Il ruolo dell'oncologo radioterapista nella ricerca con farmaci innovativi

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Spunti per la discussione

1. *Rilevanza del problema*

2. *La ricerca in «chemioterapia» , i suoi risultati e il suo finanziamento: pratiche, costi, sostenibilità, equità.. Quali differenze con la ricerca in «radioterapia»?*

1. Rilevanza del problema

American Cancer Society

JOIN THE FIGHT AGAINST CANCER

The Global Cancer Burden

Cancer causes 1 in 8 deaths worldwide and is rapidly becoming a global pandemic. According to the International Agency for Research on Cancer, there were 14.1 million new cancer cases and 8.2 million cancer deaths in 2012. If rates don't change, the global cancer burden is expected to increase to 21.7 million cases and 13 million deaths by 2030. According to the World Health Organization (WHO), the toll of cancer and other chronic diseases is greater in low- and middle-income countries, where people develop chronic diseases "at younger ages, suffer longer – often with preventable complications – and die sooner

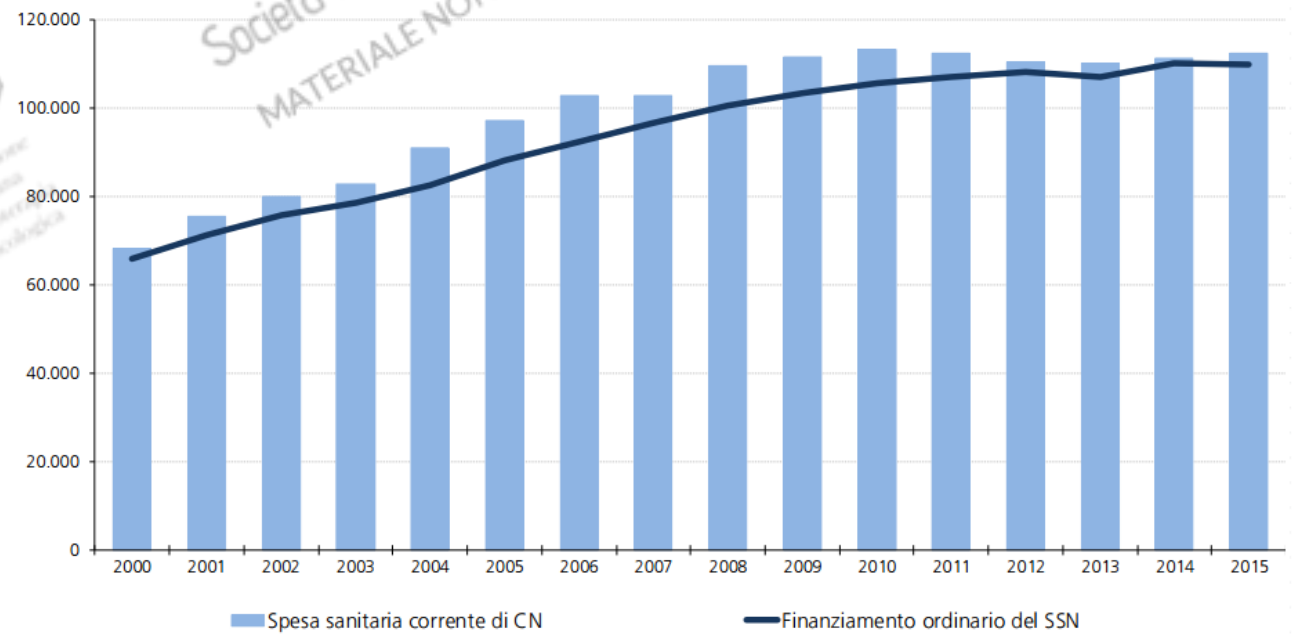
MEF Ragioneria Generale dello Stato

MINISTERO DELL'ECONOMIA E DELLE FINANZE
DIPARTIMENTO DELLA RAGIONERIA GENERALE DELLO STATO

IL MONITORAGGIO DELLA SPESA SANITARIA

Roma, agosto 2016

Fig. 2.3: spesa sanitaria corrente di CN e finanziamento ordinario del SSN - Anni 2000-2015 *(valori assoluti in milioni di euro)*



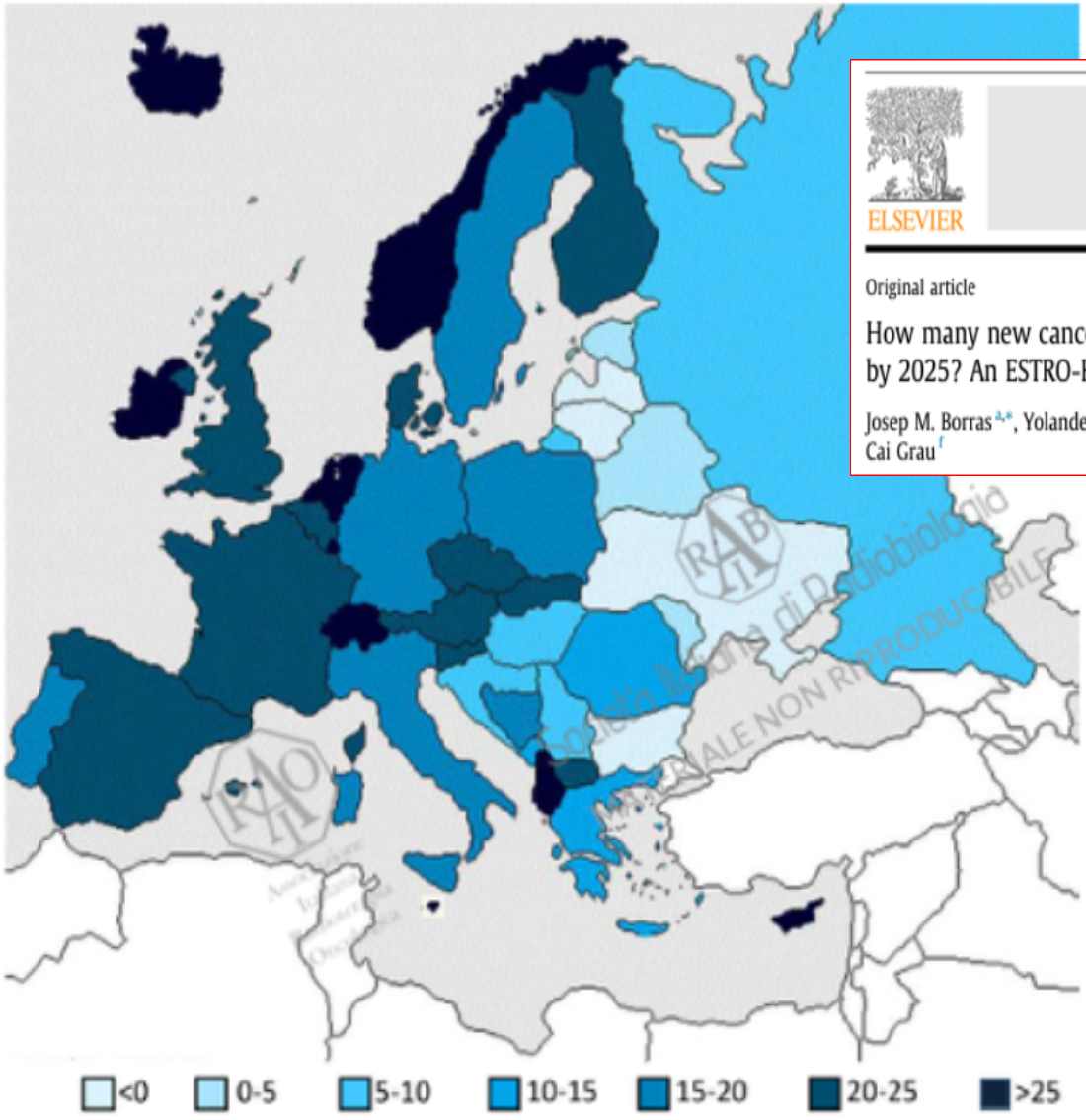


Fig. 1. Increase in new cancer patients that would require radiotherapy by 2025 by country (%).

