Terapia radiometabolica: effetti e gestione

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ASL 5 – Spezzino

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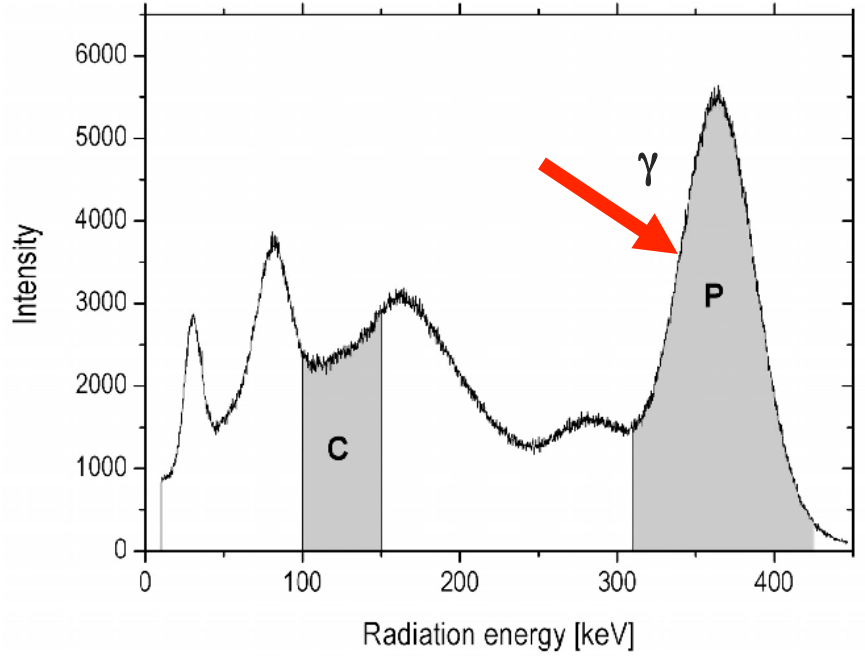
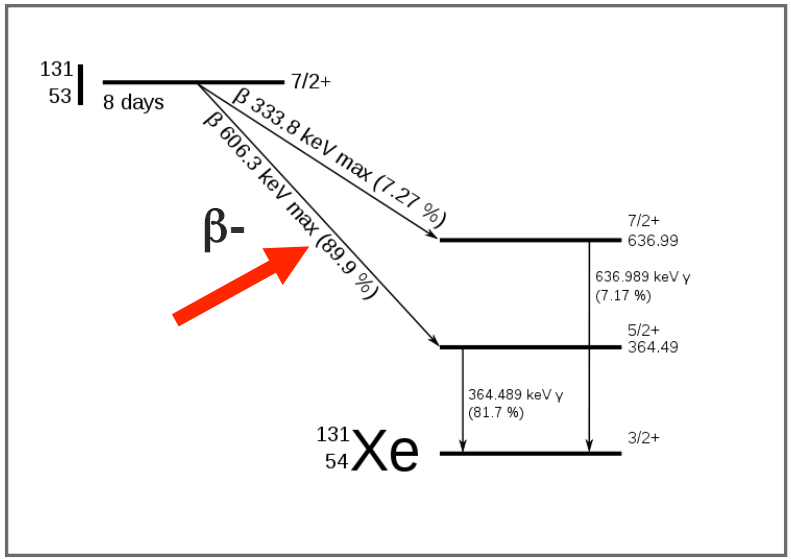
Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario: Sanofi Aventis-Genzyme

Decadimento ^{131}I

$^{131}I \rightarrow {}^{131}Xe + \beta^- + \gamma$





Terapia con radioiodio e fertilità

... Quali applicazioni cliniche?

Ipertiroidismo

Carcinoma differenziato della tiroide


GENTS

Clinical Endocrinology (2006) 65, 446–452 doi: 10.1111/j.13

ORIGINAL ARTICLE

Testicular function after ^{131}I therapy for hyperthyroidism

Claudia Ceccarelli*, Domenico Canale*, Paolo Battisti†, Carolina Caglieresi*, Cecilia Moschini*, Emilio Fiore*, Lucia Grasso*, Aldo Pinchera* and Paolo Vitti*

Patients and measurements Nineteen male hyperthyroid patients were enrolled in the study before ^{131}I therapy. Seventeen of the patients had Graves' disease and two had toxic adenoma. The study was subdivided into two parts: a dosimetric and a clinical study. Six patients were enrolled for the dosimetric study and 13 for the clinical study. The β dose delivered to the testes was evaluated by the Medical Internal Radiation Dose (MIRD) method. The γ dose was measured by thermoluminescent dosimeters (TLDs) placed on the skin overlying the inferior poles of the testes for 3 weeks after therapy. The clinical evaluation included hormone determination, ultrasound (US) of the testes and sperm analysis. Patients were followed up for 12 months after ^{131}I therapy.

