Radiobiologia
e diagnostica medico nucleare

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outline

- **why Radiobiology *for* nuclear medicine**
- **high *vs* low doses**
- **experimantal limits**
  - from dosimetry to radiobiology
  - experimental models
  - epidemiological limits

Radiobiology *for* nuclear medicine

spontaneous DNA damage

- **oxidative metabolism**
  - reactive oxygen species (ROS)
    - micronutrient deficiency
    - various toxic compound from environment

- **under physiological** conditions
  - 10,000 genetic modifications spontaneously occur every hour in the human body;
  - in particular every year 4.4 x 10^7 SSBs and 1.4 x 10^7 base lesions are induced by natural or environmental toxic agents

contribution of radiation-induced cell damage

- Radiation-induced DNA damage is **very little**
  - it is estimated that **10 DNA** alterations are produced **every 10 mSv**

- low frequency of irradiation
  - Radiation-induced DNA damage
    - many order of magnitude **lower than that originating from nonradiation sources**

contribution of radiation-induced cell damage

- **radiation-induced DNA damage**
  - **more severe** than most damages by metabolic ROS
  - Probability 10^5 higher

- **overall** background radiation-induced DSB
  - **1,000 times lower** than the DSB incidence from metabolic ROS.

defence mechanisms

- **protective system** against endogenous and exogenous **oxidative stress**
  - **enzymes**, such as superoxide dismutase, catalase, and glutathion peroxidase
  - **radical scavengers**
    - intracellular components **glutathion, vitamin C and E**

repair

- **low doses** of x- or γ-rays
  - induce the synthesis of repair systems
    - (with a delay of up to a few hours)
  - **improved protection** against **renewed and other nonradiation sources** of damage for hours to weeks after a single irradiation
- maximally expressed after <0.1-<0.5 Gy
  - fail to appear with higher doses
  - similar to physiologic response to oxygen stress