Contents lists available at ScienceDirect

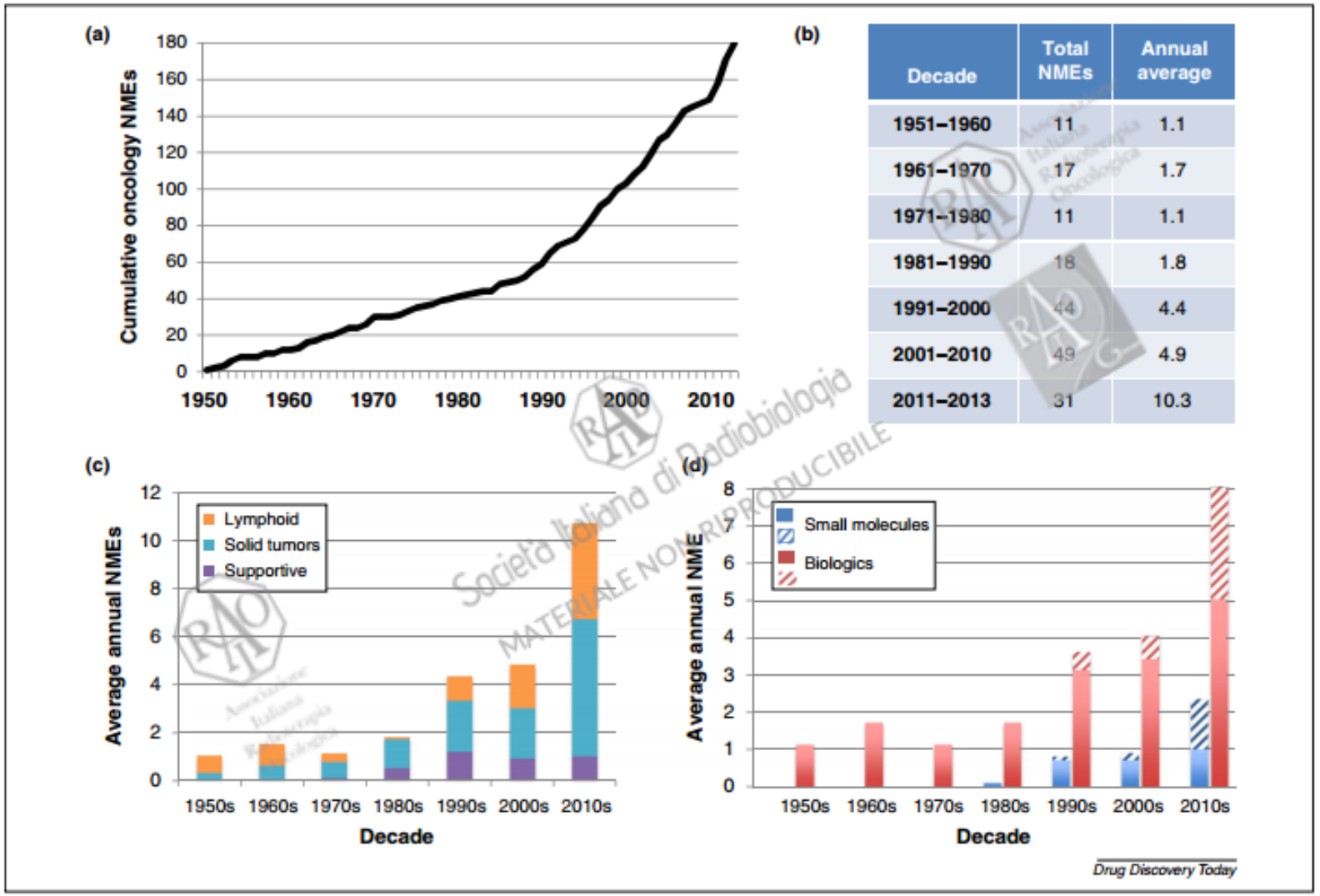
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis

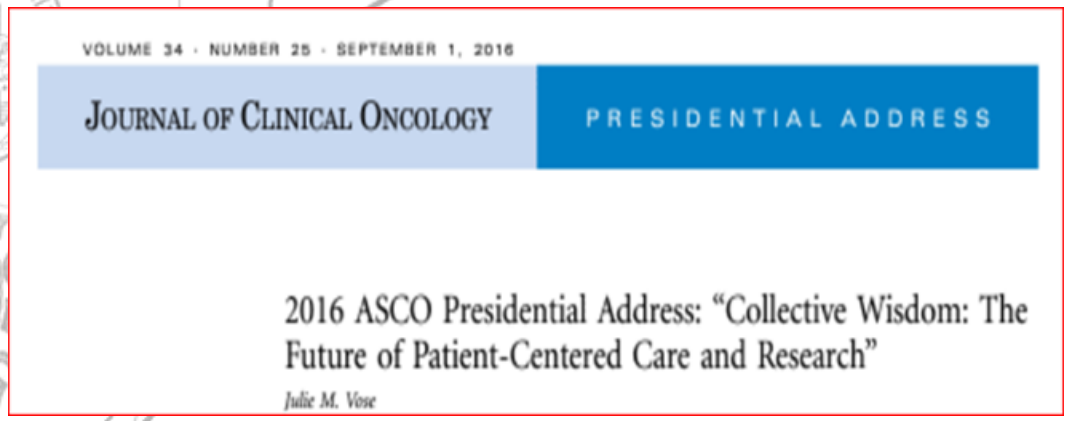
Josep M. Borras[a,*], Yolande Lievens[b], Michael Barton[c], Julieta Corral[d], Jacques Ferlay[e], Freddie Bray[e], Cai Grau[f]



Decade	Total NMEs	Annual average
1951–1960	11	1.1
1961–1970	17	1.7
1971–1980	11	1.1
1981–1990	18	1.8
1991–2000	44	4.4
2001–2010	49	4.9
2011–2013	31	10.3

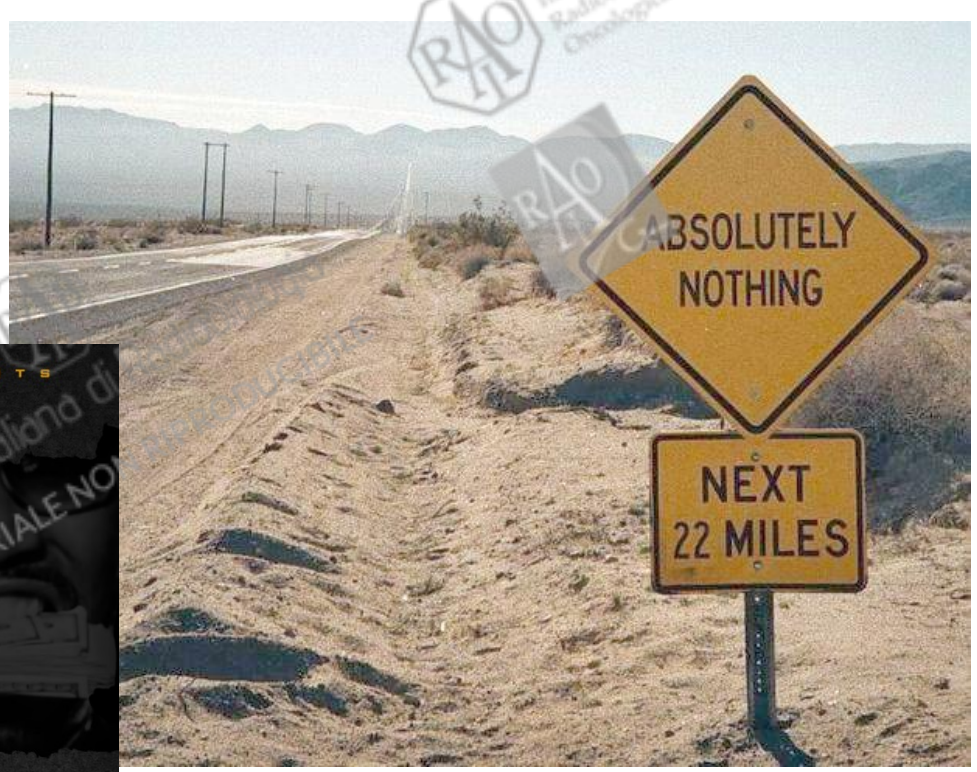
FIGURE 1

Growth of the anticancer arsenal. **(a)** The cumulative number of new molecular entities targeting oncology for their initial approval from FDA is shown over time. **(b)** NME approval rates were compared on a decade-by-decade basis. **(c)** An evaluation of major categories reveals lymphoid tumors were initially emphasized by new drugs for until the 1970s, when an increasing number of NMEs targeting solid tumors and drugs providing supportive care were introduced. **(d)** The absolute and relative growth of small-molecule- and biologics-based drugs are shown. The striped lines indicate NMEs initially approved as an orphan drug.



« Price is what you pay, but value is what you get. If we face a cancer tsunami, if globally there will soon be more than 20 million new cancer diagnoses each year, then our focus must be not on simply more treatments but on delivering more high-value quality care.»

2. La ricerca in «chemioterapia» , i suoi risultati e il suo finanziamento: pratiche, costi, sostenibilità, equità.. Quali differenze con la ricerca in «radioterapia»?



LE *DOMANDE* CUI LA RICERCA CONDOTTA DALL'ONCOLOGO CLINICO (RADIOTERAPISTA, CHIRURGO, CHEMIOTERAPISTA) CERCA RISPOSTE SONO *SEMPRE LE STESSE*….