Pazienti arruolati = 19
17 pz con GD
2 pz con AT

37-851 MBq (10-23 mCi)

A) studio dosimetria (n=6 pz)
β= MIRD
γ=TLDs

B) studio clinico (n=13 pz)

Terapia con radiodiodio e fertilità maschile: terapia dell'ipertiroidismo

Fig.4: parametri spermatici dei pazienti al momento del 131I e dei controlli

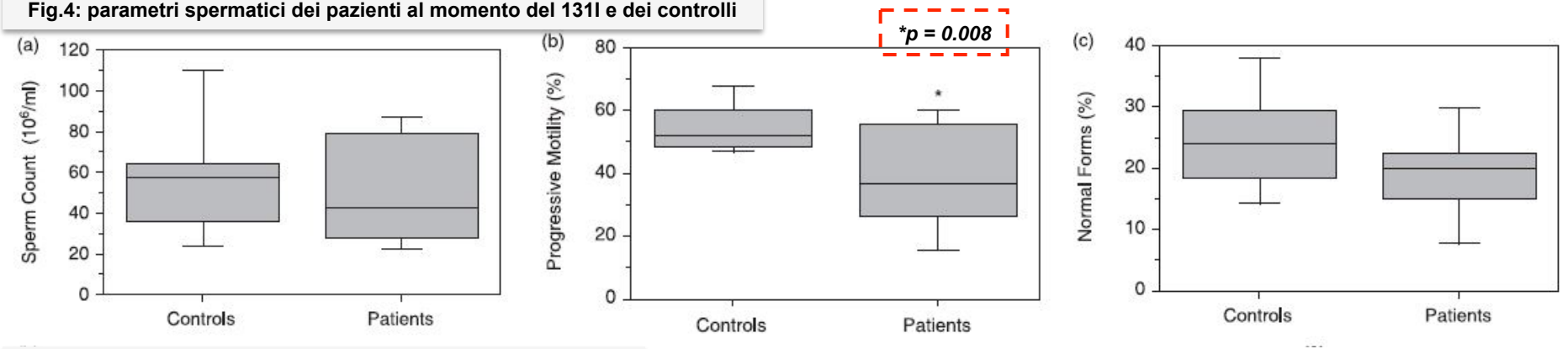
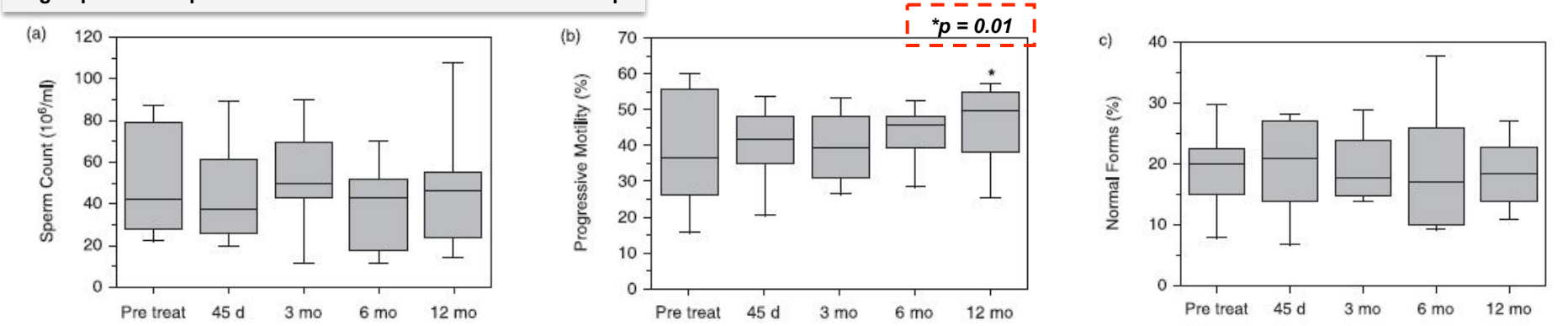
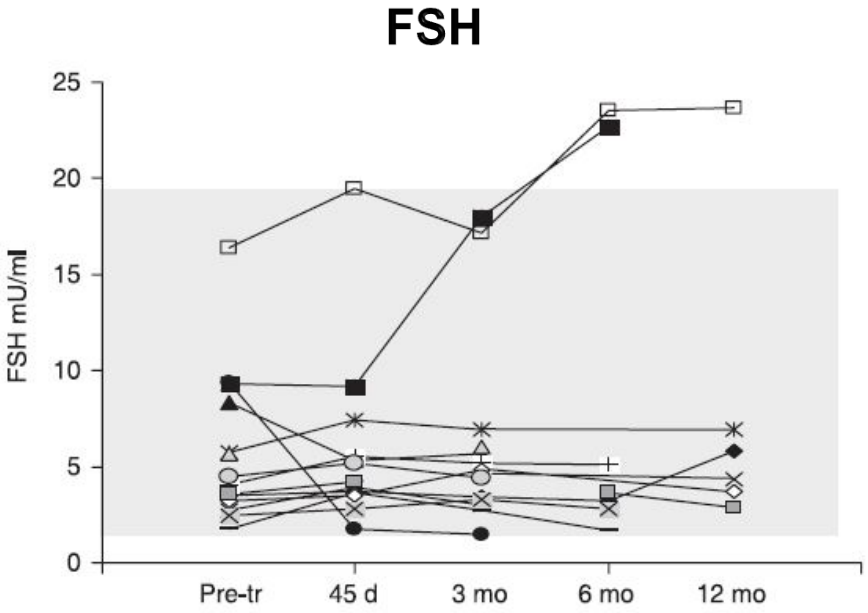