» adaptive response

adaptive response

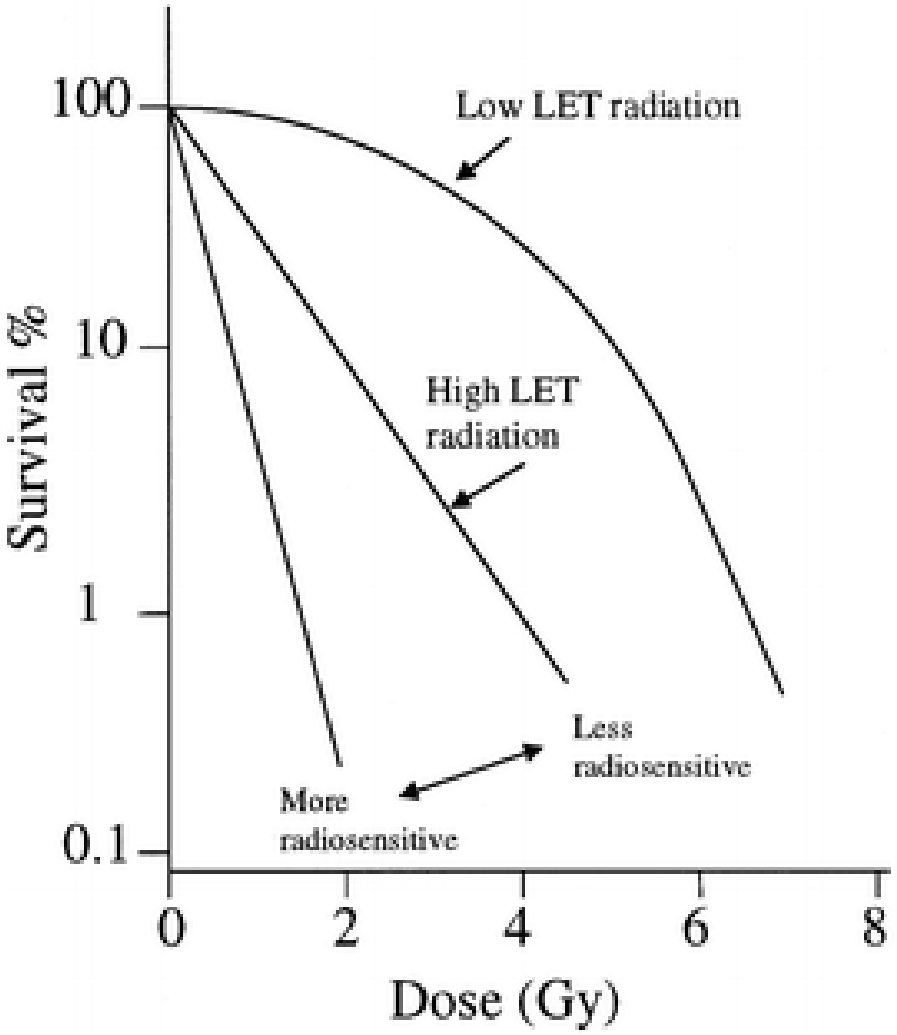
- **in vitro**

  A. lymphocytes **pre-irradiated with low-dose**

  B. lymphocytes **non pre-irradiated**

  - **irradiation with high doses**
    - **much lower number of DNA modifications**
      - in **pre-irradiated lymphocytes**