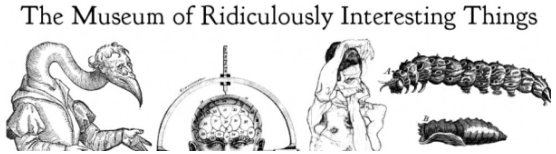
(IN ORDINE *GERARCHICO* DI INTERESSE *PER IL PAZIENTE*):

1. FUNZIONA ? (FARMACO, RADIOTERAPIA, CHIRURGIA)

2. QUALE FUNZIONA MEGLIO (COMBINAZIONI INCLUSE)?

3. QUALE MODALITA' TECNICA – APPLICATIVA FUNZIONA MEGLIO?

(*TIPO DI SOMMINISTRAZIONE DEL FARMACO, SOTTOTIPO DI FARMACO DI UNA DATA CLASSE, TECNICA E APPARECCHIATURA PER RADIOTERAPIA, TECNICA DI ESECUZIONE DELL'INTERVENTO O LORO COMBINAZIONI*)



I *METODI* DELLA RICERCA CONDOTTA DALL'ONCOLOGO CLINICO (RADIOTERAPISTA, CHIRURGO, CHEMIOTERAPISTA) *SONO SOSTANZIALMENTE GLI STESSI* E DEBBONO ESSERE UGUALMENTE RIGOROSI

CONSENSUS STATEMENT

OPEN

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma[1], Ruth Plummer[2], Julie K. Stock[3], Tessa A. Greenhalgh[4], Ozlem Ataman[5], Stephen Kelly[6], Robert Clay[7], Richard A. Adams[8], Richard D. Baird[9], Lucinda Billingham[10], Sarah R. Brown[11], Sean Buckland[6], Helen Bulbeck[12], Anthony J. Chalmers[13], Glen Clack[14], Aaron N. Cranston[15], Lars Damstrup[16], Roberta Ferraldeschi[17], Martin D. Forster[1], Julian Golec[18], Russell M. Hagan[19], Emma Hall[20], Axel-R. Hanauske[21], Kevin J. Harrington[20], Tom Haswell[12], Maria A. Hawkins[4], Tim Illidge[22], Hazel Jones[3], Andrew S. Kennedy[23], Fiona McDonald[20], Thorsten Melcher[24], James P. B. O'Connor[22], John R. Pollard[18], Mark P. Saunders[22], David Sebag-Montefiore[11], Melanie Smitt[25], John Staffurth[8], Ian J. Stratford[22] and Stephen R. Wedge[2] on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

Box 1 | Consensus statements

1. Drug–radiotherapy combinations
Approximately, 4 out of 10 patients with cancer who are cured by treatment receive radiotherapy. Combining novel drugs with radiotherapy has clear potential to significantly improve patient outcomes. When companies are considering testing a novel combination for an agent, they should consider drug–radiotherapy combinations as important as drug–drug combinations. Collaborative groups involving academia and pharmaceutical companies should prioritise the evaluation of appropriate novel drug–radiotherapy combinations early in the clinical development plan of a drug to potentially improve response and survival rates. Proposed combinations should have a sound scientific basis in radiobiology, immuno-oncology, molecular biology and pharmacology.

2. Route to registration
Currently, there are no published guidelines on how to design studies using novel drug–radiotherapy combinations and there is limited guidance on regulatory aspects. In the absence of specific guidance, drug–radiotherapy combinations should be viewed as similar in concept to novel drug–drug combinations. There should be a strong scientific rationale for the combination based on an understanding of mechanisms of action and a clear line of sight to registration for the combination, based on clinical need.

3. Clinical end points
Early communication between regulators and researchers with regard to the most meaningful clinical end point(s) for a specific tumour site and patient population will accelerate development of novel combination therapies. Inclusion of clinically relevant early and intermediate end points will accelerate clinical development by generating compelling data in a timely and cost-effective manner. Regulators should recognize that end points must be pragmatic, relevant to patients and applicable in a 'real world' setting, and should reflect (i) the important clinical benefits of durable locoregional control, and (ii) the balance of effects on tumour control and normal tissue toxicity. Composite or co-primary end points might be necessary or advantageous. Secondary end points should usually include assessment of effects on normal tissues.

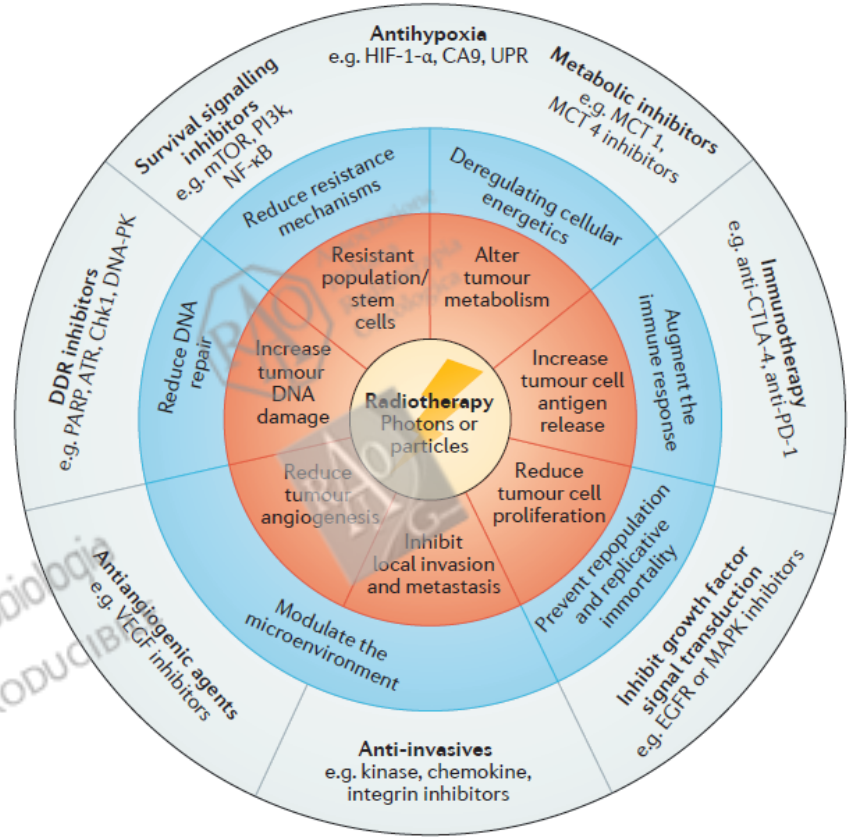
4. Changing the standard of care
The treatment intent and the current standard of care for each disease being treated must be defined by the investigators, including any potential variation across countries. Potential changes in the standard of care must be predicted by clinical experts if the path to registration is to succeed.

5. Clinical trial methodology
Radiotherapy–combination research requires use of appropriate trial designs and robust statistical strategies based on appropriate end points at each stage in the development plan. Studies that take advantage of gaps between planning and starting radiotherapy, or between radiotherapy and surgery, are opportunities for early-phase trials and related pharmacokinetic, pharmacodynamic and imaging studies.

6. Radiotherapy quality assurance
Quality assured radiotherapy is critical to the success of drug-radiotherapy studies. The components include detailed development of the protocol resulting in a transparent description of the chosen technique. Target volume definition and the minimization of irradiation to surrounding normal tissues must be described. Pretrial and trial-specific review of radiotherapy treatment planning and treatment delivery is essential and should be determined for each study.

