SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Società Medico Chirurgica di Ferrara

Genere e appropriatezza clinico-diagnostica

PDTA Polmone

Società Medico Chirurgica di Ferrara

Ferrara 24 Settembre 2016

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Premessa

JAMA Surg. 2016 Aug 17. doi: 10.1001/jamasurg.2016.2032. [Epub ahead of print]

Determining If Sex Bias Exists in Human Surgical Clinical Research.

Mansukhani NA[1], Yoon DY[1], Teter KA[1], Stubbs VC[1], Helenowski IB[1], Woodruff TK[2], Kibbe MR[3].

⊕ Author information

Abstract

IMPORTANCE: Sex is a variable that is poorly controlled for in clinical research.

OBJECTIVES: To determine if sex bias exists in human surgical clinical research, to determine if data are reported and analyzed using sex as an independent variable, and to identify specialties in which the greatest and least sex biases exist.

DESIGN, SETTING, AND PARTICIPANTS: For this bibliometric analysis, data were abstracted from 1303 original peer-reviewed articles published from January 1, 2011, through December 31, 2012, in 5 surgery journals.

MAIN OUTCOMES AND MEASURES: Study type, location, number and sex of participants, degree of sex matching of included participants, and inclusion of sex-based reporting, statistical analysis, and discussion of data.

RESULTS: Of 2347 articles reviewed, 1668 (71.1%) included human participants. After excluding 365 articles, 1303 remained: 17 (1.3%) included males only, 41 (3.1%) included females only, 1020 (78.3%) included males and females, and 225 (17.3%) did not document the sex of the participants. Although female participants represent more than 50% (n = 57 688 606) of the total number (115 377 213) included, considerable variability existed with the number of male (46 111 818), female (58 805 665), and unspecified (10 459 730) participants included among the journals, between US domestic and international studies, and between single vs multicenter studies. For articles included in the study, 38.1% (497 of 1303) reported these data by sex, 33.2% (432 of 1303) analyzed these data by sex, and 22.9% (299 of 1303) included a discussion of sex-based results. Sex matching of the included participants in the research overall was poor, with 45.2% (589 of 1303) of the studies matching the inclusion of both sexes by 50%. During analysis of the different surgical specialties, a wide variation in sex-based inclusion, matching, and data reporting existed, with colorectal surgery having the best matching of male and female participants and cardiac surgery having the worst.

CONCLUSIONS AND RELEVANCE: Sex bias exists in human surgical clinical research. Few studies included men and women equally, less than one-third performed data analysis by sex, and there was wide variation in inclusion and matching of the sexes among the specialties and the journals reviewed. Because clinical research is the foundation for evidence-based medicine, it is imperative that this disparity be addressed so that therapies benefit both sexes.

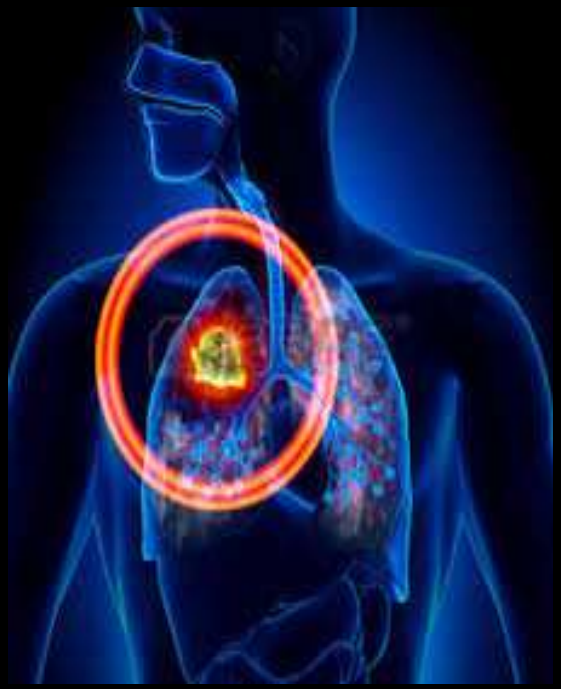
Tumore del polmone non a piccole cellule (NSCLC)

