdzonych przerzutów do węzłów u chorych z NDRP, poddanych zabiegom resekcyjnym, ocenianych metodą losowania systematycznego w porównaniu z całkowitą resekcją węzłów

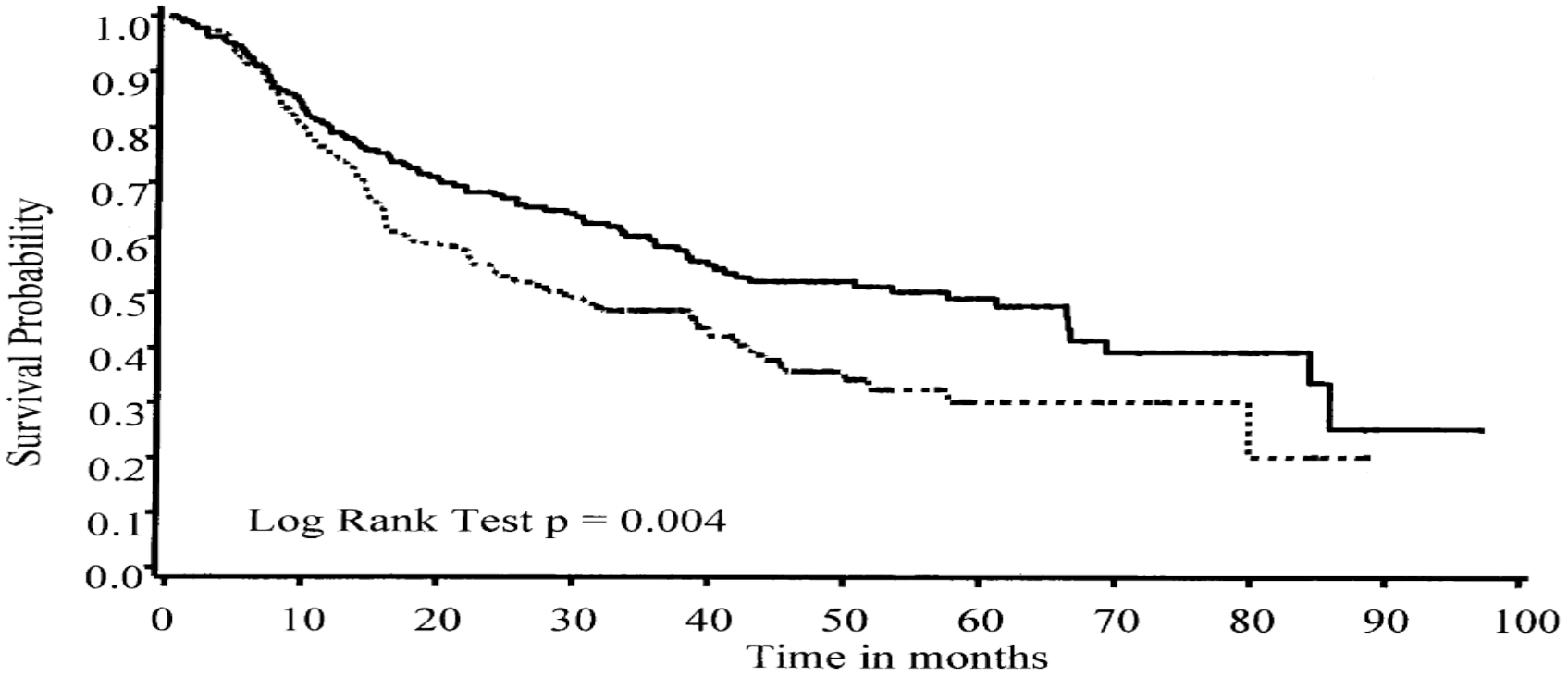
	SS (n = 187) (%)	Complete MLND (n = 186) (%)	*p* Value (Fisher's Exact Test)
N1 only	75 (40)	76 (41)	0.92
N2 only (skip metastases)	39 (21)	38 (20)	1.0
N1 and N2	73 (39)	72 (39)	1.0
Multiple N2 Levels[a]	13 (12)	33 (30)	0.001

[a] Calculated as percent of patients with N2 disease.

MLND = mediastinal lymph node dissection; SS = systematic sampling.

Źródło: Keller S.M., Adak S., Wagner H. i wsp.: Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. Ann. Thorac. Surg. 2000; 70: 358-365; discussion: 365-356.

Przeżycia chorych po resekcji NDRP z oceną węzłów chłonnych metodą losowania systematycznego w porównaniu z całkowitą limfadenektomią



	TOTAL	DEAD	ALIVE	MEDIAN
Complete MLND	186	95	91	57.5
Systematic Sampling	187	116	71	29.2

Źródło: Keller S.M., Adak S., Wagner H. i wsp.: Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. Ann. Thorac. Surg. 2000; 70: 358-365; discussion: 365-356.

Przewaga całkowitej limfadenektomii nad metodą losowania systematycznego w ocenie cechy N

Site-Related Negative Predictive Value of SS

	Right lung cancer ($n = 65$)	Left lung cancer ($n = 45$)*	Whole group ($n = 110$)*
S (+) D (+)	12	5	17
S (–) D (+)	7	2	9
S (–) D (–)	46	38	84
Sensitivity	63.2%	71.4%	65.4%
NPV	86.8%	95.0%	90.3%

S (–) D (–) = negative node in SS, additional negative node in SMLD; S (–) D (+) = negative node in SS, additional positive node in SMLD; S (+) D (+) = positive node in SS; NPV = negative predictive value; SMLD = systematic lymph node dissection; SS = systematic sampling.

*One case of left carcinoid was excluded.

Źródło: Wu N., Yan S., Lv C. i wsp. : Comparison of systematic mediastinal lymph node dissection versus systematic sampling for lung cancer staging and completeness of surgery. J. Surg. Res. 2011; 171(2): e169-73. epub 2011 May 20.

Metaanaliza badań PORT w NDRP

Trial	Radiotherapy dose				Prescription technique	Machine used	Average field size (cm)	Clinical target volume	Technique
	Total dose (Gy)	Fractions	Duration (weeks)	Gy/day					
Belgium[10]	60	30	6	2	Isodose 90%	Co60	15x9	Bronchial stump, hilum, mediastinum	SCB,OF,LF
LCSG 773[11]	50	25·0–27·5	5·0–5·5	1·8–2·0	Central axis, at midplane	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
CAMS[12]	60	30	6	2	At midplane	Co60 & linac	6x12	Hilum, mediastinum	SCB,OF,LF
Lille[13]	45–60	22·5–30·0	6	2	Isodose 90%	Co60 & linac	12x12	Hilum, upper mediastinum	SCB,OF,LF
EORTC 08861	56	28	5·5	2	Central axis, at midplane	linac	15x10	Hilum, mediastinum	Composite plans
MRC LU11[14]	40	15	3	2·6	Central axis, at midplane	Co60 & linac	*	Hilum, mediastinum, supraclavicular fossae†	SCB,OF,LF
GETCB 04CB86	60	24–30	6	2·0–2·5	Isocentre	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
Slovenia[15]	30	10–12	2	2·5–3·0	Central axis, at midplane	linac	9x12	Hilum, mediastinum	OF,LF
GETCB 05CB88	60	24–30	6	2·0–2·5	Isocentre	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF

SCB = spinal cord blocks; OF = oblique fields; LF = lateral fields; linac=linear accelerator; Co60=cobalt-60.
Only one trial (EORTC 08861) used computed tomography for planning, and two trials (EORTC 08861 and Lille) used lung-factor corrections.
*Information not available; †For upper lobe tumours.

Źródło: 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, THE LANCET • Vol 352 • July 25, 1998

Charakterystyka chorych z i bez PORT

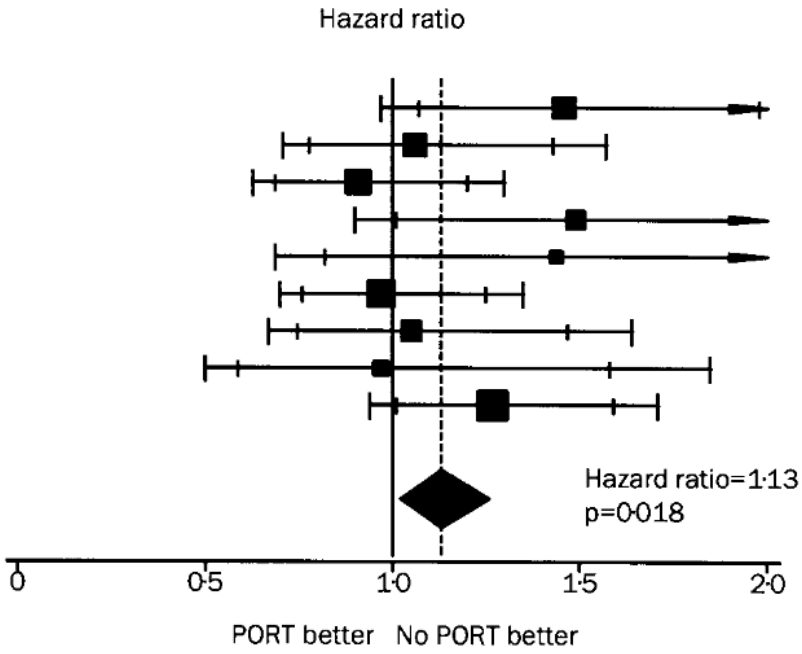
Characteristic	Postoperative radiotherapy	Surgery only	Total
Age (years)			
<54	271	296	567
55–59	240	243	483
60–64	258	252	510
>65	287	280	567
Unknown	0	1	1
Sex			
M	894	901	1795
F	162	170	332
Not recorded	0	1	1
Histology*			
Adenocarcinoma	161	174	335
Squamous	460	488	948
Other	55	47	102
Unknown	380	363	743
Meta-analysis stage†			
I	277	285	562
II	352	366	718
III	408	400	808
IV	1	0	1
Unknown	18	21	39
WHO performance status‡			
Good (0,1)	144	143	287
Poor (2,3,4)	77	83	160
Unknown	20	21	41

*Available from seven trials. † Eight trials used TNM staging, one trial used AJC staging (table 1). ‡ Available from three trials.