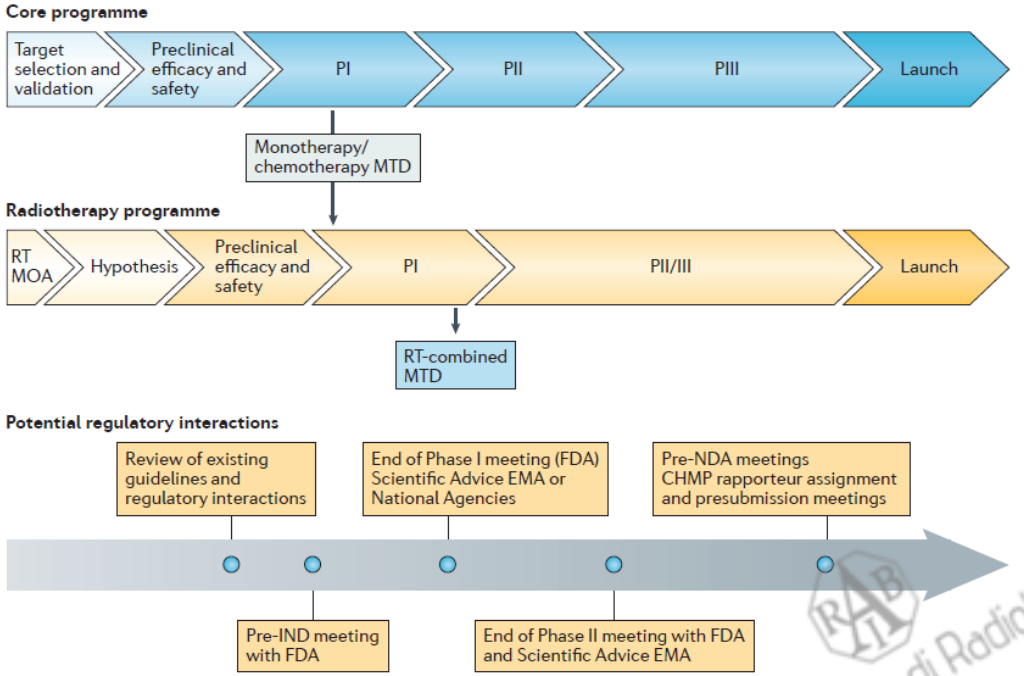
7. Preclinical dataset and target population
Similar to novel drug–drug combinations, a standard for a minimum preclinical dataset for justifying early-phase clinical development of a new drug–radiotherapy combination does not currently exist. However, it is recommended that the dataset should address four considerations: i) demonstrate that the novel drug improves the efficacy of radiotherapy in clinically relevant models; ii) define an effective dose schedule; iii) provide an assessment of normal tissue toxicity for the drug–radiotherapy combination to identify potential clinical risks; and iv) identify potential responsive patient subpopulations and the associated candidate biomarkers.

8. Patient and consumer involvement and raising awareness
Patients and consumer groups should be involved from the concept stage onwards for a clearer understanding of patient priorities and what will be considered acceptable by patients who may or may not wish to participate in a clinical trial. Efforts to raise public awareness of the efficacy of radiotherapy and drug–radiotherapy combinations should include clear statements of the potential benefits of the research to improve cancer treatment.



- **Concomitant**
- **Sequential**
- **«Window of opportunity»**

Per la cortesia: Elvio Russi e Anna Merlotti



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PRIME: priority medicines

PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

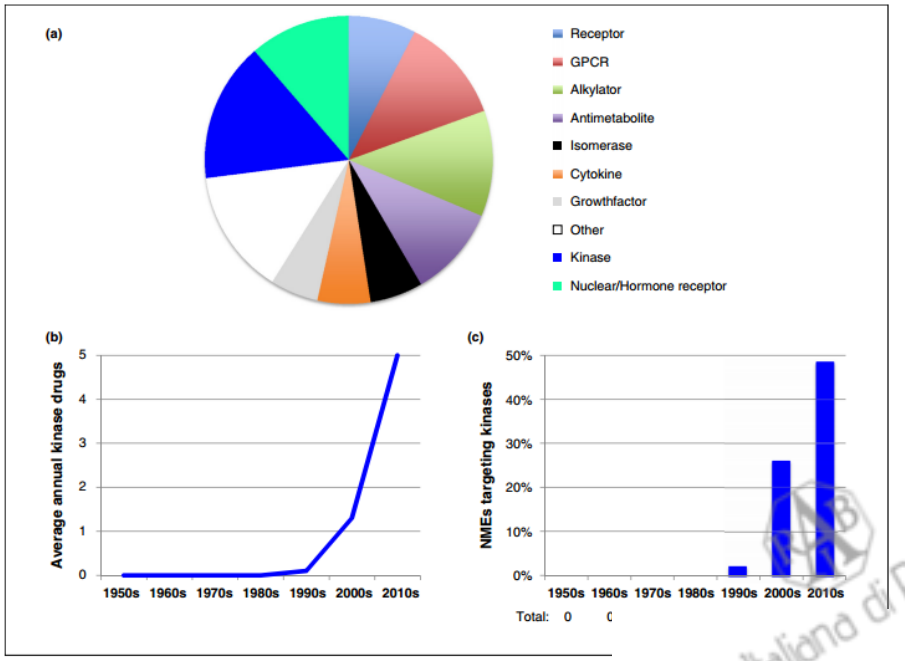


FIGURE 3

Mechanistic analysis of new cancer drugs. **(a)** The target type or mechanistic basis for each FDA-approved cance categories. The relatively recent emergence of cancer drugs targeting kinases is shown in absolute terms **(b)** an that decade **(c)**.

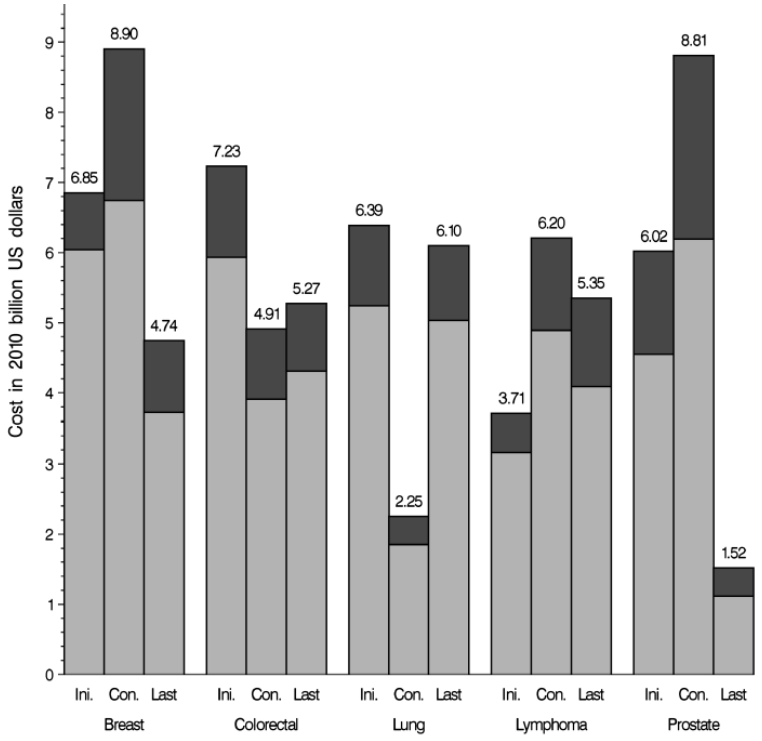
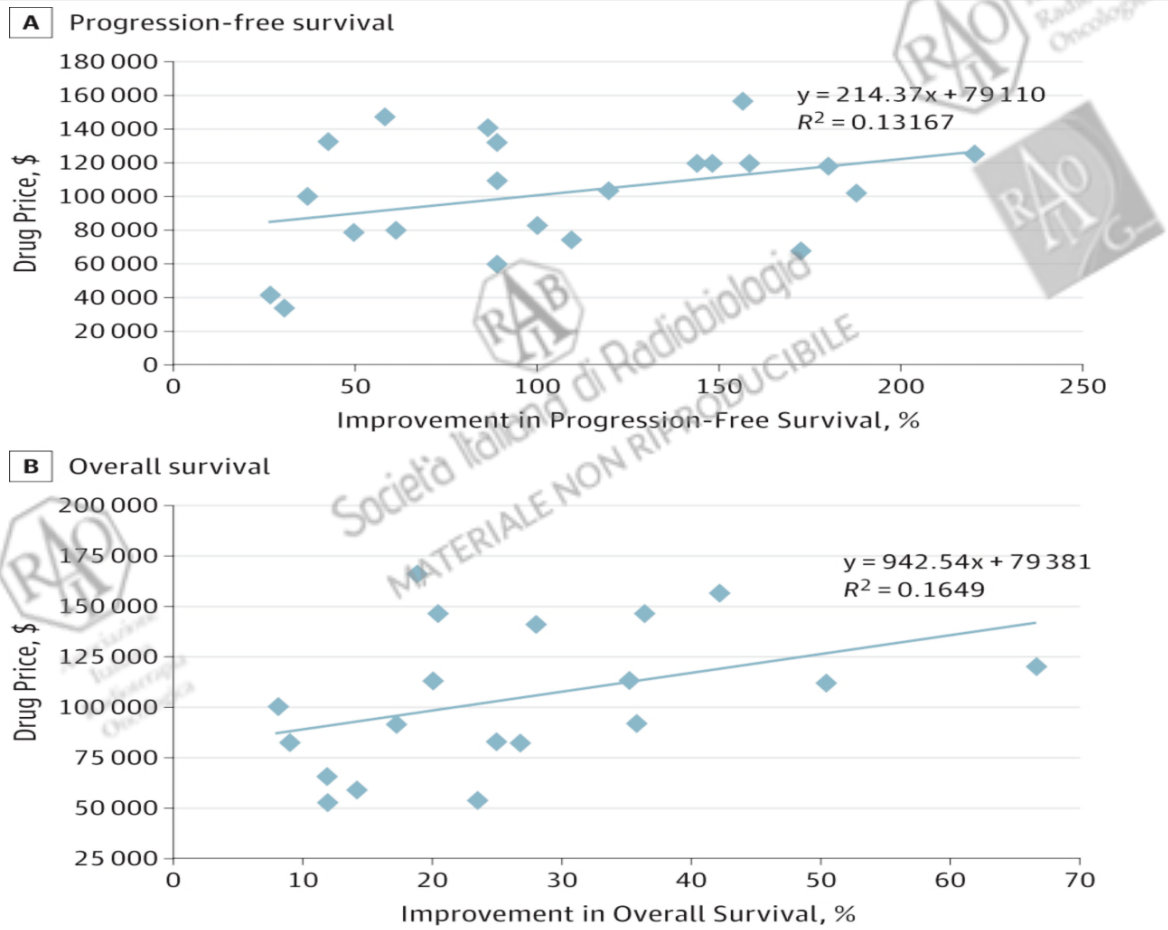


Figure 3. Estimates of the national expenditures for cancer care in 2010 (**light gray areas**) and the estimated increase in cost in 2020 (**dark gray areas**) because of the aging and growth of the US population under assumptions of constant incidence survival and cost for the major cancer sites. Costs in 2010 billion US dollars by phase of care: initial year after diagnosis (Ini.) continuing care (Con.) and last year of life (Last).