REGISTRO ITALIANO DEI TUMORI 2013

92 NUOVI CASI OGNI 100 000 ABITANTI

NUOVI CASI / ANNO
38 460

- 27 440 UOMINI
- 11 020 DONNE



22 830 DECESSI /ANNO

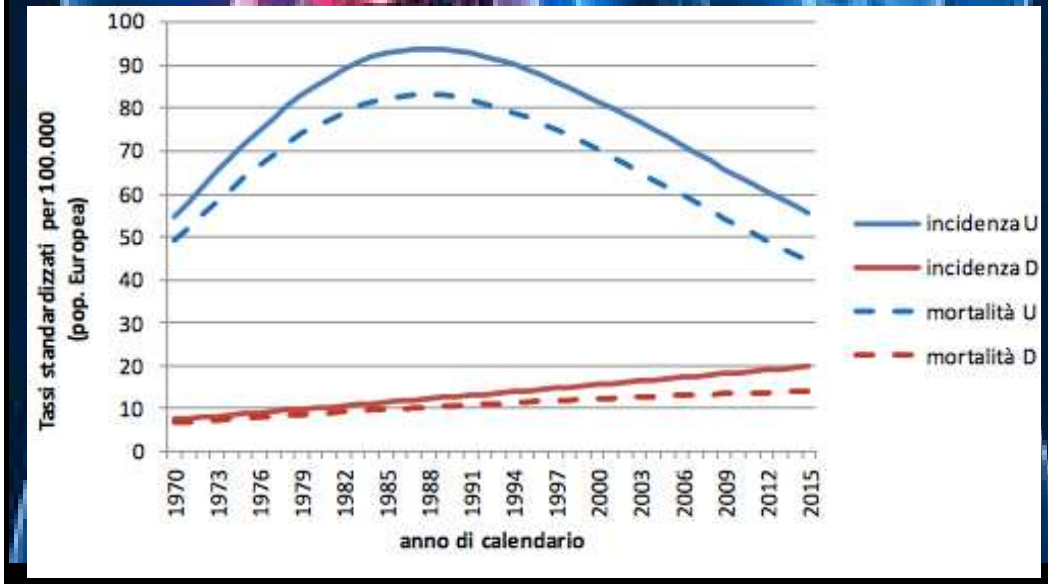
PRIMA CAUSA DI MORTE PER TUMORE

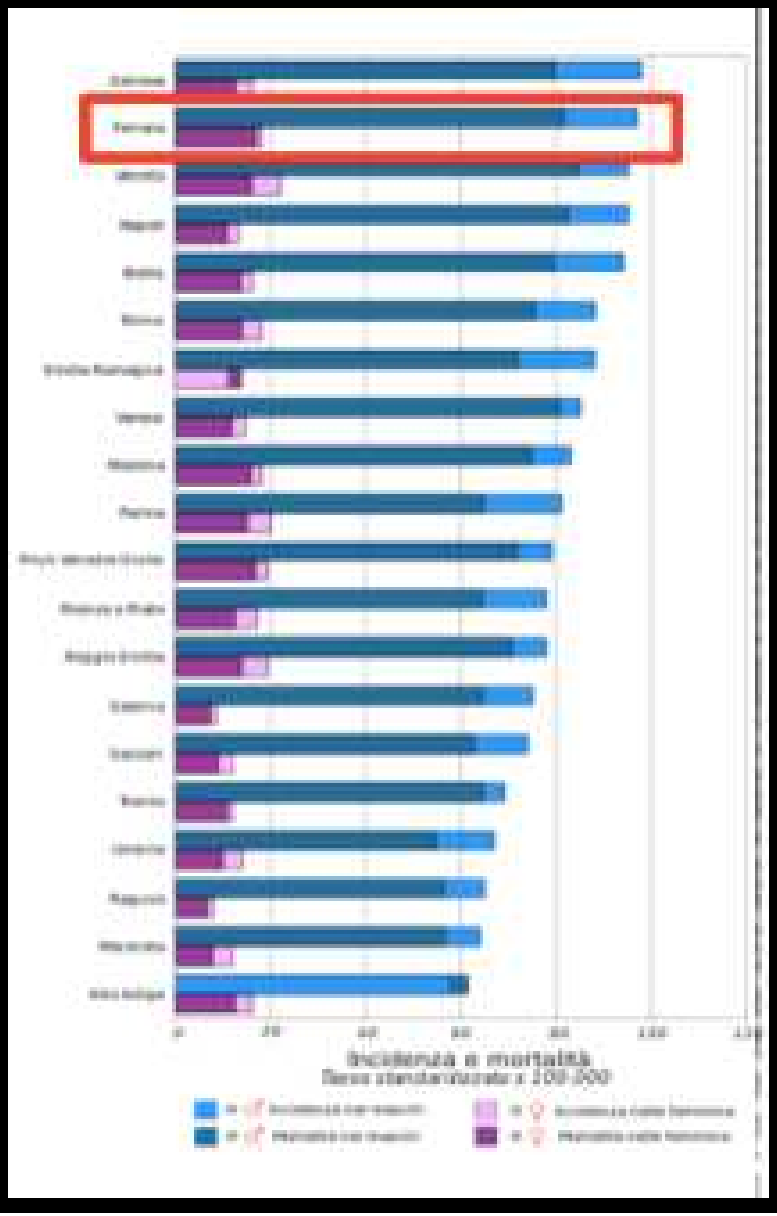
Genere e appropriatezza clinico-diagnostica Società Medico Chirurgica di Ferrara Ferrara 24 Settembre 2016