Fig.5: parametri spermatici al momento del 131I e nel follow-up

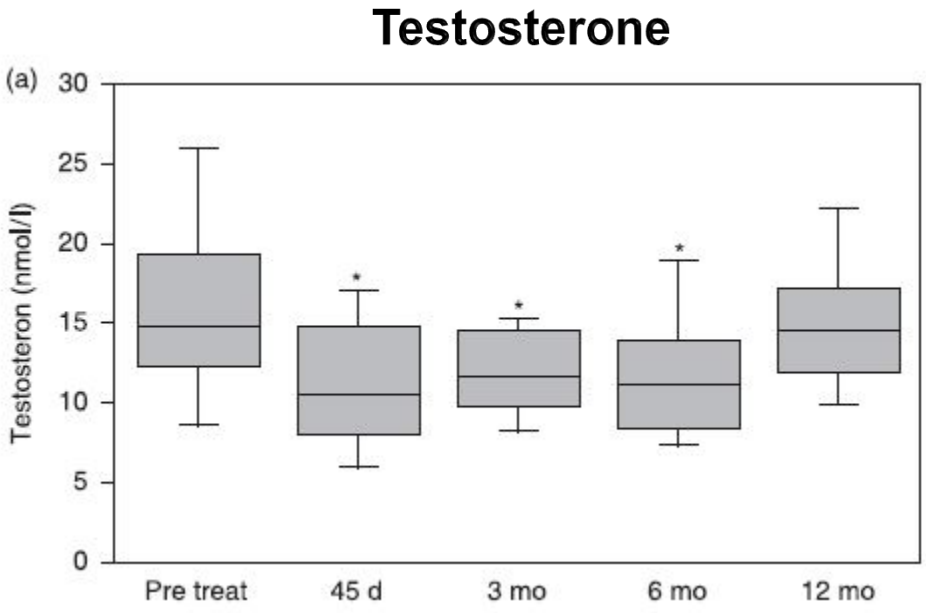


Ceccarelli et al. (2006)

Terapia con radiodiodio e fertilità maschile: terapia dell'ipertiroidismo



Nella maggior parte dei pazienti i valori di FSH non si modificavano significativamente dopo il trattamento con 131I



Riduzione dei valori di T dopo 131I (p=*0.04)* con ritorno ai valori basali dopo 12 mesi dal trattamento

Ceccarelli et al. (2006)

Terapia con radiodiodio e fertilità maschile: terapia dell'ipertiroidismo

The radiation dose to the testes resulting from ^{131}I treatment of hyperthyroidism may account for a small amount of damage both to the germinal epithelium and Leydig cells. However, it is difficult to distinguish this damage from that produced by hyperthyroidism *per se*, unlike that observed in cancer patients, in whom testicular damage after ^{131}I treatment is well documented. Therefore, ^{131}I treatment can be safely prescribed in hyperthyroid male patients. Given the currently high number of infertile males in Western countries, ^{131}I treatment for hyperthyroidism represents a minor challenge to fertility potential, but this small degree of damage should be kept in mind when treating male patients who already have partial fertility impairment. Thus, caution should be used in younger patients for whom fertility is a concern and in whom a pre-existing potentially damaging condition (cryptorchidism, varicocele, etc.) is present. In these cases, an andrological consultation and a semen analysis should be performed before ^{131}I therapy.