J Natl Cancer Inst 2011;103:117–128

From: **Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs**

JAMA Oncol. 2015;1(4):539-540. doi:10.1001/jamaoncol.2015.0373



Linear Regression Analysis of Drug Price vs Percentage Improvement in Survival. Each point on the graphs represents 1 drug.

Percentuali e valori assoluti.....

Table. La… …s Approved Between 2009 and 2013 by the US Food and Drug Administration

…on	Cost per Year of Treatment, $[a]	Parent Drug	Mechanism of Action	Clinical Benefit
…b for papillary thyroid cancer	140 984	NA	First approved VEGFR and RAS tyrosine kinase inhibitor	Median PFS, 10.8 vs 5.8 mo
Crizotinib for non-small-cell lung cancer	156 544	NA	Anaplastic lymphoma kinase inhibitor	Median PFS, 7.7 vs 3.0 mo
Ibrutinib for mantle cell lymphoma	157 440	NA	Bruton tyrosine kinase inhibitor	RR, 66%; median DOR, 17.5 mo
Obinutuzumab for chronic lymphocytic leukemia	74 304	Rituximab	Anti-CD20 monoclonal antibody	Median PFS, 23.0 vs 11.1 mo
Pertuzumab for breast cancer	78 252	Trastuzumab	Anti-her2 monoclonal antibody	Pathologic CR, 39.3% vs 21.5%
Nab-paclitaxel[b] for pancreatic cancer	82 231	Paclitaxel	Albumin-bound paclitaxel (microtubule inhibitor)	Median OS, 8.5 vs 6.7 mo
Afatinib for non-small-cell lung cancer	79 920	Erlotinib	EGFR tyrosine kinase inhibitor	Median PFS, 11.1 vs 6.9 mo; median OS, NS
Lenalidomide for mantle-cell lymphoma	124 870	Thalidomide	Immunomodulatory drug (thalidomide analogue)	RR, 26%; median DOR, 16.6 mo
Trametinib for malignant melanoma	125 280	NA	First approved mek inhibitor	Median PFS, 4.8 vs 1.5 mo
Dabrefenib for malignant melanoma	109 440	Vemurafenib	BRAF inhibitor	Median PFS, 5.1 vs 2.7 mo; median OS, NS
Radium 223 for prostate cancer	82 800	NA	First approved radiotherapeutic drug	Median OS, 14.0 vs 11.2 mo
Erlotinib for non-small-cell lung cancer	82 827	NA	First approved EGFR tyrosine kinase inhibitor	Median PFS, 10.4 vs 5.2 mo; median OS, NS
Ado-trastuzumab emtansine for breast cancer	113 161	NA	First approved anti-her2 antibody drug conjugate	Median PFS, 9.6 vs 6.4 mo; median OS, 25.1 vs 20.9 mo
Pomalidomide for multiple myeloma	150 408	Thalidomide	Immunomodulatory drug (thalidomide analogue)	RR, 29%; median DOR, 7.4 mo
Bevacizumab for colorectal cancer	59 422	NA	First anti-VEGF monoclonal antibody	Median PFS, 5.7 vs 4 mo; median OS, 11.2 vs 9.8 mo
Ponatinib for chronic myeloid leukemia and Ph* acute lymphoblastic leukemia	137 952	Imatinib	Bcr-abl tyrosine kinase inhibitor	Major cytogenetic response, 54%; median DOR, 3.2-9.5 mo
Abiraterone for prostate cancer	92 092	Ketoconazole	Androgen biosynthesis inhibitor	Median OS, 35.3 vs 30.1 mo
Cabozantinib for medullary thyroid cancer	118 800	NA	First multikinase (including c-met and VEGF) inhibitor	Median PFS, 11.2 vs 4 mo; median OS, NS
Omacetaxine for chronic myeloid leukemia	168 366	Homoharringtonine	Protein translation inhibitor	Major cytogenetic response, 14.3%; median DOR, 12.5 mo
Nab-paclitaxel[b] for non-small-cell lung cancer	82 231	Paclitaxel	Albumin-bound paclitaxel (microtubule inhibitor)	RR, 33% vs 25%; median OS, NS
Regorafenib for colorectal cancer	141 372	Sorafenib	Multikinase inhibitor	Median PFS, 2 vs 1.7 mo; median OS, 6.4 vs 5 mo

Abbreviations: CR, complete response; DOR, duration of response; NA, not applicable; NS, not significant; OS, overall survival; PFS, progression-free survival; Ph*, Philadelphia chromosome positive; RR, response rate; UA, unavailable; (V)EGF(R), (vascular) endothelial cell growth factor (receptor).

[a] Average wholesale prices were obtained from Redbook online ([subscription required] http://www.redbook.com/redbook/online/).

[b] This drug was approved separately for 2 indications.

The average drug developed by a major pharmaceutical company costs at least $4 billion, and it can be as much as $11 billion.

Research Spending Per New Drug

Company	Ticker	Number of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca AZN -0.54%	AZN	5	11,790.93	58,955
GlaxoSmithKline GSK -0.43%	GSK	10	8,170.81	81,708
Sanofi SNY +%	SNY	8	7,909.26	63,274
Roche Holding RHHBY +% AG	RHHBY	11	7,803.77	85,841
Pfizer PFE +0.14% Inc.	PFE	14	7,727.03	108,178
Johnson & Johnson	JNJ	15	5,885.65	88,285
Eli Lilly & Co.	LLY	11	4,577.04	50,347
Abbott Laboratories	ABT	8	4,496.21	35,970
Merck & Co Inc	MRK	16	4,209.99	67,360
Bristol-Myers Squibb Co.	BMY	11	4,152.26	45,675
Novartis AG	NVS	21	3,983.13	83,646
Amgen Inc.	AMGN	9	3,692.14	33,229

Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems

The Washington Post

Wonkblog

Big pharmaceutical companies are spending far more on marketing than research

By Ana Swanson February 11, 2015

The NEW ENGLAND JOURNAL of MEDICINE

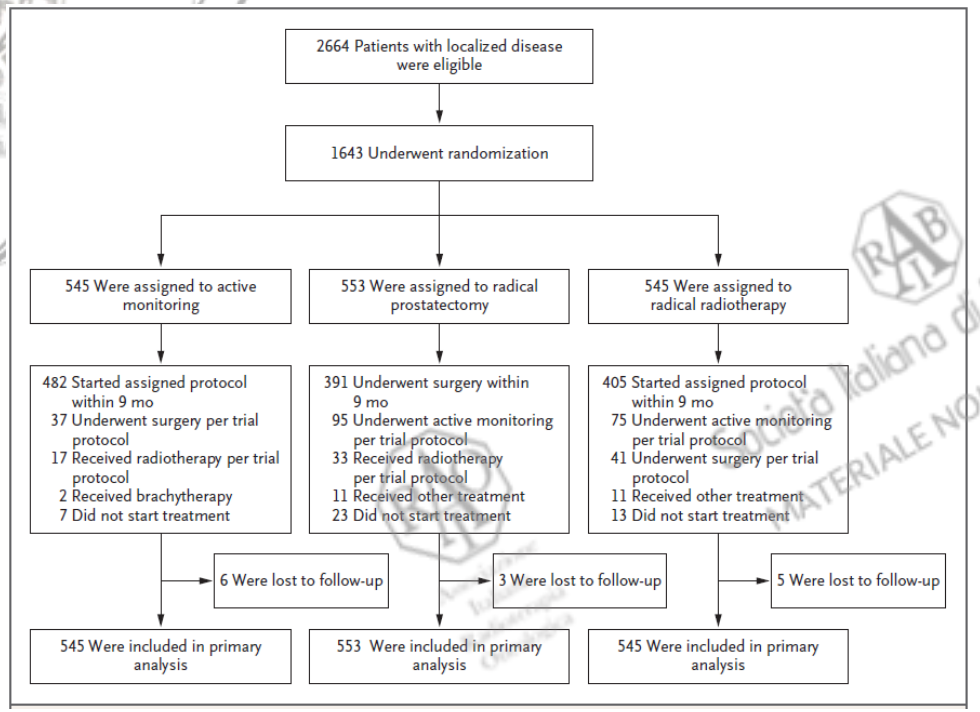
ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