Tumore del polmone non a piccole cellule (NSCLC)

NELLE DONNE L'INCIDENZA E MORTALITA' SONO IN COSTANTE AUMENTO:

- **INCIDENZA: 2% INCREMENTO ANNUO**
- **MORTALITA': 1% INCREMENTO ANNUO**





Women against lung cancer in Europe (WALCE)

Mutazione EGFR

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

ABSTRACT

BACKGROUND

Most patients with non–small-cell lung cancer have no response to the tyrosine kinase inhibitor gefitinib, which targets the epidermal growth factor receptor (EGFR). However, about 10 percent of patients have a rapid and often dramatic clinical response. The molecular mechanisms underlying sensitivity to gefitinib are unknown.

METHODS

We searched for mutations in the *EGFR* gene in primary tumors from patients with non–small-cell lung cancer who had a response to gefitinib, those who did not have a response, and those who had not been exposed to gefitinib. The functional consequences of identified mutations were evaluated after the mutant proteins were expressed in cultured cells.

RESULTS

Somatic mutations were identified in the tyrosine kinase domain of the *EGFR* gene in eight of nine patients with gefitinib-responsive lung cancer, as compared with none of the seven patients with no response ($P<0.001$). Mutations were either small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain. Similar mutations were detected in tumors from 2 of 25 patients with primary non–small-cell lung cancer who had not been exposed to gefitinib (8 percent). All mutations were heterozygous, and identical mutations were observed in multiple patients, suggesting an additive specific gain of function. In vitro, EGFR mutants demonstrated enhanced tyrosine kinase activity in response to epidermal growth factor and increased sensitivity to inhibition by gefitinib.