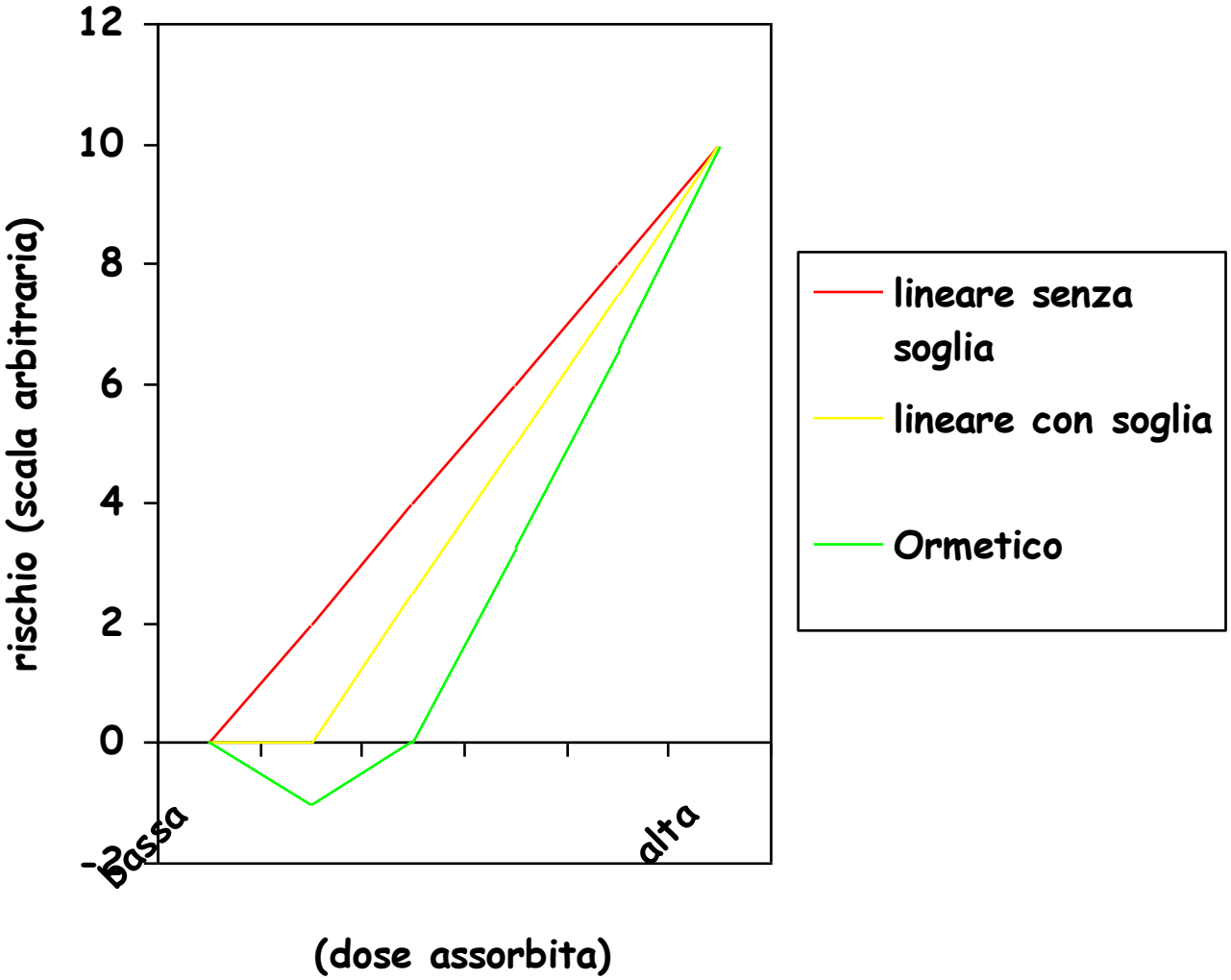
high *vs* low doses


100
10
1
0.1
Survival %
Low LET radiation
High LET
radiation
Less
radiosensitive
More
radiosensitive
0
2
4
6
8
Dose (Gy)

- at **high doses** effect are known and predictable
- at **low doses** the complexity of the interaction
  - type of radiation
  - defense mechanism
  - repair
  - non target effect
  - adaptive responce

- may all have an influence on the **final biological consequence**
- may be **detrimental or beneficial**
- may be **different for different types of radiations**

modelli di relazione dose/effetto per la esposizione alle radiazioni ionizzanti



- what about **low dose** of ionising radiations?

- Effective dose of **100 mSv** is normally considered to be the **limit for low-dose** of ionising radiations

    - **what are the biological effects in patients and medical staff involved diagnostic nuclear medicine?**

theoretical estimates and practical epidemiology

- most nuclear medicine exams
  - doses ranging between 1 and 5 mSv

- according to the estimates (**LNT**)
  - **incidence of cancer** in patients undergoing nuclear medicine exams **should be much higher** than that actually observed worldwide in normal practice

- **a dose and a dose-rate effectiveness factor** is needed **to convert risk estimates to the low dose** and low dose rates encountered in medical practice

- **animal studies** suggested a factor **between 2 and 10**

- the **ICRP** assumes a value of **2**

The British Journal of Radiology, 74 (2001), 507–519

100 years of observation on British radiologists: mortality from cancer and other causes 1897–1997

[1]A BERRINGTON, BSc, MSc, [2]S C DARBY, BSc, MSc, PhD, [3]H A WEISS, BSc, MSc, PhD and [2]R DOLL, MD, FRCP, FRS

one hundred years of health of British radiologists

- perhaps the most important study about the health effects of radiation on humans ever published

- data divided in different period
  - < 1920: effective dose: > 1 Sv/1 yr
  - > 1936: effective dose: < 200 mSv/yr
  - > 1954: effective dose: < 20 mSv/yr

one hundred years of health of British radiologists

- impressive conclusions
- even **before 1920s** the **excess rate of cancer mortality** was 75%, but with an associated **reduction in mortality from other causes** (the vast majority) of 14%.

- **after 1920s**, the **mortality from cancer** of British radiologists
  - **reduced compared** to the members of the other groups of **the population**

- **after 1955**
  - was **reduced compared to other medical practitioners**

Table 7. Comparison of the observed radiation risks in the radiologists with the predicted risks for radiologists based upon estimates from the atomic bomb survivors (SMR, standardized mortality ratio)

Cause of death	1897–1920				1921–1935				1936–1954				1955–1979			
	Observed		Predicted		Observed		Predicted		Observed		Predicted		Observed		Predicted	
	SMR	(90% CI)	SMR	(90% CI)	SMR	(90% CI)	SMR	(90% CI)	SMR	(90% CI)	SMR	(90% CI)	SMR	(90% CI)	SMR	(90% CI)
Cancer	1.75	(1.40–2.17)	6.2	(3.6–8.6)	1.24	(0.97–1.57)	2.0	(1.5–2.4)	1.12	(0.93–1.34)	1.3	(1.2–1.5)	0.71	(0.52–0.95)	1.03	(1.01–1.04)
Non-cancer diseases[a]	0.90	(0.80–1.00)	3.4	(2.8–4.0)	0.88	(0.78–0.98)	1.5	(1.3–1.6)	0.95	(0.85–1.05)	1.15	(1.1–1.2)	0.63	(0.51–0.77)	1.01	(1.01–1.02)
Circulatory diseases	0.79	(0.68–0.92)	2.8	(1.4–4.4)	0.83	(0.72–0.95)	1.3	(1.1–1.7)	0.98	(0.86–1.10)	1.1	(1.03–1.2)	0.59	(0.45–0.75)	1.01	(1.0–1.02)
Respiratory diseases	0.94	(0.69–1.24)	4.6	(2.2–7.2)	0.89	(0.61–1.26)	1.7	(1.2–2.2)	1.34	(0.95–1.85)	1.2	(1.08–1.4)	1.34	(0.67–2.42)	1.02	(1.01–1.03)