Źródło: 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, THE LANCET • Vol 352 • July 25, 1998

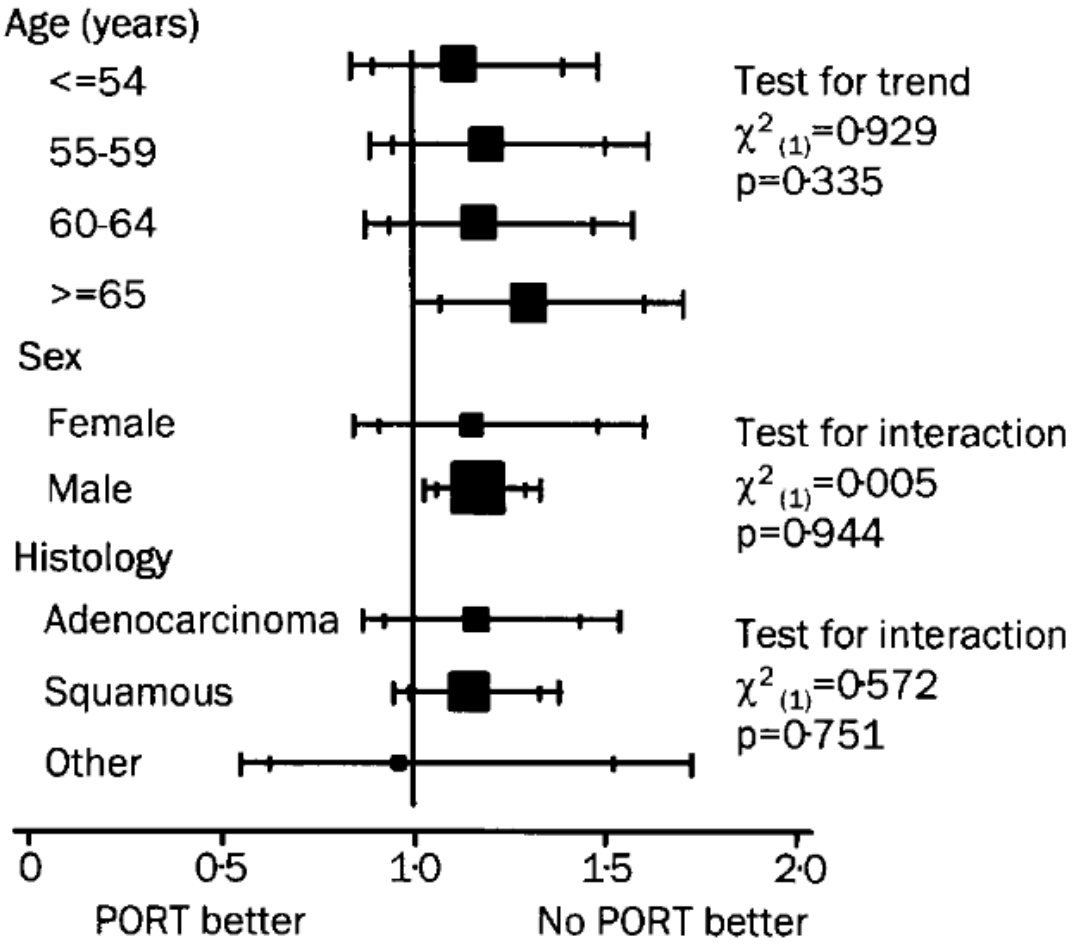
Prawdopodobieństwo przeżycia bez wznowy w poszczególnych badaniach

Trial	PORT	No PORT	O-E	Variance
Belgium (10)	88/98	80/104	15·39	40·68
LCSG 773(11)	87/110	84/120	2·43	42·46
CAMS(12)	93/153	115/164	-4·88	51·45
Lille (13)	60/81	45/82	10·33	25·95
EORTC 08861	28/52	23/54	4·52	12·50
MRC LU11 (15)	120/154	125/154	-1·67	60·87
GETCB 04CB86	72/99	62/90	1·58	33·10
Slovenia (16)	30/35	33/39	-0·55	15·65
GETCB 05CB88	161/274	141/265	17·68	74·76
Total	739/1056	708/1072	44·82	357·42



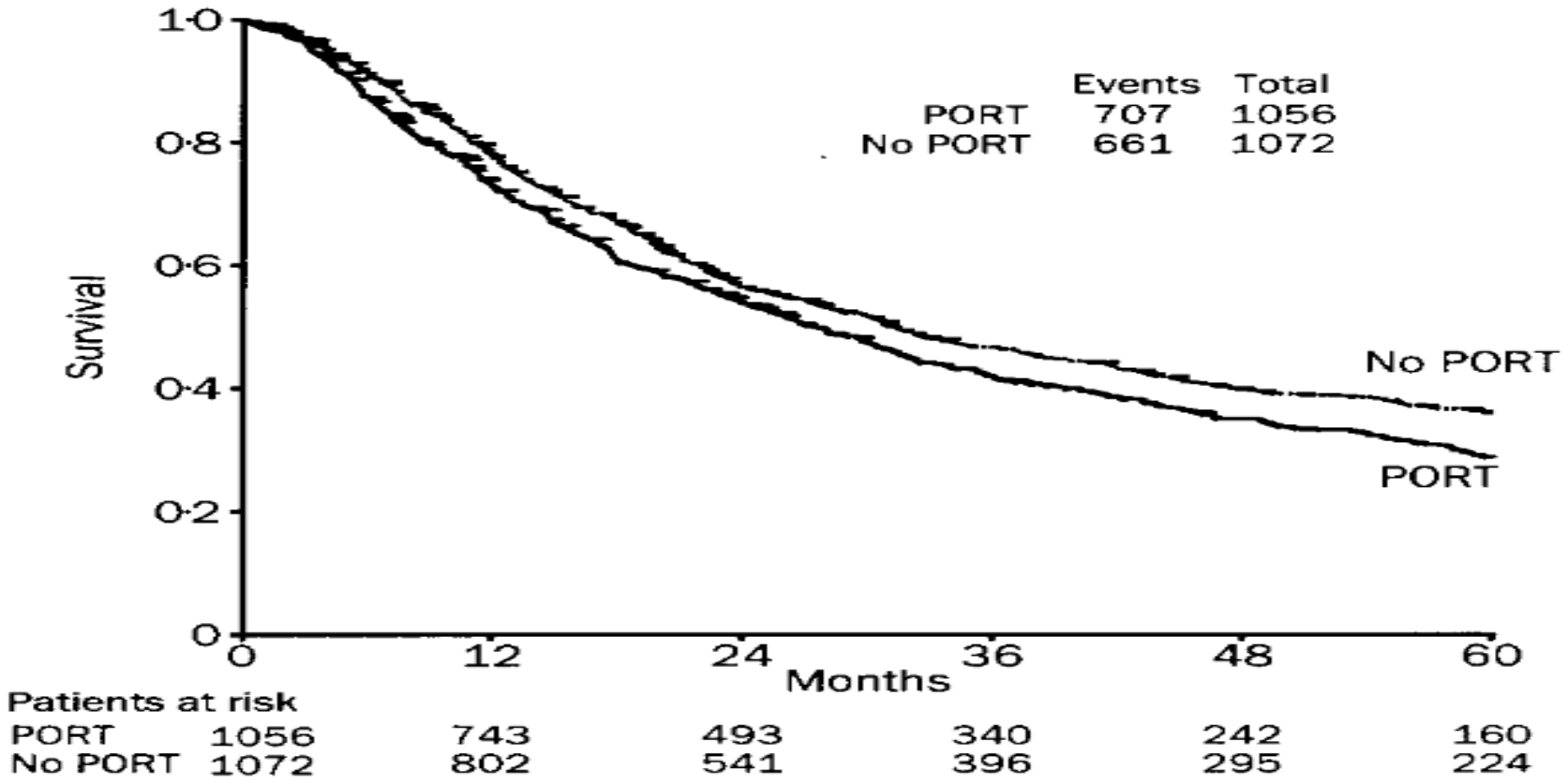
Źródło: Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group, THE LANCET • Vol 352 • July 25, 1998

Prawdopodobieństwo przeżycia bez wznowy w zależności od wieku, płci i histologii



Źródło: 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, THE LANCET • Vol 352 • July 25, 1998

Krzywa przeżycia (Kaplan-Meier)



Źródło: 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, THE LANCET • Vol 352 • July 25, 1998

Podsumowanie

Metaanaliza wykazała pogorszenie o 7% dwuletniego przeżycia w grupie chorych poddanych PORT (48%) w porównaniu z grupą bez interwencji (55%). Wykazano 21- procentowy wzrost względnego ryzyka zgonu, który związany był prawie całkowicie z pogorszeniem przeżycia napromienianych chorych w I-szym i II-gim stopniu zaawansowania i wiązany był z toksycznością radioterapii.

U chorych z cechą N2 napromienianie nie miało ani pozytywnego ani negatywnego wpływu na rokowanie.