CONCLUSIONS

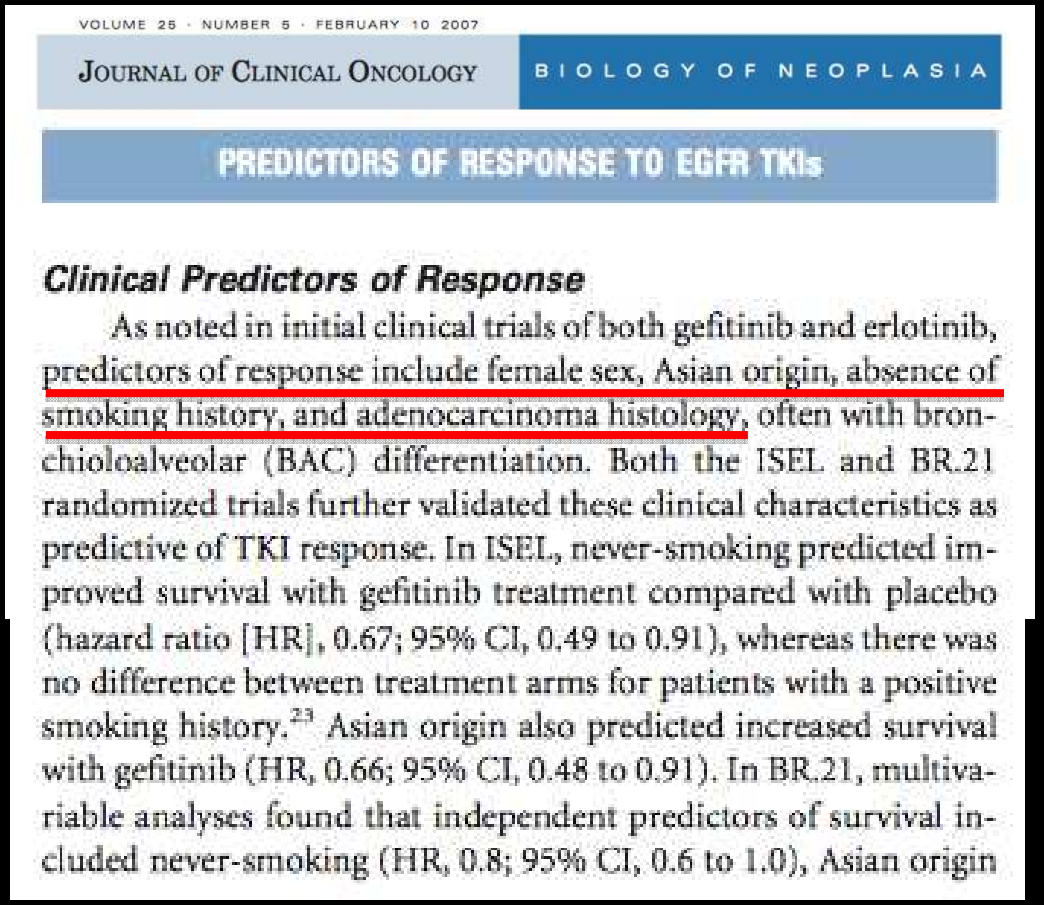
A subgroup of patients with non–small-cell lung cancer have specific mutations in the *EGFR* gene, which correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib. These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify patients who will have a response to gefitinib.

From the Cancer Center (T.J.L., D.W.B., R.S., S.G., R.A.O., B.W.B., P.L.H., S.M.H., J.G.S., F.G.H., D.N.L., D.C.C., J.S., D.A.H.) and the Departments of Medicine (T.J.L., D.W.B., J.G.S., F.G.H., D.C.C., J.S., D.A.H.) and Pathology (D.N.L.), Massachusetts General Hospital and Harvard Medical School; and the Harvard School of Public Health (S.G., D.C.C.) — all in Boston. Address reprint requests to Dr. Haber at MGH Cancer Center, Bldg. 149, 13th St., Charlestown, MA 02129, or at haber@helix.mgh.harvard.edu.

Drs. Lynch, Bell, and Sordella contributed equally to the article.

This article was published at www.nejm.org on April 29, 2004.

N Engl J Med 2004;350:2129-39.



VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

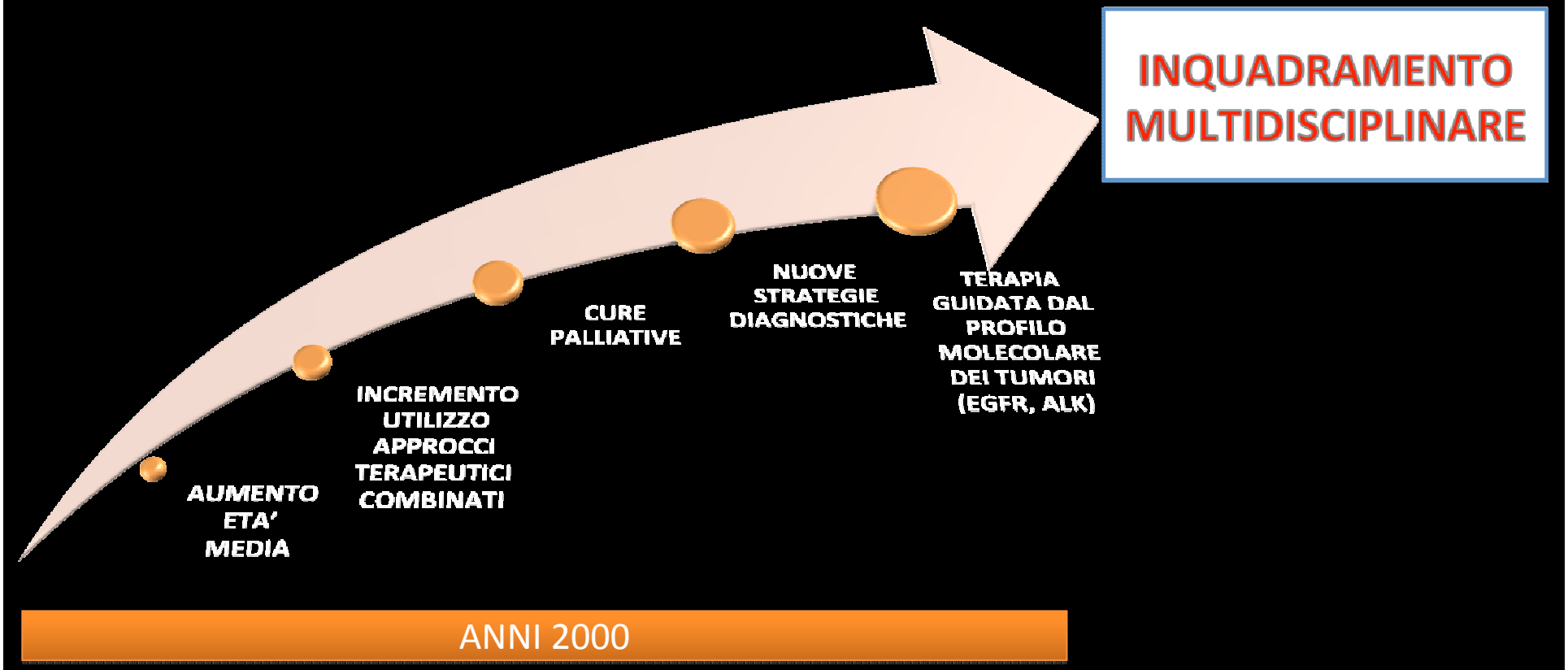
JOURNAL OF CLINICAL ONCOLOGY BIOLOGY OF NEOPLASIA

PREDICTORS OF RESPONSE TO EGFR TKIs

Clinical Predictors of Response

As noted in initial clinical trials of both gefitinib and erlotinib, predictors of response include female sex, Asian origin, absence of smoking history, and adenocarcinoma histology, often with bronchioloalveolar (BAC) differentiation. Both the ISEL and BR.21 randomized trials further validated these clinical characteristics as predictive of TKI response. In ISEL, never-smoking predicted improved survival with gefitinib treatment compared with placebo (hazard ratio [HR], 0.67; 95% CI, 0.49 to 0.91), whereas there was no difference between treatment arms for patients with a positive smoking history.[23] Asian origin also predicted increased survival with gefitinib (HR, 0.66; 95% CI, 0.48 to 0.91). In BR.21, multivariable analyses found that independent predictors of survival included never-smoking (HR, 0.8; 95% CI, 0.6 to 1.0), Asian origin

Evoluzione nella gestione del paziente oncologico



Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561–6.
Pfeiffer SI, Naglieri JA. An investigation of multidisciplinary team decision-making. J Learn Disabil 1983;16:588–90.