Observed SMRs and 90% CIs are from Tables 2 and 5 and are based on the expected rates for all medical practitioners.

The predicted SMR was calculated as the (excess relative risk per Sv × estimated average lifetime dose)+1.

The excess relative risk per Sv and 90% CI for the atomic bomb survivors is 0.26 (0.13–0.38) for solid cancers in males aged 40 years at exposure, 0.12 (0.09–0.15) for non-cancer diseases, 0.09 (0.02–0.17) for circulatory disease and 0.18 (0.06–0.31) for respiratory diseases [3, 27].

The average lifetime dose for each group (according to year of first registration) was estimated to be 20 Sv in those who registered between 1897 and 1920, 3.8 Sv for 1921–1935 radiologists, 1.25 Sv in 1936–1954 radiologists and 0.1 Sv in radiologists registering between 1955 and 1979.

[a]Excluding external causes of death.

- physical effect → Compton, ionisation etc
- biological effect → DNA damage
- clinical effect → cancer
  deterministic effects

diagnostic nuclear medicine

- low dose
- low dose rate
- indirectly ionising radiation

comparison with radiology: therapeutic applications

- **external radiotherapy**:
  - **increased incidence of late-onset solid tumours** and of leukaemia

- **treatment hyperthyroidism and of differentiated thyroid tumours**
  - **rarely (if) observed**

» whole body dose produced by **radionuclide therapy** significantly **lower** compared to external radiotherapy.

nuclear medicine *is* different


CRÈME
POUDRE
THO-RADIA
EMBELLISSANTES PARCE QUE CURATIVES
à base de thorium et de radium selon la formule du
DOCTEUR ALFRED CURIE
EXCLUSIVEMENT CHEZ LES
CRÈME
POUDRE

experimantal limits

from dosimetry to radiobiology

- **dosimetry**:
  - **not always predictive** of
    - biological damage and or the clinical effect

- **renal toxicity** in patients treated we Y90-dota-TOC
- correlates with **biological effective dose** and **not with absorbed dose**

» Barone R, *J Nucl Med 2005 46:99S-106S.*

how can we explain differences between radiology and nuclear medicine?

- **increase in number of micronuclei**
  - treatment with **131I for thyroid** diseases: n=32
  - patients treated with **EBR** for
    - cancer of the **cervix** the n=298
    - Hodgkin's **disease** n=640

  - **biological dosimetry** is the way to go
    - Monsieurs MA, *Nucl Med Commun 1999, 20:911-917.*

experimental models

- the majority of **experimental results** are from animal model treated with **external beam irradiation**

- **incidence of secondary** cancer from **diagnostic nuclear medicine**
  - **so little**
    - **very high number of animals**

epidemiological limits

- the estimate of risk in affected patients
  - other imaging modalities
  - other treatments (chemotherapy)
  - EBR

conclusive remarks

- **low level** of ionising radiations induces biological effects that can be **readily and fully repaired** in the vast majority of cases

- when the **dose and the dose rate increase** the **repair mechanisms become insufficient** and a **clinical consequence may develop**

conclusions

- no conclusiva data
- different methods must be used for calculation of biological effcts
- different experimental models

conclusions

- **american Health Physics Associations**
  - in an **adult man** exposed to **low doses** of ionising radiation (<50 mSv in one year or <100 mSv in a lifetime), summed to the natural background of radiation
    - **detrimental health effects** are either **not existent or too little** to be measured