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Radiotherapy and Oncology 62 (2002) 11–19

RADIOTHERAPY & ONCOLOGY
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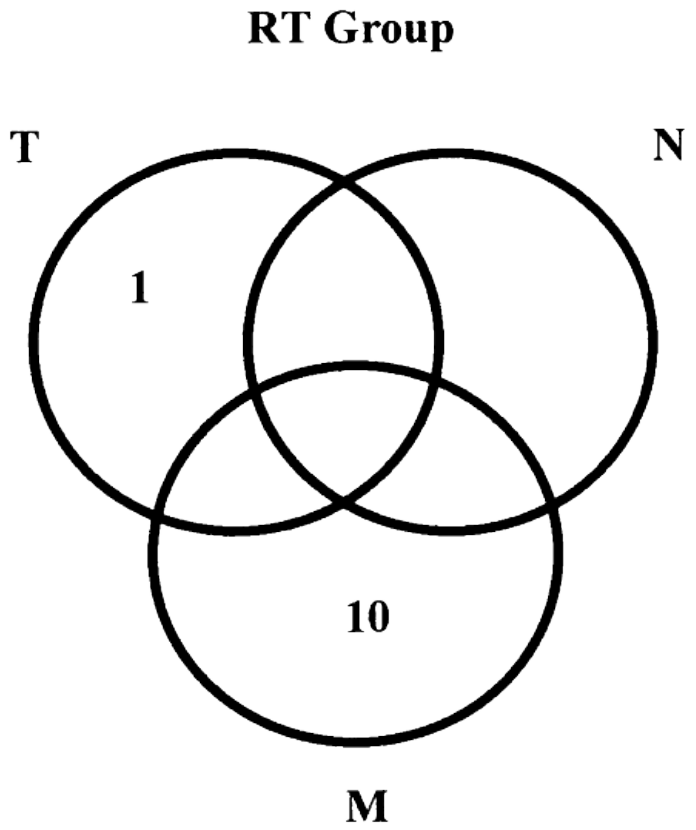
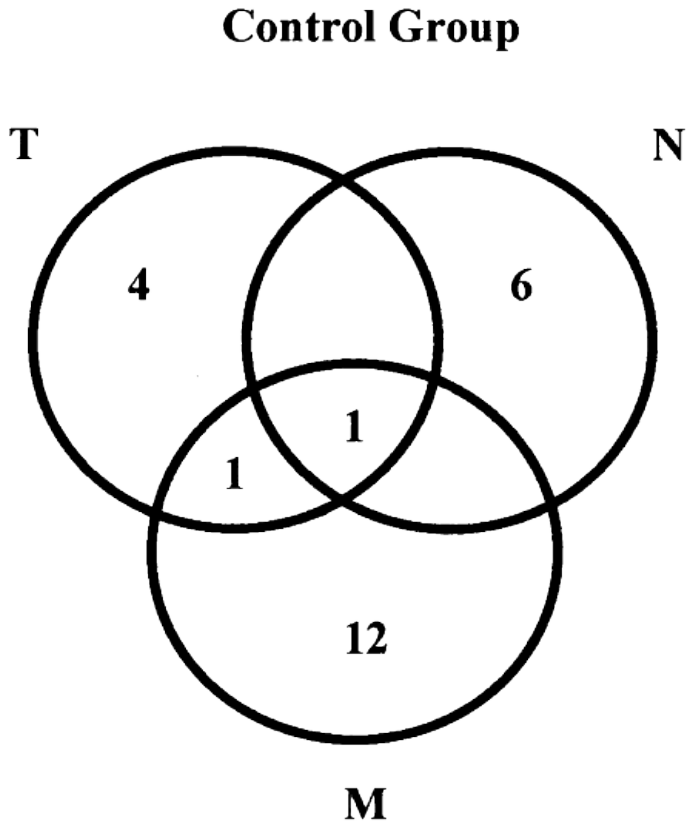
Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial

Lucio Trodella[a,*], Pierluigi Granone[b], Salvatore Valente[c], Vincenzo Valentini[a], Mario Balducci[a], Giovanna Mantini[a], Adriana Turriziani[a], Stefano Margaritora[b], Alfredo Cesario[b], Sara Ramella[a], Giuseppe M. Corbo[c], Rolando M. D'Angelillo[a], Antonella Fontana[a], Domenico Galetta[b], Numa Cellini[a]

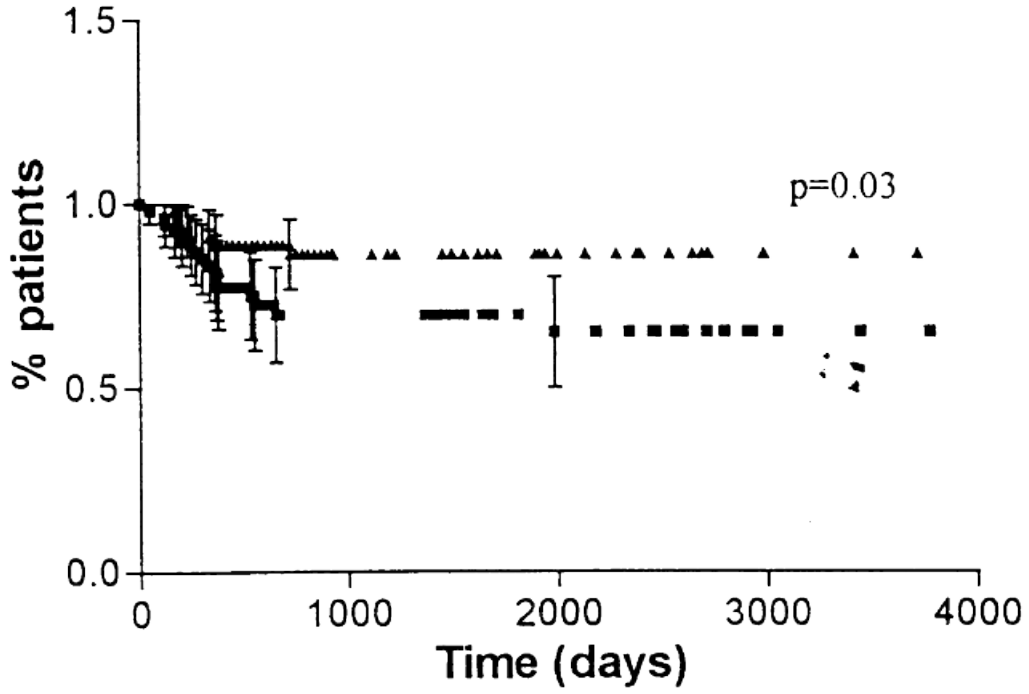
Porównanie przyczyn niepowodzeń leczenia w grupach z PORT i bez interwencji





Źródło: Trodella L., Granone P., Valente S. i wsp. : Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother. Oncol. 2002; 62: 11-19.

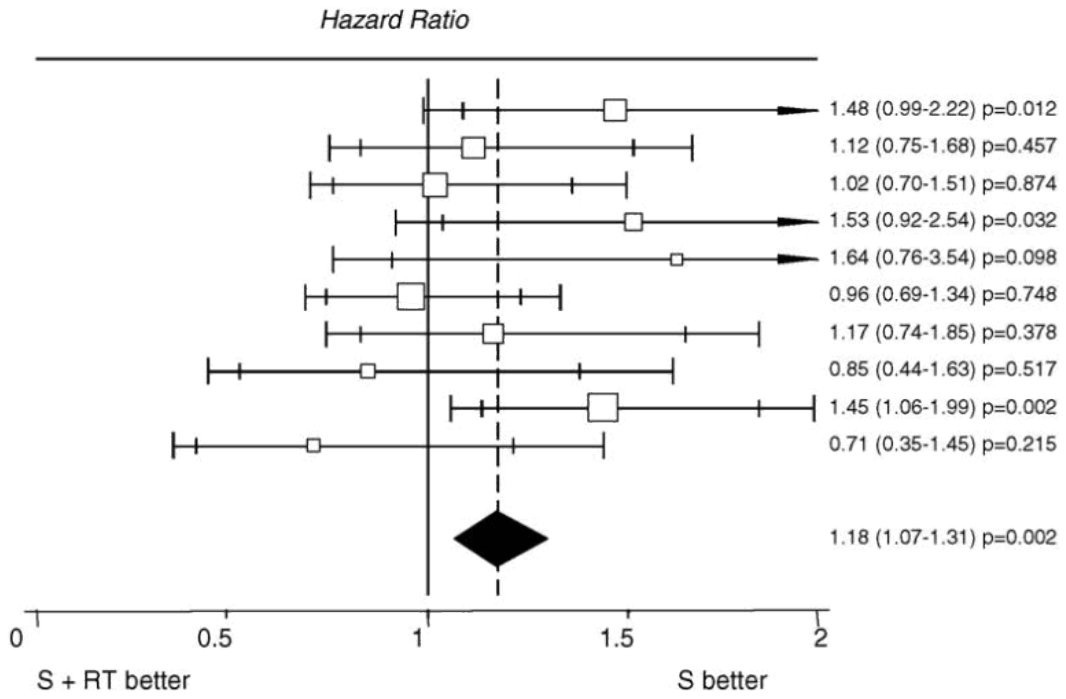
Czas przeżycia chorych z PORT - Δ i bez interwencji - □



Źródło: Trodella L., Granone P., Valente S. i wsp. : Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother. Oncol. 2002; 62: 11-19.

Powtórna metaanaliza z uwzględnieniem badania włoskiego – Trodella i wsp.

	S + RT	S
Belgium	88/98	80/104
LCSG 773	84/110	81/120
CAMS	83/153	100/164
Lille	59/81	45/82
EORTC 08861	26/52	20/54
MRC LU11	116/154	123/154
GETCB 04CB86	69/99	59/90
Slovenia	30/35	33/39
GETCB 05CB88	152/274	120/265
Italy (3)	23/51	30/53
Total	730/1107	691/1125



HR=1.18 (95% CI 1.07-1.31) $\chi^2_{(1)}$=9.88, p=0.002; Het $\chi^2_{(9)}$=16.62, p=0.06

Źródło: PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst. Rev. 2005; 2: CD002142.

Dominujący wpływ jednego badania, w którym obserwowano szczególnie dużą częstość zgonów toksycznych; dawka radioterapii 60 Gy; dominacja liczebności w stosunku do badań objętych metaanalizą - 728 chorych; u zaledwie 221 chorych I-szy stopień zaawansowania, u 180 - II-gi i u aż 327 - III-ci.