Median age: 62 yrs
Median PSA: 4.6 ng/ml
77% GS 6
76% T1c

No significant intergroup differences



This article was published on September 14, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1606220

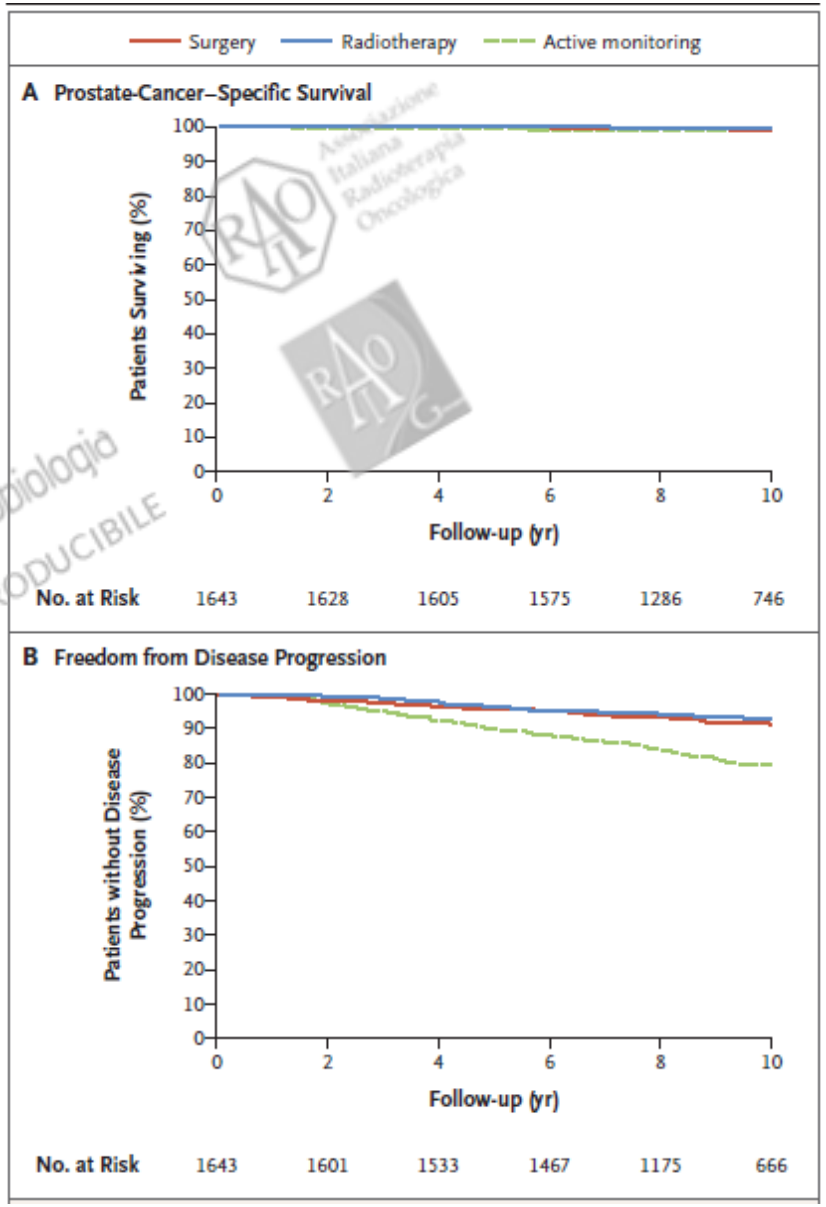


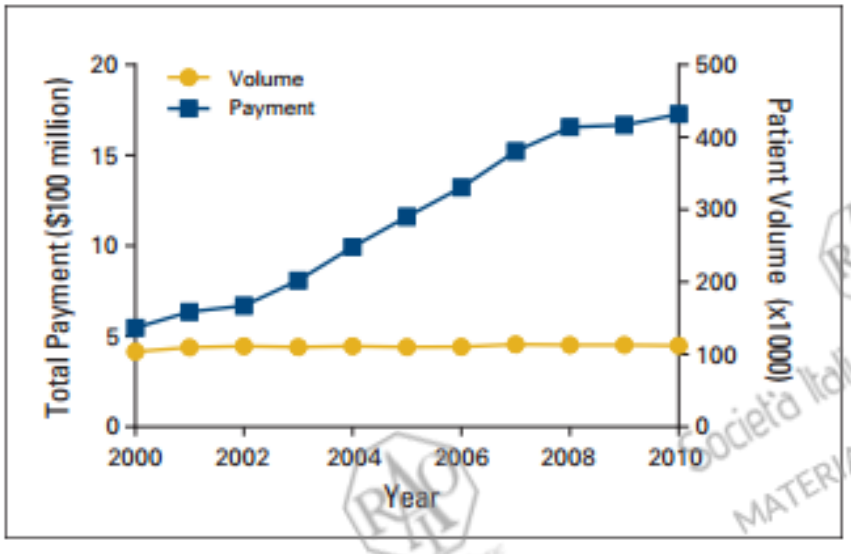
Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

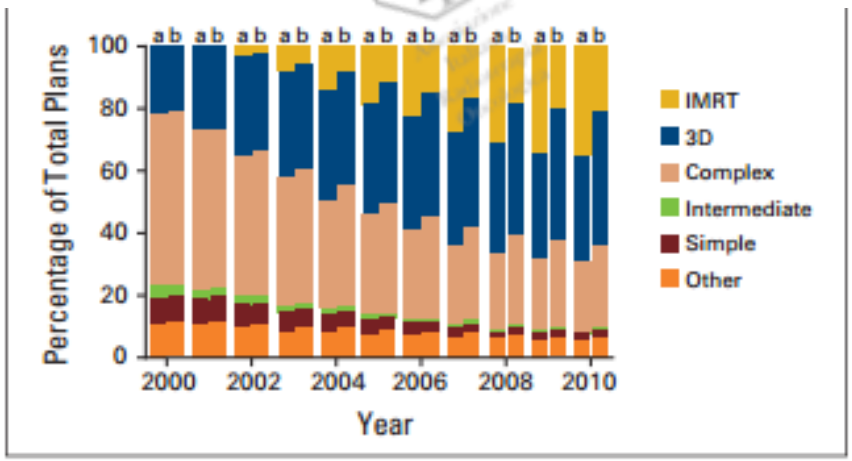
Variable	Active Monitoring (N = 545)	Surgery (N = 553)	Radiotherapy (N = 545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004
All-cause mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to any cause	59	55	55	
All-cause deaths per 1000 person-yr (95% CI)	10.9 (8.5–14.1)	10.1 (7.8–13.2)	10.3 (7.9–13.4)	0.87