Percorso diagnostico terapeutico assistenziale (PDTA)

" PIANO MULTIDISCIPLINARE E MULTIPROFESSIONALE, COSTRUITO A LIVELLO LOCALE SULLA BASE DI RACCOMANDAZIONI RICONOSCIUTE, AL FINE PROGRAMMARE UN PERCORSO DI CURA A PAZIENTI AFFETTI DA SPECIFICA CONDIZIONE MORBOSA, DEFINENDO LA MIGLIORE SEQUENZA TEMPORALE E SPAZIALE POSSIBILE DELLE ATTIVITÀ DIAGNOSTICHE, TERAPEUTICHE ED ASSISTENZIALI DA SVOLGERE AL FINE DI RAGGIUNGERE OBIETTIVI DI SALUTE, DEFINITI A PRIORI, CON UN'EFFICIENZA ED UN'EFFICACIA OTTIMALI."

CORE TEAM

CHIRURGO

ANATOMO PATOLOGO

PNEUMOLOGO

MEDICO NUCLEARE

PAZIENTE

RADIOTERAPISTA

RADIOLOGO

NURSE CASE MANAGER

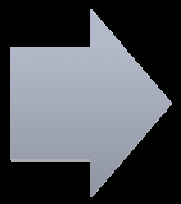
ONCOLOGO

EXTENDED TEAM

Cambiamento nella gestione del paziente oncologico

GESTIONE DEL PAZIENTE DEL SINGOLO SPECIALISTA

- RITARDO NELL'INIZIO DEL TRATTAMENTO
- VARIETA' DEI TRATTAMENTI OFFERTI
- RIDOTTO TASSO DI STAGING INVASIVO
- FALLIMENTO NELL'OFFRIRE UN PERCORSO TERAPEUTICO PER GLI ANZIANI CON BUON PERFORMANCE STATUS