	Detailed protocol		Simplified protocol		All patients			
	Control	Radiotherapy	Control	Radiotherapy	Control	Radiotherapy	Total	*P* value[a]
Total no. of patients	90	99	265	274	355	373	728	
Gender								
Female	12	13	52	38	64	51	115	0.17
Male	78	86	213	236	291	322	613	
Age (yrs)								
<60	48	49	138	131	187	180	367	0.23
≥60	42	50	127	143	168	193	361	
Surgical procedure								
Lobectomy	39	36	167	183	206	219	425	0.85
Pneumonectomy	51	63	98	91	149	154	303	
TNM classification								
T								
T1	11	11	46	49	57	60	117	0.98
T2	58	58	138	150	196	208	404	
T3	21	30	81	75	102	105	207	
N								
N0	6	6	142	135	148	141	289	0.32
N1	51	53	72	73	123	126	249	
N2	33	40	51	66	84	106	190	
Stage								
I	5	6	103	107	108	113	221	0.91
II	36	36	54	54	90	90	180	
III	49	57	108	113	157	170	327	
Histologic type								
Squamous cell	52	59	162	184	214	243	457	0.23
Adenocarcinoma	32	31	87	66	119	97	216	
Large cell and others	6	9	16	24	22	33	55	

[a] Chi-square test.

Źródło: Dautzenberg B., Arriagada R., Chammard A.B. i wsp.: A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer 1999; 86: 265-273.

Dominujący wpływ jednego badania, w którym obserwowano szczególnie dużą częstość zgonów toksycznych; dawka radioterapii 60 Gy; dominacja liczebności w stosunku do badań objętych metaanalizą - 728 chorych; u zaledwie 221 chorych I-szy stopień zaawansowania, u 180 - II-gi i u aż 327 - III-ci.

	Median (mos)	2-yr survival	5-yr survival	RR of events (95% CI) and *P* value[b]	Adjusted[a] RR of events (95% CI) and *P* value[b]
Overall survival				1.33 (1.11–1.59)	1.28 (1.04–1.58)
Control	42	0.62	0.42		
Radiotherapy	27	0.55	0.30	$P = 0.002$	$P = 0.018$
Local recurrences				0.85 (0.64–1.14)	0.94 (0.68–1.28)
Control	—	0.76	0.66		
Radiotherapy	—	0.78	0.72	$P = 0.28$	$P = 0.67$
Distant recurrences				1.06 (0.85–1.31)	1.02 (0.80–1.29)
Control	62	0.62	0.51		
Radiotherapy	48	0.58	0.48	$P = 0.60$	$P = 0.88$
Cancer-related deaths				1.07 (0.88–1.31)	1.09 (0.87–1.38)
Control	51	0.65	0.47		
Radiotherapy	34	0.62	0.39	$P = 0.50$	$P = 0.44$
Intercurrent deaths				3.47 (2.18–5.52)	3.19 (1.77–5.76)
Control	—	0.97	0.92		
Radiotherapy	—	0.88	0.69	$P = 0.0001$	$P = 0.0001$

RR: relative risk; CI: confidence interval.

[a] Adjustment with a Cox model for age, gender, T and N classification, histologic type, and surgical procedure.

[b] *P* values are given by the score test, stratified by protocol.

Źródło: Dautzenberg B., Arriagada R., Chammard A.B. i wsp.: A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer 1999; 86: 265-273.

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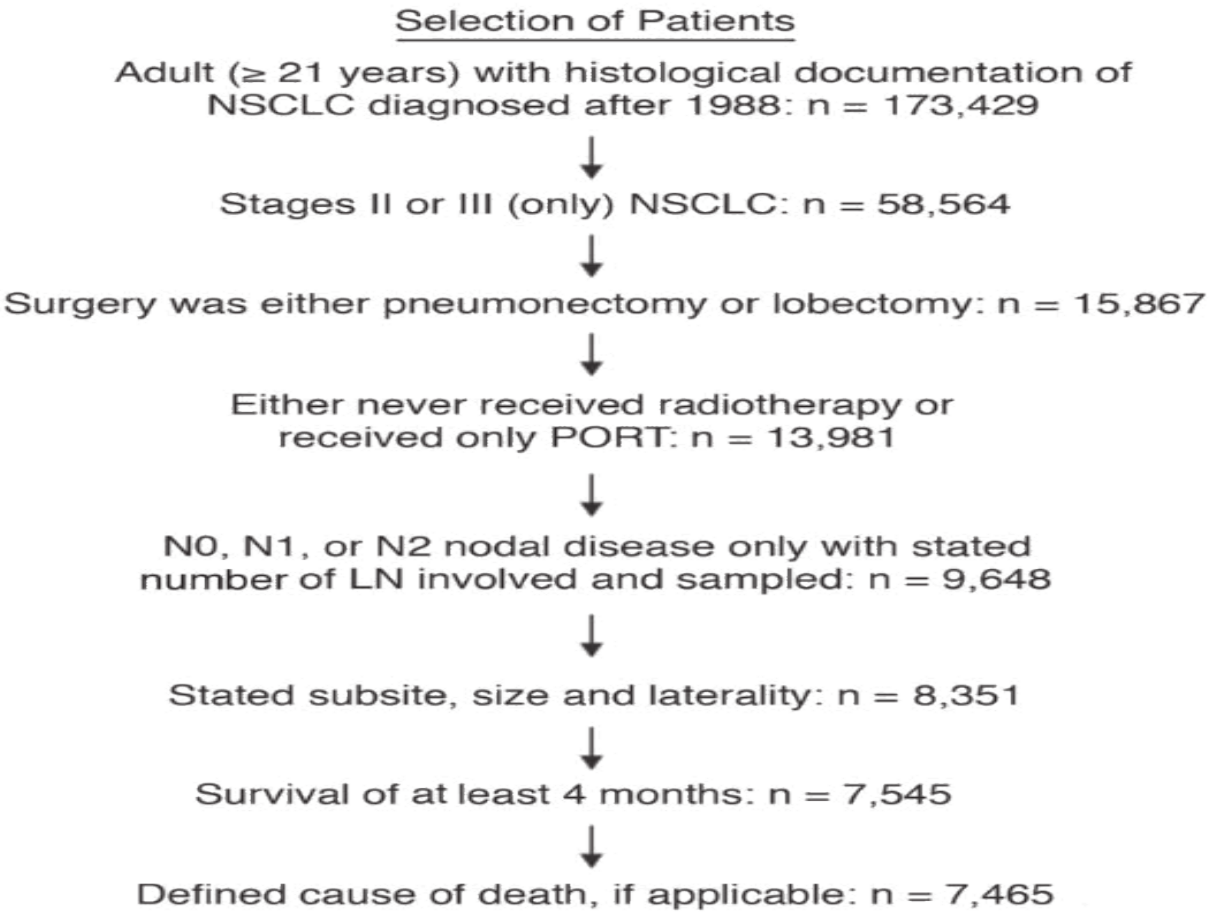
Causes of Death According to Treatment Group

Deaths	Control group (n = 355)	Radiotherapy group (n = 373)
Total no. of deaths	218	262
Cancer-related deaths		
Distant recurrence	122	127
Local recurrence	39	33
Both	33	30
Total cancer-related deaths	194	190
Intercurrent deaths[a]		
Toxic[b]	0	5
Cardiac	6	19
Infectious	1	10
Respiratory	1	5
Brain vascular disorder	2	5
Other primary malignancy	4	11
Others	12	17
Total intercurrent deaths	24	72

[a] Intercurrent deaths were all deaths unrelated to lung carcinoma (see end point definitions in text).
[b] Toxic deaths were sudden deaths during radiotherapy, hemoptysis during radiotherapy, radiation pneumonitis (2 cases), and paraplegy and radiation myelitis after radiotherapy.

Źródło: Dautzenberg B., Arriagada R., Chammard A.B. i wsp.: A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer 1999; 86: 265-273.

Metoda selekcji chorych z NDRP operowanych – z i bez PORT



Źródło: Lally B.E., Zelterman D., Colasanto I.M. i wsp.: Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J. Clin. Oncol. 2006; 24: 2998-3006.

Porównanie całkowitych przeżyć i przeżyć bez wznowy w zależności od stopnia zaawansowania cechy N

	Univariate Analysis				Multivariate Analysis					
	Overall Survival		Disease-Specific Survival		Overall Survival			Disease-Specific Survival		
Nodal Stage	5-Year Rate (%)	*P*	5-Year Rate (%)	*P*	HR	95% CI	*P*	HR	95% CI	*P*
N0										
Radiotherapy	31	< .0001	39	< .0001	1.176	1.005 to 1.376	.0435	1.361	1.134 to 1.633	.0009
Observation	41		53		1.00 (Ref)			1.00 (Ref)		
N1										
Radiotherapy	30	.0006	38	< .0001	1.097	1.015 to 1.186	.0196	1.082	0.990 to 1.182	.0822
Observation	34		44		1.00 (Ref)			1.00 (Ref)		
N2										
Radiotherapy	27	.0036	36	.0298	0.855	0.762 to 0.959	.0077	0.850	0.748 to 0.967	.0133
Observation	20		27		1.00 (Ref)			1.00 (Ref)		

Abbreviations: HR, hazard ratio; Ref, reference.

Źródło: Lally B.E., Zelterman D., Colasanto I.M. i wsp.: Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J. Clin. Oncol. 2006; 24: 2998-3006.

Badanie ANITA. Odsetek pacjentów przeżywających 5 lat w zależności od rodzaju leczenia i statusu cechy N

Treatment group	pN0	pN1	pN2
Observation (%)	62.3	31.4	16.6
Observation + PORT (%)	43.8	42.6	21.3
Chemotherapy* (%)	59.7	56.3	34.0
Chemotherapy* + PORT (%)	44.4	40.0	47.4

Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association.; PORT = postoperative radiation therapy.