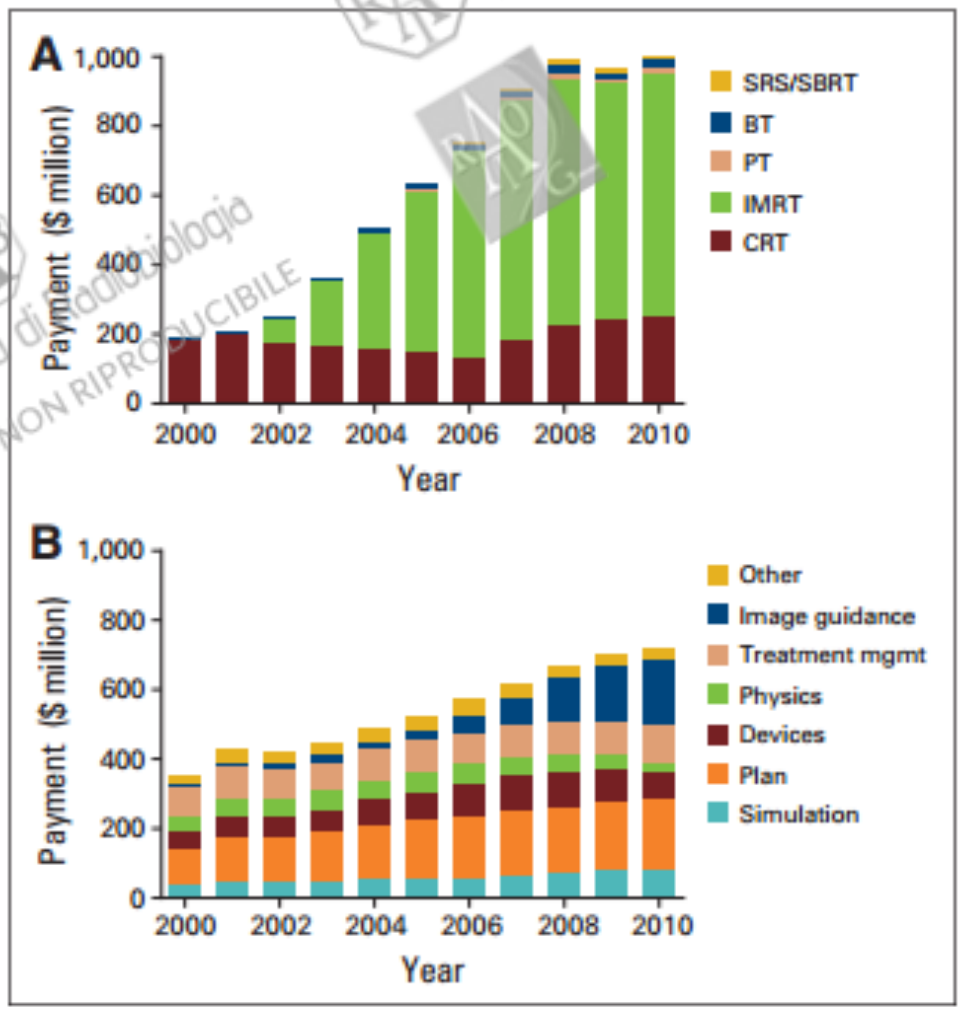
Radiation Oncology Services in the Modern Era: Evolving Patterns of Usage and Payments in the Office Setting for Medicare Patients From 2000 to 2010

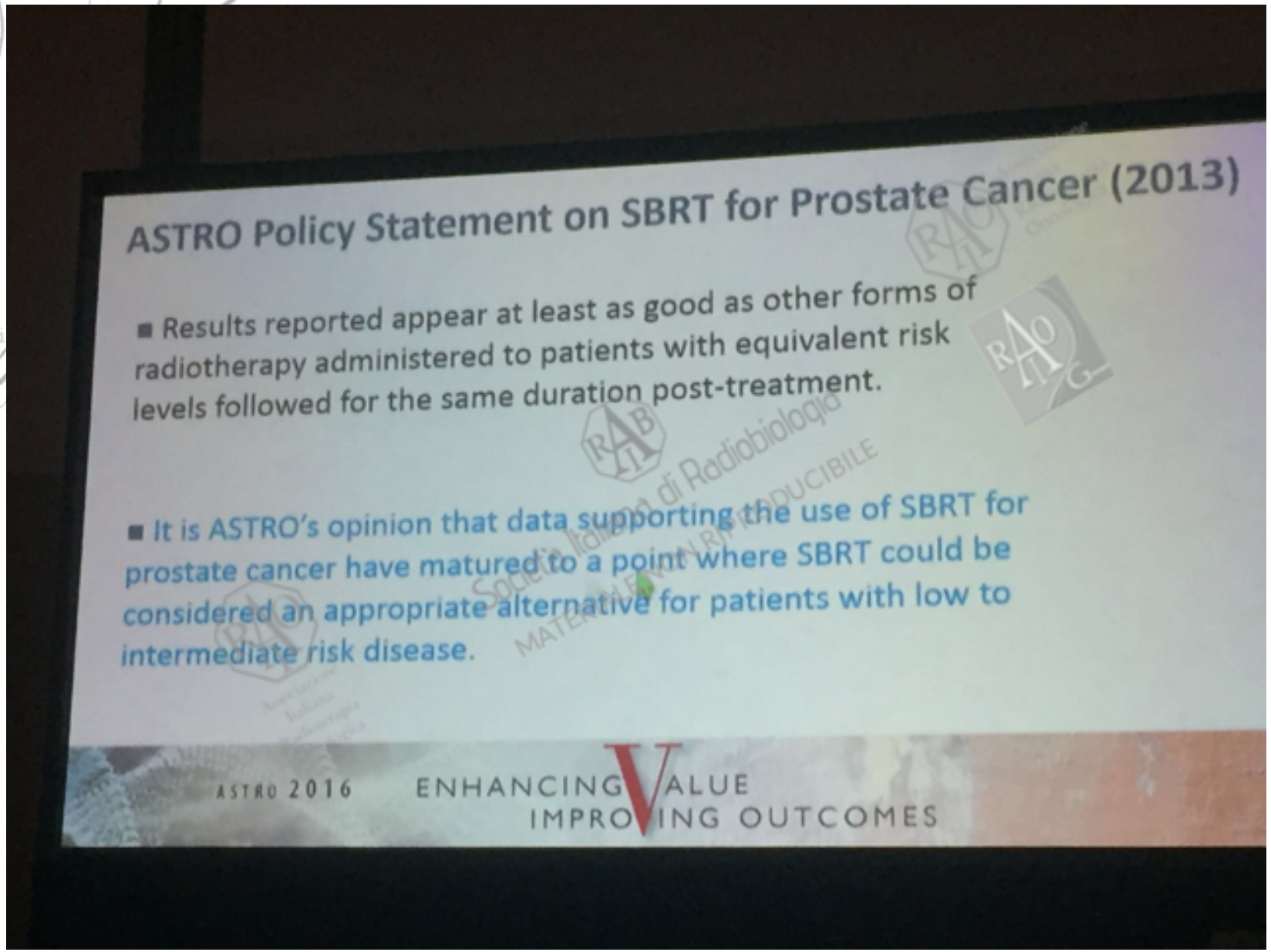
By Xinglei Shen, MD, Timothy N. Showalter, MD, Mark V. Mishra, MD, Sanford Barth, Vijay Rao, MD, David Levin, MD, PhD, and Laurence Parker, PhD

DOI: 10.1200/JOP.2013.001270; published online ahead of print at jop.ascopubs.org on April 22, 2014.








ASTRO Policy Statement on SBRT for Prostate Cancer (2013)
■ Results reported appear at least as good as other forms of radiotherapy administered to patients with equivalent risk levels followed for the same duration post-treatment.
■ It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for patients with low to intermediate risk disease.
ASTRO 2016
ENHANCING VALUE
IMPROVING OUTCOMES

Cost Drivers of Cancer Care: A Retrospective Analysis of Medicare and Commercially Insured Population Claim Data 2004-2014

Prepared by

Kathryn Fitch, RN, MEd
Principal and Healthcare Management Consultant

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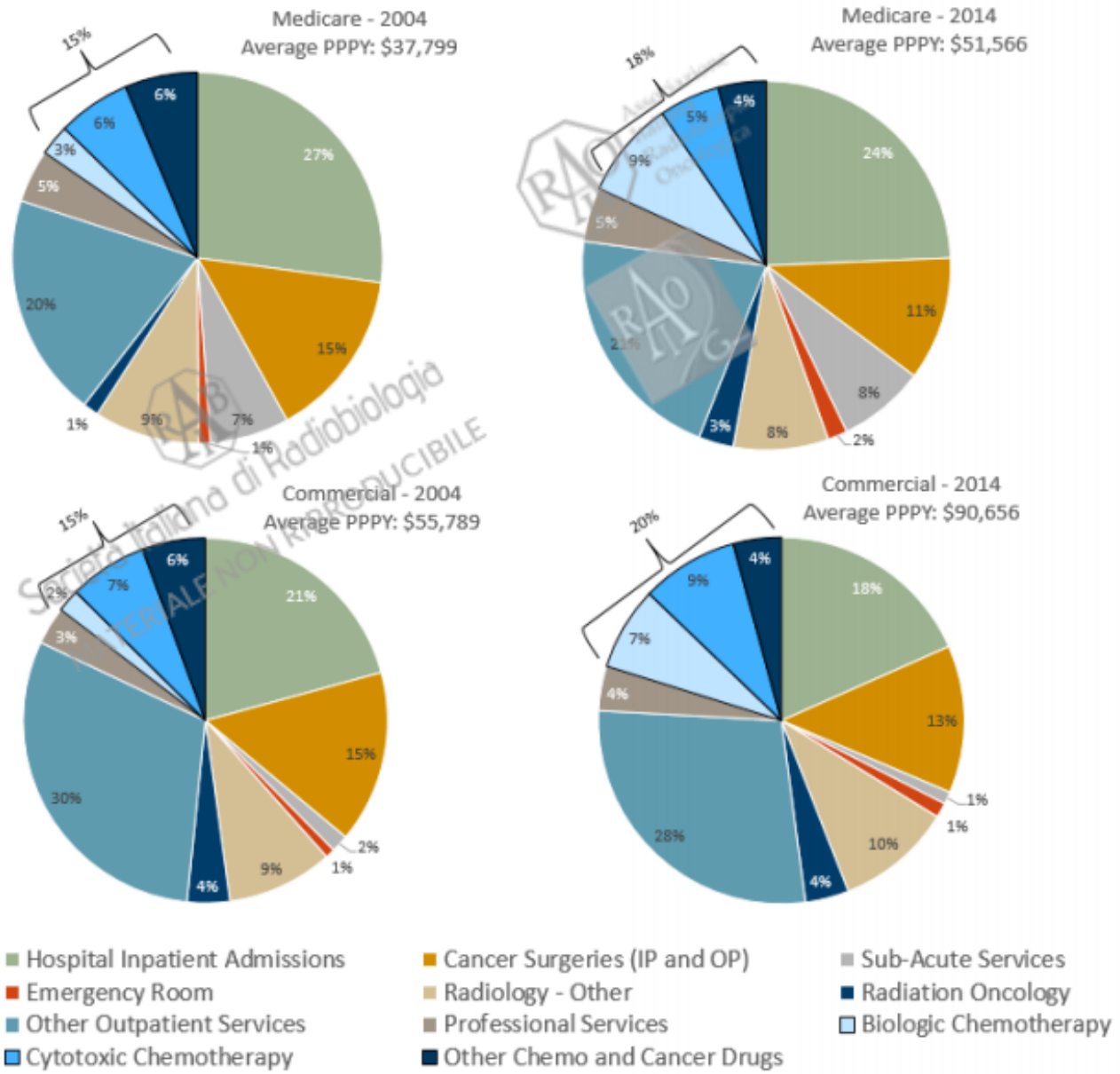
Healthcare Management Consultant