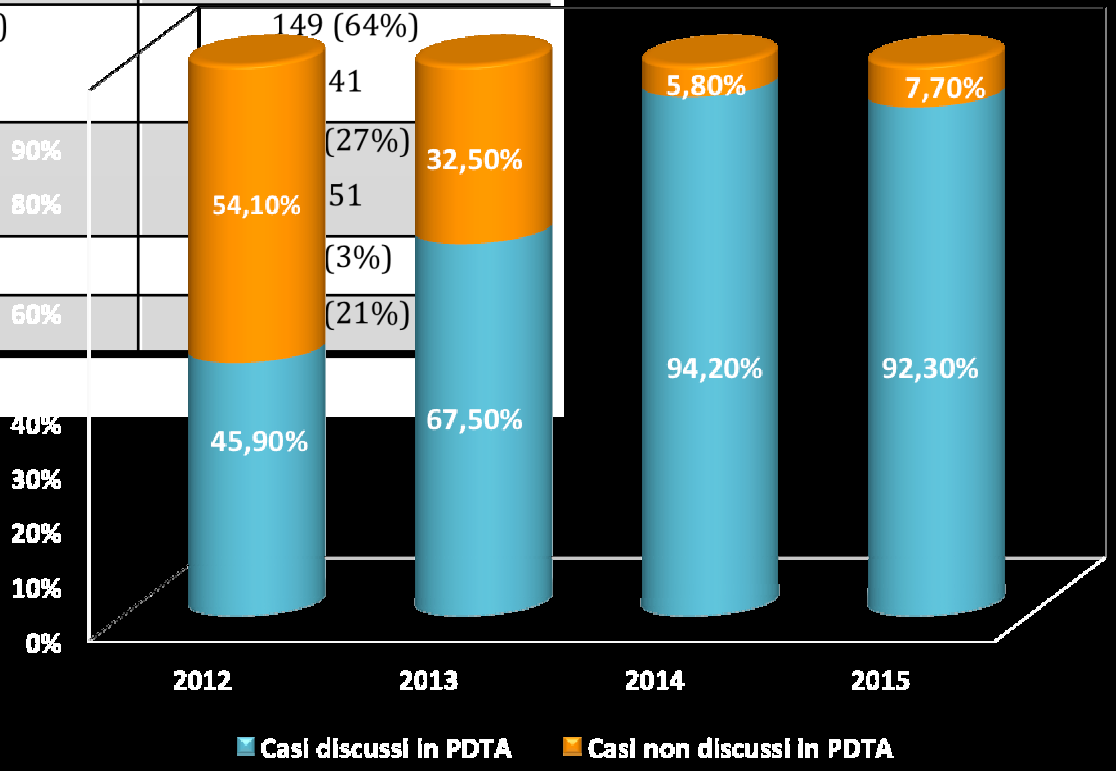


GESTIONE MULTIDISCIPLINARE DEL PAZIENTE

- MIGLIORAMENTO DELLA COMUNICAZIONE TRA SPECIALISTI
- SVILUPPO PIANI TERAPEUTICI EVIDENCE BASED
- RIDUZIONE LISTE DI ATTESA
- EVITARE ACCERTAMENTI NON NECESSARI

Outcome prima e dopo istituzione PDTA Ferrara

	PRIMA DEL 2012	DOPO IL 2012
Numero totale	246	231
Sesso femminile	57 (23%)	71 (31%)
Sesso maschile	189 (77%)	160 (69%)
Età media	69 (42 ÷ 83)	69 (45 ÷ 83)
Mai fumato	15 (6%)	21 (9%)
Ex-fumatori	159 (64%)	149 (64%)
• P-Y ex-fumatori	36,2	41
Fumatori	72 (30%)	(27%)
• P-Y fumatori	44	51
Abuso alcolico	15 (6%)	(3%)
BPCO	53 (21%)	(21%)

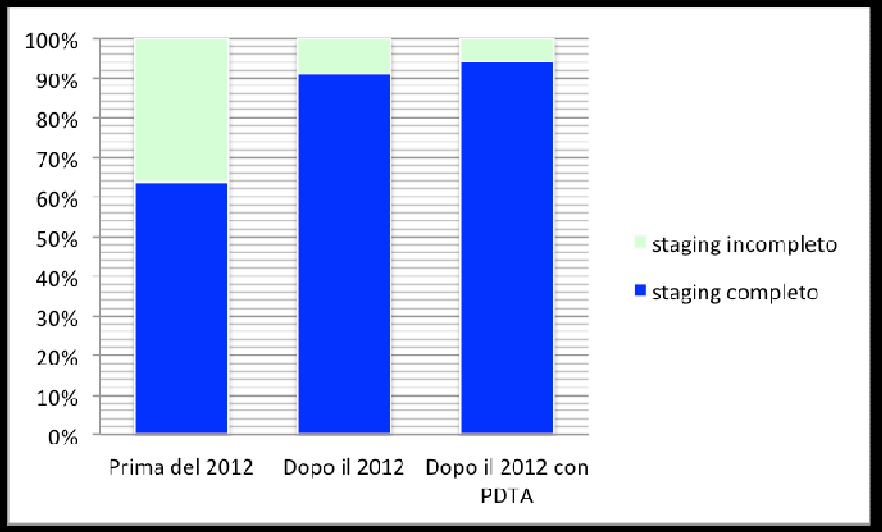


Outcome prima e dopo istituzione PDTA Ferrara
STADIAZIONE

STADIO	PRIMA DEL 2012	DOPO IL 2012
I	120 (49%)	155 (67%)
II	65 (26%)	37 (16%)
III	52 (21%)	38 (16%)
IV	9 (4%)	3 (1%)

	PRIMA DEL 2012	DOPO IL 2012	p	DOPO IL 2012 CON PDTA	p
STADI PRECOCI (I E II)	185 (75%)	192 (83%)	< 0,01	159 (86%)	0,012
STADI AVANZATI (III E IV)	61 (24,8%)	41 (17,7%)	-	27 (14%)	-

Outcome prima e dopo istituzione PDTA Ferrara



	Prima del 2012 (n=246)	Dopo il 2012 (n=231)	Dopo il 2012 con PDTA (n=185)	p
Diagnosi pre-operatoria	138 (56,1%)	124 (53,7%)	106 (57%)	n.s
Toracotomia esplorativa	8 (3,3%)	4 (1,7%)	3 (1,6%)	n.s
Indagine invasiva su N2 PET +	3 (1,2%)	3 (1,3%)	2 (1,1%)	n.s
Resezione completa	228 (92,7%)	221 (95,7%)	176 (94,6%)	n.s
Complicanze post-operatorie	104 (42,3%)	85 (36,8%)	73 (39,2%)	n.s
Mortalità post-operatoria	6 (2,4%)	4 (1,7)	2 (1,1%)	n.s