* Chemotherapy consisted of vinorelbine + cisplatin.

Źródło: Douillard J.Y., Rosell R., De Lena M. i wsp. : 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. 2008; 72: 695-701.

Am J Clin Oncol (CCT). Vol. 11, No. 5, 1988

Chemotherapy of Advanced Non-Small-Cell Lung Cancer with Cyclophosphamide, Adriamycin, Methotrexate, and Procarbazine versus Cisplatin and Etoposide

A Randomized Study

A. Veronesi, **M.D.,** M. D. Magri, **M.D.,** U. Tirelli, **M.D.,** A. Carbone,F. Mazza, **M.D.,** S. Franceschi, **M.D.,** R. Talamini, **D.Sc.,**A. Ardizzoni, **M.D.,** L. Canobbio, **M.D.,** R. Rosso, **M.D.,** and S. Monfardini, **M.D.**

TABLE 2. *Response to treatment*

	Treatment group	
	CAMP	DE
No. of eligible patients	62	71
No. of unevaluable patients	9	16
No. of evaluable patients	53	55
Type of response		
CR	0	2
PR	11	19
STAB	23	24
PRO	19	10
Response rate (responding/evaluable)	11/53 (20.8%)	21/55 ($X^2_1 = 3.93$, $p = 0.05$) (38.2%)
Response rate (responding/eligible)	11/62 (17.7%)	21/71 ($X^2_1 = 2.54$, $p = 0.11$) (29.6%)
Median duration of response in weeks (range)	21 (5–35)	27 (4–72)

CR, complete response; PR, partial response; STAB, stable disease; PRO, progression.

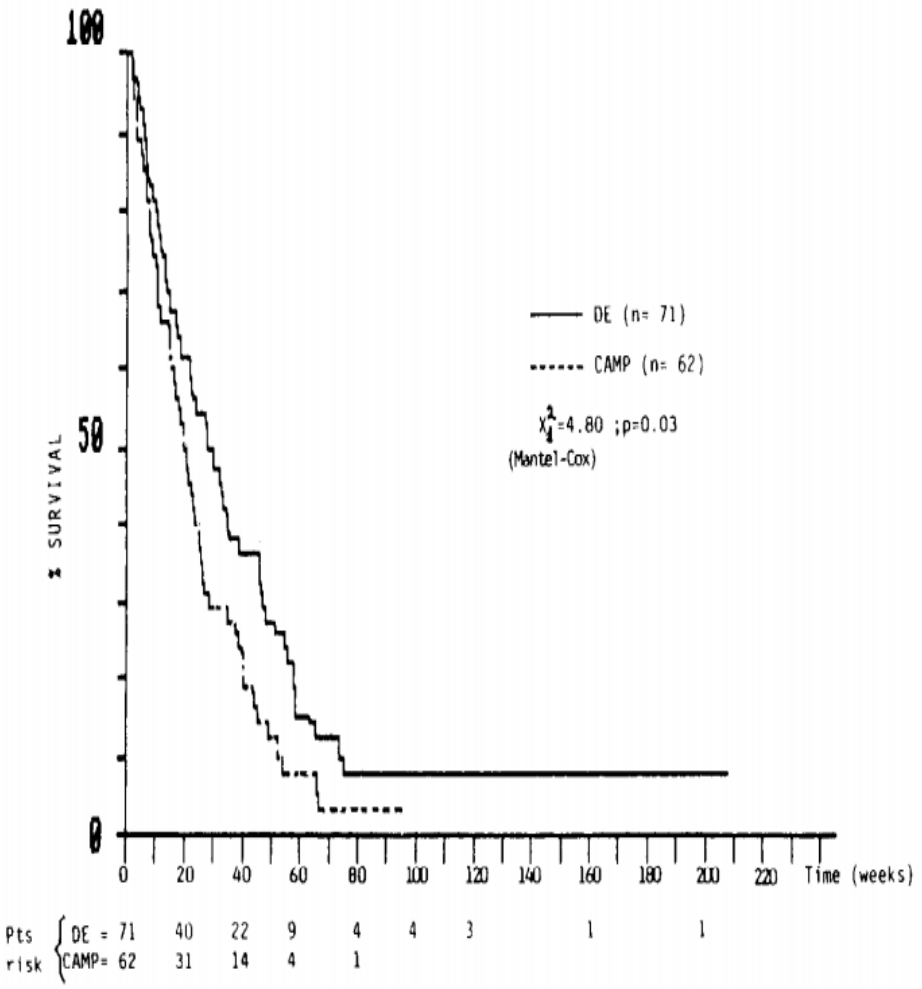


FIG. 1. Survival according to treatment. The relative risk of dying in DE patients versus CAMP patients, adjusted for sex, age, stage, PS, and histology, is 0.7 (95% confidence interval: 0.5–1.0).

NIH NATIONAL CANCER INSTITUTE

Standard Treatment Options for Stage IV NSCLC

Cytotoxic combination chemotherapy (first line)

Several randomized trials have evaluated various drugs combined with either cisplatin or carboplatin in previously untreated patients with advanced NSCLC. Based on meta-analyses of the trials, the following conclusions can be drawn:

EGFR inhibitors may benefit selected patients with *EGFR* mutations.

Maintenance chemotherapy after four cycles of platinum combination chemotherapy may improve progression-free survival (PFS) and overall survival (OS).

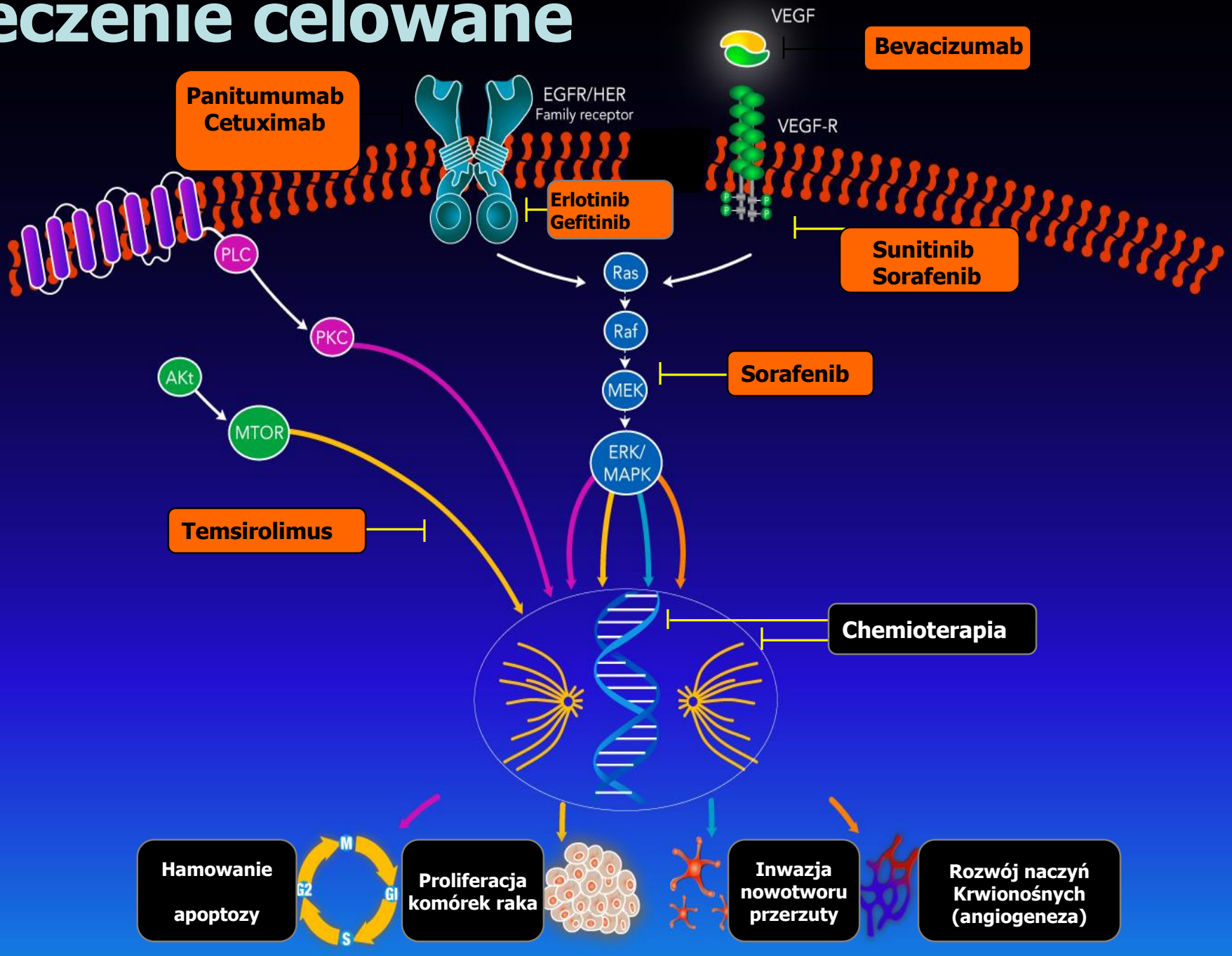
Platinum combinations with etoposide, vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan, protein-bound paclitaxel, and pemetrexed yield similar improvements in survival. Types and frequencies of toxic effects differ, and these may determine the preferred regimen for an individual patient. Patients with adenocarcinoma may benefit from pemetrexed.

Cisplatin and carboplatin yield similar improvements in outcome with different toxic effects. Some, but not all, trials and meta-analyses of trials suggest that outcomes with cisplatin may be superior, although with a higher risk of certain toxicities such as nausea and vomiting.