Bruce Pyenson, FSA, MAAA
Principal and Consulting Actuary

Commissioned by the Community Oncology Alliance

April 2016

Figure 4: PPPY allowed cost by cost category in the actively treated cancer population, Medicare and commercial[e]



Source: Based on Milliman analysis of the 2004-2014 Truven MarketScan data and Medicare 5% sample data

Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Chad G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Matthew Koshy, David J. Sher, Usama Mahmood, Ronald C. Chen, Brian F. Chapin, Brian D. Kavanagh, and Thomas J. Pugh

A B S T R A C T

Purpose

There is growing interest in the role of local therapies, including external beam radiotherapy (RT), for men with metastatic prostate cancer (mPCa). We used the National Cancer Database (NCDB) to evaluate the overall survival (OS) of men with mPCa treated with androgen deprivation (ADT) with and without prostate RT.

Methods

The NCDB was queried for men with newly diagnosed mPCa, all treated with ADT, with complete datasets for RT, surgery, prostate-specific antigen (PSA) level, Gleason score, and Charlson-Deyo comorbidity score. OS was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards models, and propensity score-matched analyses.

Results

From 2004 to 2012, 6,382 men with mPCa were identified, including 538 (8.4%) receiving prostate RT. At a median follow-up of 5.1 years, the addition of prostate RT to ADT was associated with improved OS on univariate ($P < .001$) and multivariate analysis (hazard ratio, 0.624; 95% CI, 0.551 to 0.706; $P < .001$) adjusted for age, year, race, comorbidity score, PSA level, Gleason score, T stage, N stage, chemotherapy administration, treating facility, and insurance status. Propensity score analysis with matched baseline characteristics demonstrated superior median (55 *v* 37 months) and 5-year OS (49% *v* 33%) with prostate RT plus ADT compared with ADT alone ($P < .001$). Landmark analyses limited to long-term survivors of ≥1, ≥3, and ≥5 years demonstrated improved OS with prostate RT in all subsets (all $P < .05$). Secondary analyses comparing the survival outcomes for patients treated with therapeutic dose RT plus ADT versus prostatectomy plus ADT during the same time interval demonstrated no significant differences in OS, whereas both therapies were superior to ADT alone.

Conclusion

In this large contemporary analysis, men with mPCa receiving prostate RT and ADT lived substantially longer than men treated with ADT alone. Prospective trials evaluating local therapies for mPCa are warranted.

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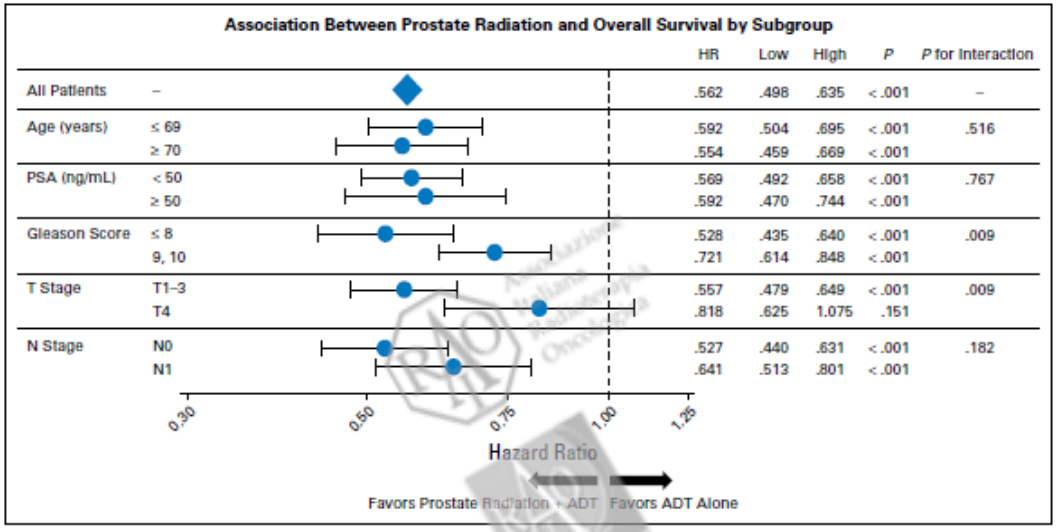

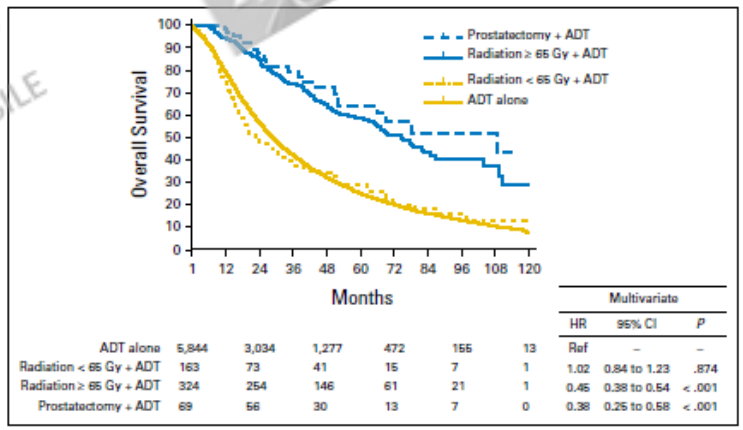

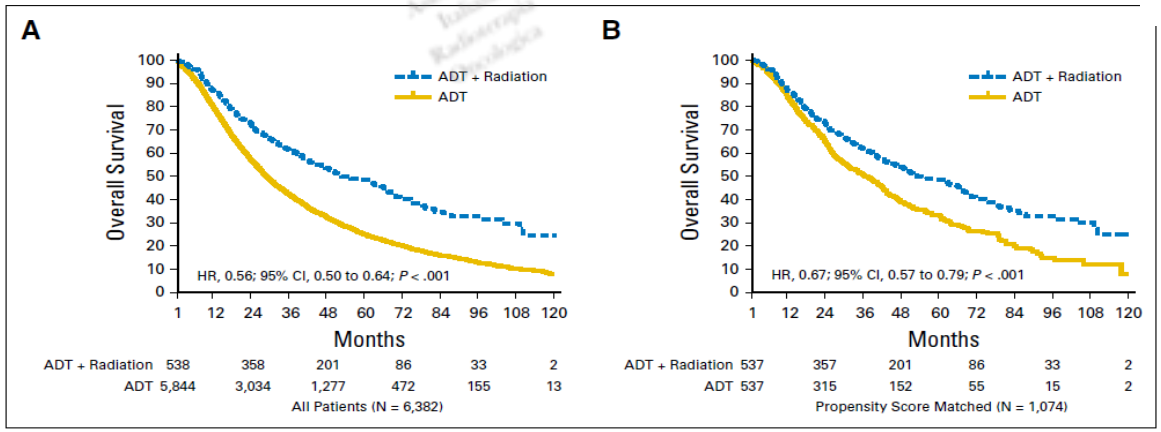

Fig 1. Overall survival for patients with metastatic prostate cancer treated with ADT with and without external beam radiation to the prostate. (A) All patients. (B) Propensity score-matched patients. ADT, androgen deprivation therapy; HR, hazard ratio.