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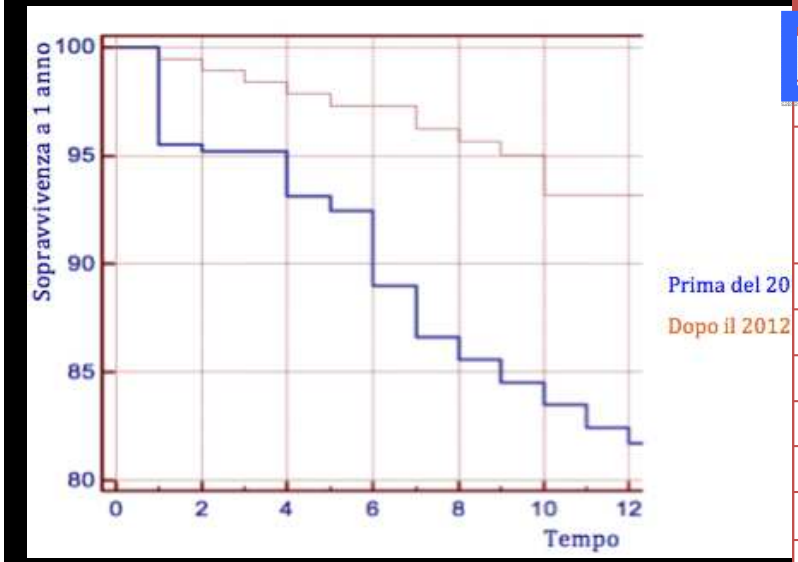
Outcome prima e dopo istituzione PDTA Ferrara



	Vivi (n=407)	Deceduti (n=70)	p
Sesso M	290 (71,3%)	59 (84,3%)	0,023
Fumo			
• **Attuale**	112 (27,5%)	20 (28,6%)	n.s.
• **Ex**	259 (63,6%)	49 (70,0%)	
Pack-years	35	40	0,146
Alcolismo	17 (3,7%)	6 (8,6%)	n.s.
Discussione PDTA	172 (42,3%)	14 (20,0%)	<0,001
Staging completo	319 (78,4%)	47 (67,1%)	0,04
ECOG > 0	34 (8,4%)	13 (18,6%)	0,008
Diagnosi pre-operatoria	219 (53,8%)	43 (61,4%)	n.s.
BPCO	85 (20,9%)	16 (22,9%)	n.s.
Charlson Index	4,7 ± 1,7	5,3 ± 1,5	0,002
Stadi avanzati	67 (16,5%)	34 (48,6%)	<0,001
Neoadiuvante	24 (5,9%)	10 (14,3%)	0,021
Istologia			
• **Adenocarcinoma**	265 (65,1%)	35 (50,0%)	<0,001
• **Ca Squamocellulare**	125 (30,7%)	24 (34,3%)	
Pneumectomia	13 (3,2%)	3 (4,3%)	n.s.
Toracotomia esplorativa	5 (1,2 %)	7 (10,0 %)	<0,001
Resezione completa	389 (95,6%)	59 (84,3%)	<0,001
Complicanze post-operatorie	152 (37,4%)	37 (52,9)	n.s.
Giorni di degenza	6 [4 ÷ 7]	6 [4 ÷ 9]	n.s.

Conclusioni

L'INTEGRAZIONE MULTIPROFESSIONALE COSTITUISCE ELEMENTO FONDAMENTALE DEL PROGETTO E CONSENTE UNA COMPLETA FOCALIZZAZIONE SUL PAZIENTE.

LA GESTIONE MULTIDICIPLINARE FAVORISCE UNA ADEGUATA CONSIDERAZIONE DELLE DIFFERENZE DI GENERE NELLE DIAGNOSI E TERAPIA DEL TUMORE DEL POLMONE

Chirurgia Toracica al femminile

GRAZIE PER L'ATTENZIONE