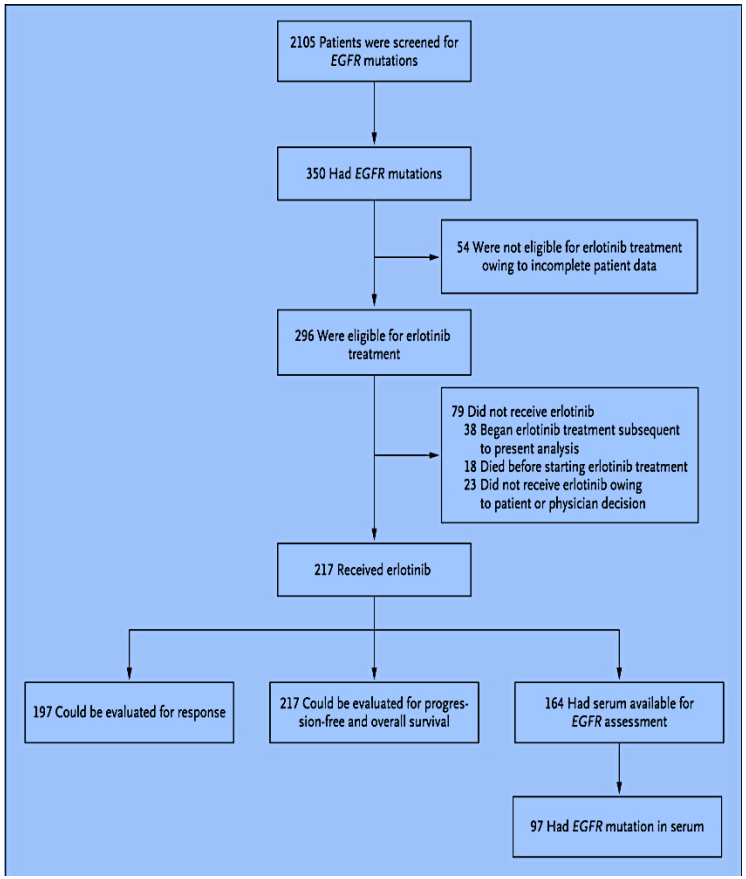
Nonplatinum combinations offer no advantage to platinum-based chemotherapy, and some studies demonstrate inferiority.

Three-drug combinations of the commonly used chemotherapy drugs do not result in superior survival and are more toxic than two-drug combinations.

Leczenie celowane



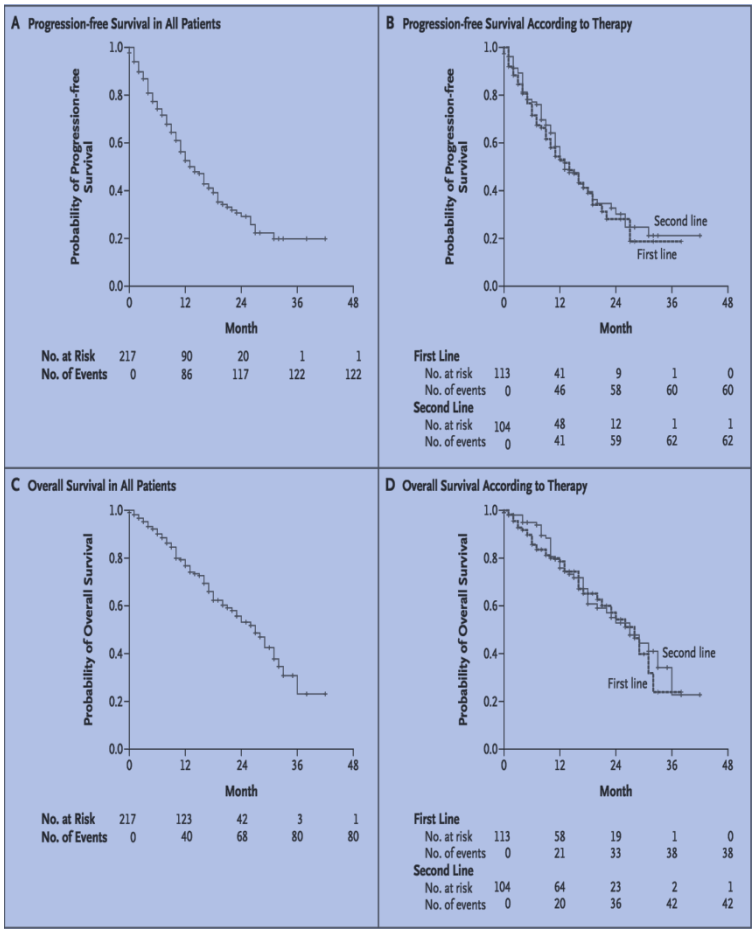
Prospektywna obserwacja leczenia erlotynibem



- populacja hiszpańska, IV stopień zaawansowania;
- częstość występowania mutacji EGFR 16,6%;
- statystycznie częstsze występowanie wśród kobiet, osób bez wywiadu nikotynizmu i z rozpoznanym rakiem gruczołowym;
- 113 osób leczone erlotynibem w pierwszej linii, 104 osoby leczone w drugiej bądź trzeciej linii
- w grupie 197 chorych zaobserwowano CR u 24 (12,2%), PR u 115 (58,4%), SD u 38 (19,3%) , PD u 20 (10,2%);

Rosell R, Moran T, Queralt C, et al. *Screening for epidermal growth factor receptor mutations in lung cancer.* New England Journal of Medicine. 2009; 361(10): 958–67

Prospektywna obserwacja leczenia erlotynibem

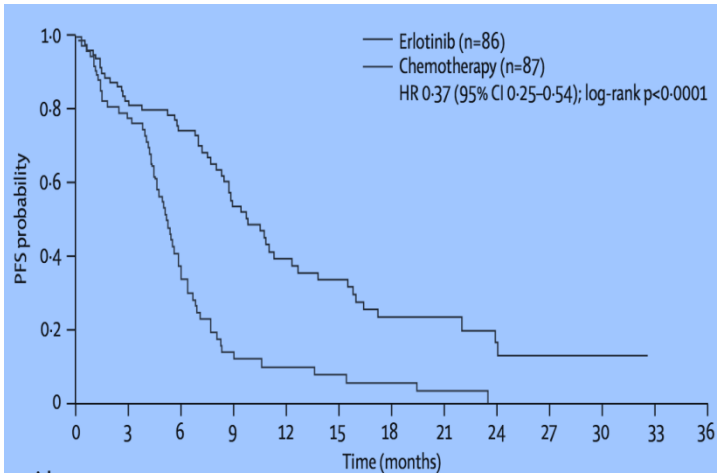


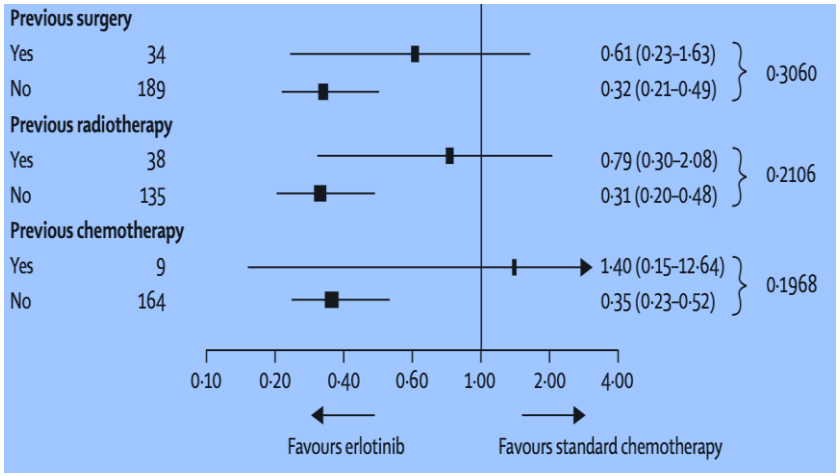
- **PFS 14,0 miesięcy**, w grupie pierwszej linii leczenia 14,0, w grupie drugiej linii 13,0 (p=0,62);
- **OS 27,0 miesięcy**, w grupie pierwszej linii leczenia 28,0, w grupie drugiej linii 27,0 (p=0,67);
- leczenie po stwierdzeniu progresji w toku leczenia erlotynibem: 55 chorych, z czego 49% otrzymało dwulekową chemioterapię, 25,5% monoterapię; ORR wynosił odpowiednio 33 i 40%;
- OS w grupie która otrzymała dodatkowe leczenie po erlotynibie 29,0 miesięcy, bez istotnej różnicy w porównaniu do pozostałej grupy chorych (p=0,48).

Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. New England Journal of Medicine. 2009; 361(10): 958–67

EURTAC

- populacja europejska (Włochy, Francja Hiszpania) IV stopień zaawansowania (wg 7 edycji TNM), potwierdzony dodatni status mutacji EGFR, możliwe wcześniejsze leczenie adjuwantowe i neoadjuwantowe; włączono chorych ze stabilnymi przerzutami do OUN;
- R 1:1 - erlotynib 150mg (86 os.) vs. chemioterapia (87 os.) - cisplatyna lub karboplatyna plus docetaksel lub gemcytabina do 4 cykli;
- zaplanowany *crossover* w momencie stwierdzenia progresji;
- PFS dla erlotynibu 9,7, dla chemioterapii 5,2 miesięcy (skorygowany po analizie 10,4 vs. 5,1 - Costa et al. (2014)).

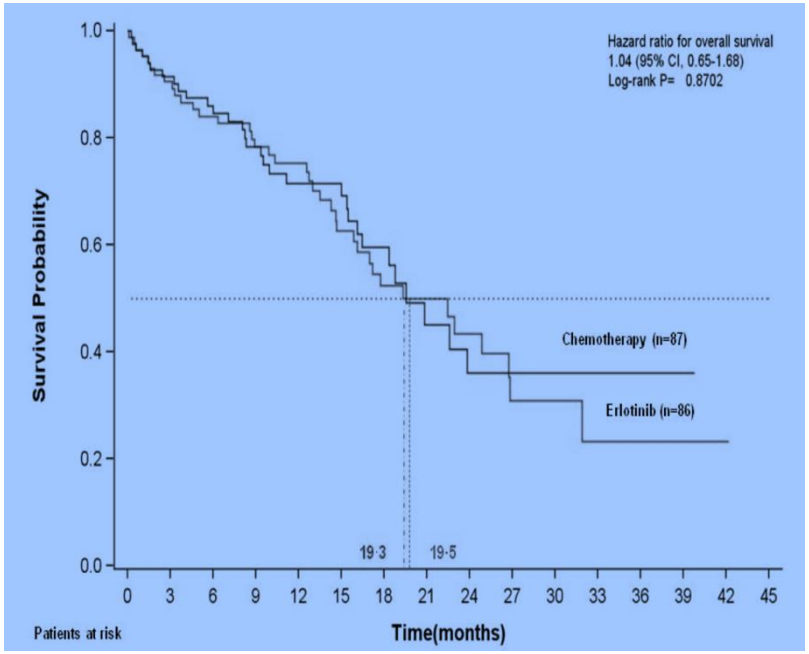




Rosell R, Carcereny E, Gervais R, et al. *Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.* The Lancet Oncology. 2012; 13(3): 239–46

EURTAC

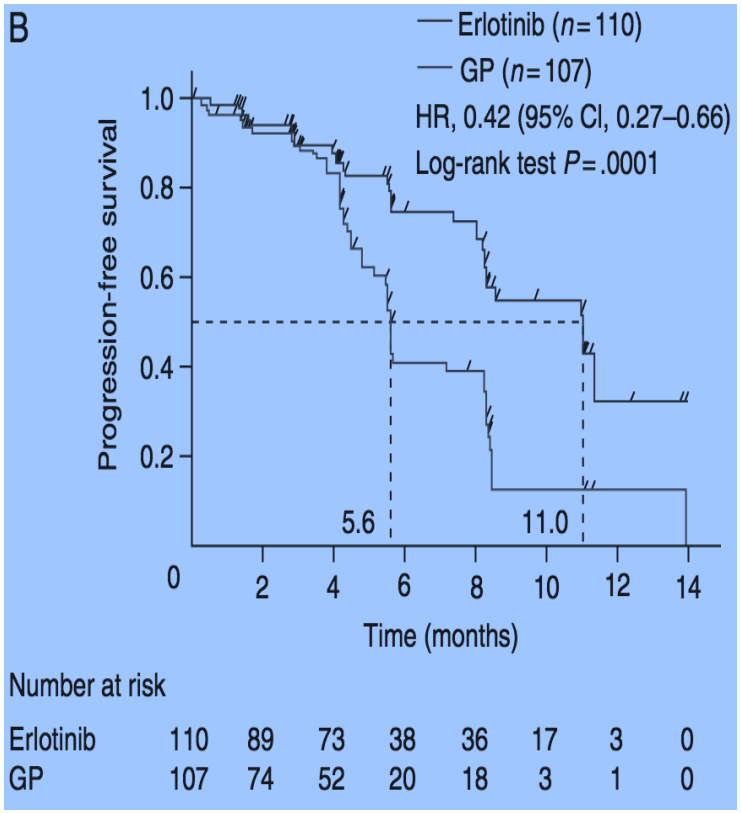
- 66 (76%) chorych z grupy chemioterapii otrzymała po stwierdzeniu progresji TKI EGFR, głównie erlotynib
- OS nie różnił się istotnie między grupą erlotynibu a chemioterapii, odpowiednio 19,3 vs. 19,5 (HR=1,04, p=0,87).



Rosell R, Carcereny E, Gervais R, et al. *Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.* The Lancet Oncology. 2012; 13(3): 239–46

ENSURE

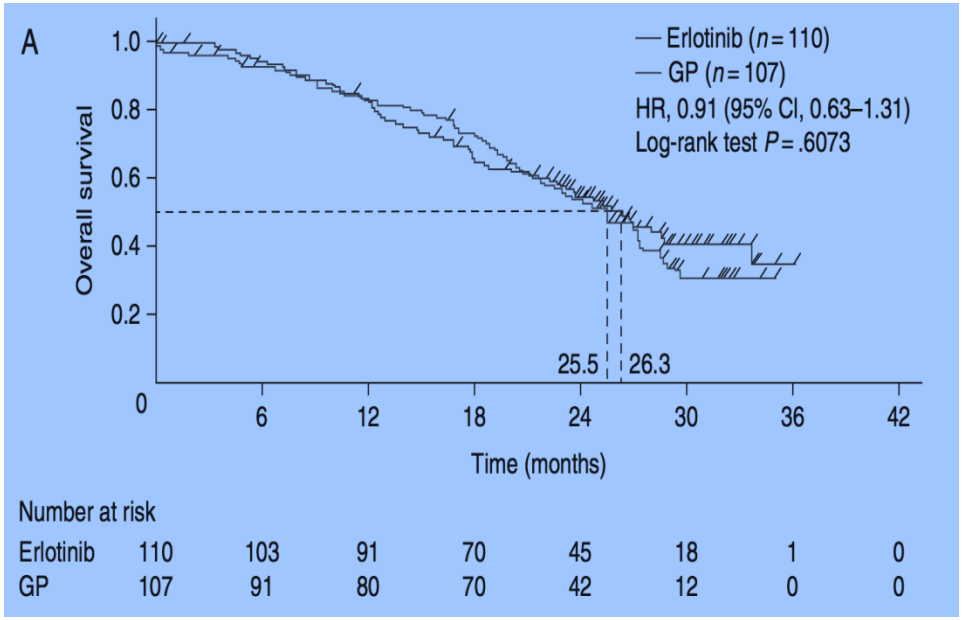
PFS dla erlotynibu 11,0 vs. dla chemioterapii 5,6 miesięcy (HR 0,42, p=0,00001)

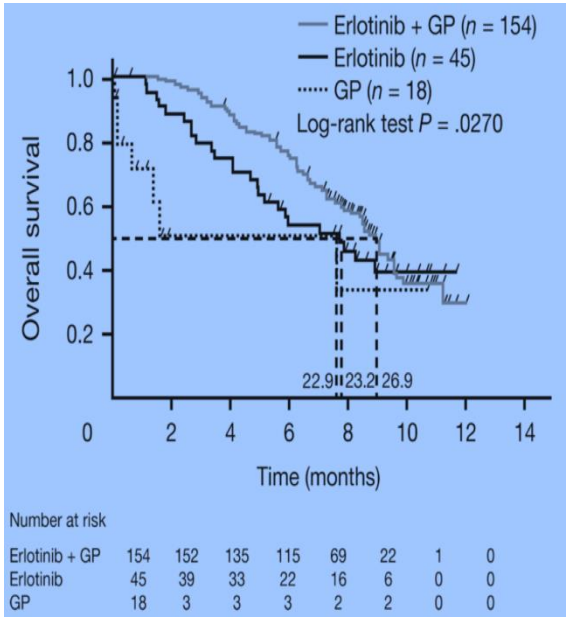


Wu YL, Zhou C, Liam CK, et al. *First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study*. Annals of Oncology. 2015; 26(9): 1883–9

ENSURE

Całkowite przeżycia dla erlotynibu 26,3 vs. dla chemioterapii 25,5 miesięcy (HR 0,91, p=0,607)





Źrodło: Wu YL, Zhou C, Liam CK, et al.

First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Annals of Oncology. 2015; 26(9): 1883–9

OPTIMAL, CTONG-0802

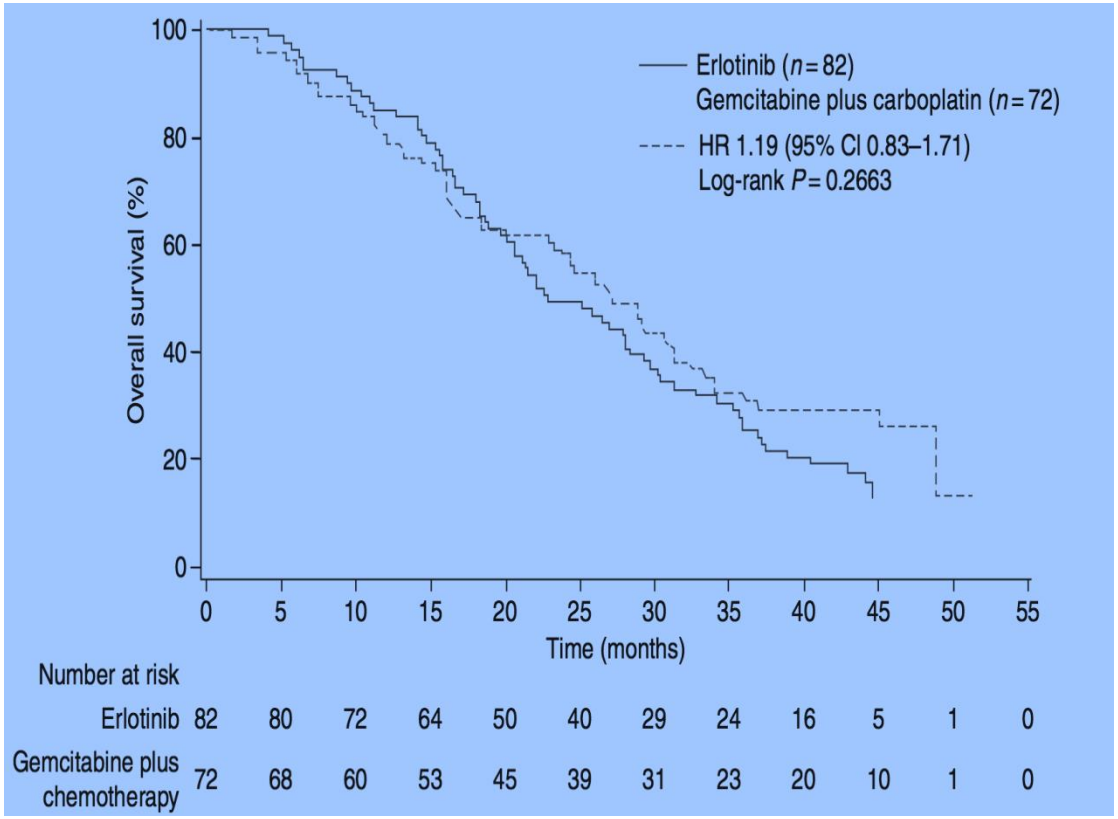
- populacja chińska, IIIB lub IV stopień zaawansowania, potwierdzony dodatni status mutacji EGFR, bez wcześniejszego leczenia systemowego;
- R 1:1 - erlotynib 150mg (82 os.) vs. gemcytabina 1000mg/m2 D1+D8 plus karboplatyna AUC=5 co 21 dni, do 4 kursów (72 os.);
- możliwy *crossover*, zastosowane leczenie po stwierdzeniu progresji było oceniane retrospektywnie.

Treatment, *n* (%)	Overall population	
	Erlotinib (*N* = 82)	G/C (*N* = 72)
None	30 (36.6)	16 (22.2)
Continued first-line study treatment	3 (3.7)	0
Chemotherapy only[a]	29 (35.4)	4 (5.6)
EGFR-TKI only[b]	1 (1.2)	26 (36.1)
Non-EGFR-TKI targeted therapies only[c]	2 (2.4)	0
Chemotherapy[a] + EGFR-TKI[b]	15 (18.3)	22 (30.6)
Chemotherapy[a] + non-EGFR-TKI targeted therapies	4 (4.9)	1 (1.4)
Chemotherapy[a] + non-EGFR-TKI targeted therapies + EGFR-TKI[b]	1 (1.2)	2 (2.8)
Others	0	1 (1.4)

Zhou C, Wu YL, Chen G, et al. *Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802).* Annals of Oncology. 2015; 26(9): 1877–83

OPTIMAL, CTONG-0802

Całkowite przeżycie w ramieniu erlotynibu 22,8 m-ca, w ramieniu chemioterapii GC 27,2, p=0,2663;



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non–Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial

Karen Kelly, Nasser K. Altorki, Wilfried E.E. Eberhardt, Mary E.R. O'Brien, David R. Spigel, Lucio Crinò, Chun-Ming Tsai, Joo-Hang Kim, Eun Kyung Cho, Philip C. Hoffman, Sergey V. Orlov, Piotr Serwatowski, Jiuzhou Wang, Margaret A. Foley, Julie D. Horan, and Frances A. Shepherd

Results

A total of 973 patients were randomly assigned (November 26, 2007, to July 7, 2010). There was no statistically significant difference in DFS (median, 50.5 months for erlotinib and 48.2 months for placebo; hazard ratio, 0.90; 95% CI, 0.74 to 1.10; $P = .324$). Among the 161 patients (16.5%) in the *EGFR*m-positive subgroup, DFS favored erlotinib (median, 46.4 *v* 28.5 months; hazard ratio, 0.61; 95% CI, 0.38 to 0.98; $P = .039$), but this was not statistically significant because of the hierarchical testing procedure. OS data are immature. Rash and diarrhea were common adverse events occurring in 528 (86.4%) and 319 (52.2%) patients treated with erlotinib, respectively, versus 110 (32.1%) and 54 (15.7%) patients receiving placebo. The most common grade 3 adverse events in patients treated with erlotinib were rash (22.3%) and diarrhea (6.2%).

Conclusion

Adjuvant erlotinib did not prolong DFS in patients with *EGFR*-expressing NSCLC or in the *EGFR*m-positive subgroup. Further evaluation of erlotinib is warranted in the *EGFR*m-positive subgroup.

J Clin Oncol 33:4007-4014.

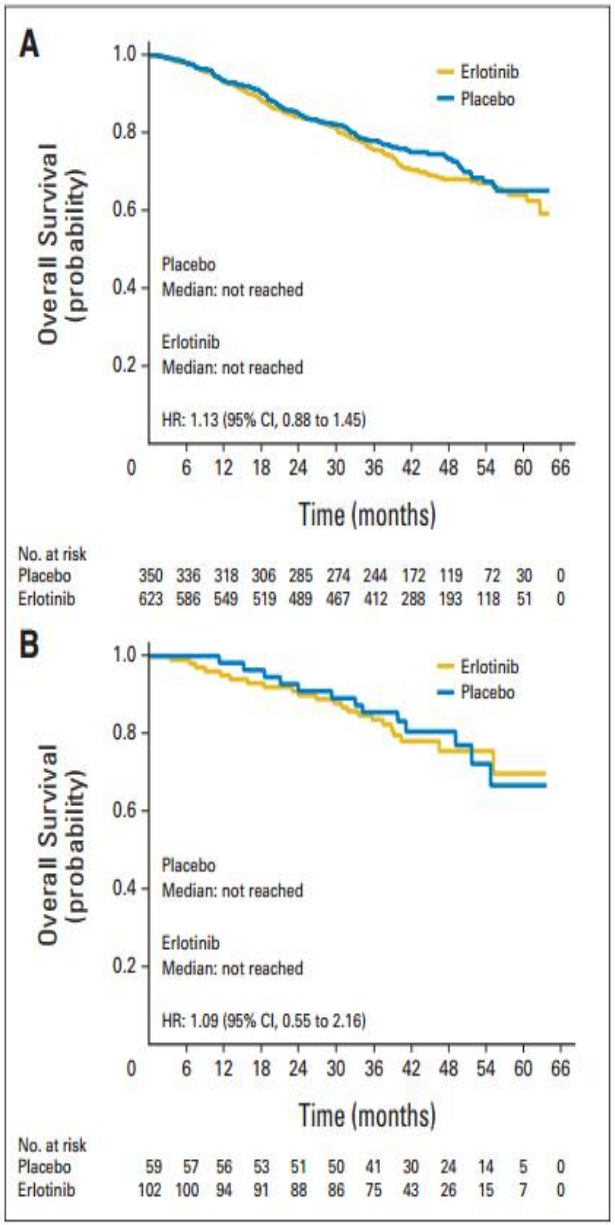

Fig A1. Overall survival in (A) the intent-to-treat population, and (B) the subgroup with epidermal growth factor receptor–activating mutations. HR, hazard ratio.

Respiratory Medicine (2006) 100, 1642–1646

ELSEVIER

respiratoryMEDICINE

Variation in lung cancer survival rates between countries: Do differences in data reporting contribute?

Claire A. Butler[a,b], Karen M. Darragh[a,b], Graeme P. Currie[c], Wendy J.A. Anderson[a,b,*]

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Received 1 October 2005; accepted 11 December 2005

Table 1 Comparison of international lung cancer survival statistics.

Country	Time period	% of population in database	Exclusions from the 5-year survival statistic	5-year relative survival (%)	
				Male	Female
United States	1995–2000	26	Patients without proven histology	Whites 13.7 Black 11.9	Whites 17.4 Blacks 15.4
England and Wales	1996–1999	63	None	6	6
Scotland	1992–1996	100	None	5.7	6
Northern Ireland	1996–1999	100	None	9.5	10.2
Austria	1990–1994	8	None	13.4	16.0
France	1990–1994	3	None	13.1	15.9
Germany	1990–1994	2	None	10.8	10.5
Spain	1990–1994	15	None	12.4	12.8
Denmark	1990–1994	100	None	6.1	5.9

Źródło : Claire A. Butler, Karen M. Darragh, Graeme P. Currie, Wendy J.A. Anderson. Variation in lung cancer survival rates between countries: Do differences in data reporting contribute? Respiratory Medicine, September 2006Volume 100, Issue 9, Pages 1642–1646

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Variation in lung cancer survival rates between countries: Do differences in data reporting contribute?

„The omission of patients without histology in the SEER database is likely to lead to more favourable US survival statistics. Twenty-seven percent of the Northern Ireland population with lung cancer did not have a histological diagnosis and the 5-year survival in this group was 4%, compared to 13.1% for the non-small cell subgroup. Other UK cancer registries do include all cases diagnosed as lung cancer with or without histology. The impact of excluding patients without histology from the data will depend on the rate of histological confirmation within the population. EUROCARE 2 illustrates the varying rates of histological confirmation within Europe and goes on to demonstrate survival differences between patients with the same confirmed histology suggesting that within Europe the interaction between histology and survival is complex."

Źródło : Claire A. Butler, Karen M. Darragh, Graeme P. Currie, Wendy J.A. Anderson. Variation in lung cancer survival rates between countries: Do differences in data reporting contribute? Respiratory Medicine, September 2006Volume 100, Issue 9, Pages 1642–1646

THE LANCET

Articles

Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2)

Claudia Allemani, PhD, Hannah K Weir, PhD, Helena Carreira, MPH, Rhea Harewood, MSc, Devon Spika, MSc, Xiao-Si Wang, PhD, Finian Bannon, PhD, Jane V Ahn, MSc, Christopher J Johnson, MPH, Audrey Bonaventure, MD, Rafael Marcos-Gragera, PhD, Charles Stiller, MSc, Prof Gulnar Azevedo e Silva, MD, Wan-Qing Chen, PhD, Prof Olufemi J Ogunbiyi, FWACP, Bernard Rachet, FFPH, Matthew J Soeberg, PhD, Hui You, MAppStats, Tomohiro Matsuda, PhD, Prof Magdalena Bielska-Lasota, MD, Hans Storm, MD, Prof Thomas C Tucker, PhD, Prof Michel P Coleman, FFPH, the CONCORD Working Group[†]