Ceccarelli et al. (2006)

Terapia con radiodiodio e fertilità maschile: terapia del carcinoma tiroideo

Clinical Endocrinology (2015) 82, 295–299 doi: 10.1111/cen.12514

ORIGINAL ARTICLE

Effects of radioiodine treatment for differentiated thyroid cancer on testis function

Domenico Canale, Claudia Ceccarelli, Carolina Caglieresi, Agnese Moscatelli, Silvia Gavioli, Pierina Santini, Rossella Elisei and Paolo Vitti

DISEGNO STUDIO

- Studio prospettico longitudinale (durata dello studio 3 anni)
- Parametri misurati:
  - Livelli ormonali (FSH, LH, T, PRL)
  - Liquido seminale (secondo linee guida WHO)
  - Volume testicolare
- Valutazione andrologica: esame obiettivo, ecografia scrotale, spermiogramma, dosaggi ormonali
- Timing: tempo 0 (al momento della dose), dopo 6 e 12 mesi

Terapia con radiodiodio e fertilità maschile: terapia del carcinoma tiroideo

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Effects of radioiodine treatment for differentiated thyroid cancer on testis function

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- 98 pazienti affetti da CDT arruolati e trattati con 131I (età 18-50 aa)
- Solo 20/98 hanno proseguito lo studio per almeno 1 anno post-RAI:
  - 18 pz con ca. papillare e 2 pz con ca. follicolare
  - età media 30.8 ± 5.4 aa (range 19-39)

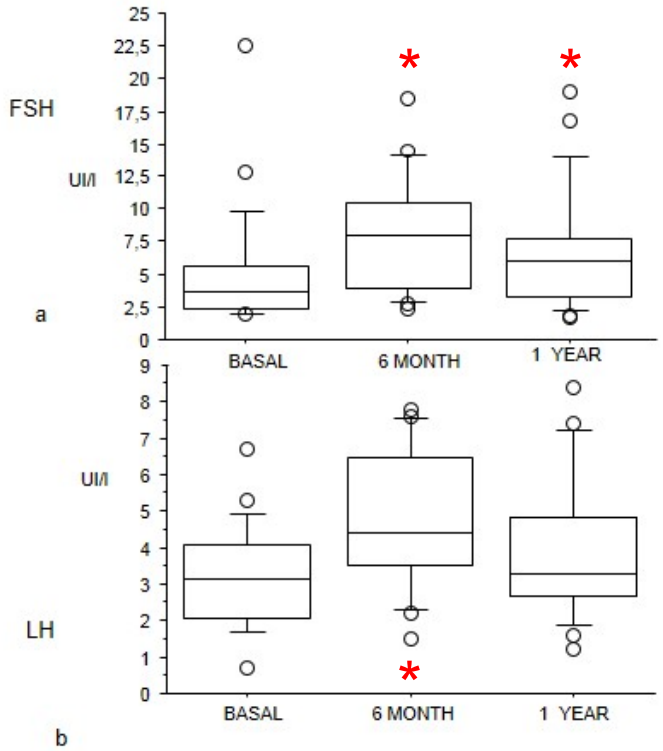
Gruppo 1:
"DOSE ABLATIVA SINGOLA" post-Tx:

- 10 pazienti
- età media 30.1 ± 6.7 aa
- attività 131I: 1.1 GBq (29.7 mCi)

Gruppo 2:
"DOSI MULTIPLE":

- 10 pazienti
- età media 32.1 ± 3.5 aa
- attività 131I: 4.8 GBq – 3.2 GBq (130 - 870 mCi)
- media 1.3 MBq = 345 mCi

Terapia con radiodiodio e fertilità maschile: terapia del carcinoma tiroideo - ORMONI (1)



Box plot representation of FSH (panel a) and LH (panel b) values in basal conditions before RAI and at 6 months and 1 year post-RAI treatment in the whole population

FSH: 6 month vs. basal p <0.005; 1 year vs. basal p <0.05;

LH: 6 month vs. basal p <0.05; 1 year vs. basal NS

Canale D. et al (2015)

Terapia con radiodiodio e fertilità maschile: terapia del CTD-ORMONI (2)

	BASAL	6 MONTH	1 YEAR	STATISTICS
SINGLE	3.8	5.5	4.3	ns
MULTIPLE	6.4 *a*	10.3 *b*	9.0 *c*	*a* vs. *b* **p <0.01** *a* vs. *c* **p = 0.02**
	NS	**p < 0.01**	**p < 0.05**	*b* vs. *c* NS

Table 1: **FSH values in patients treated with one single and multiple RAI treatments: basal, 6 month and 1 year control**

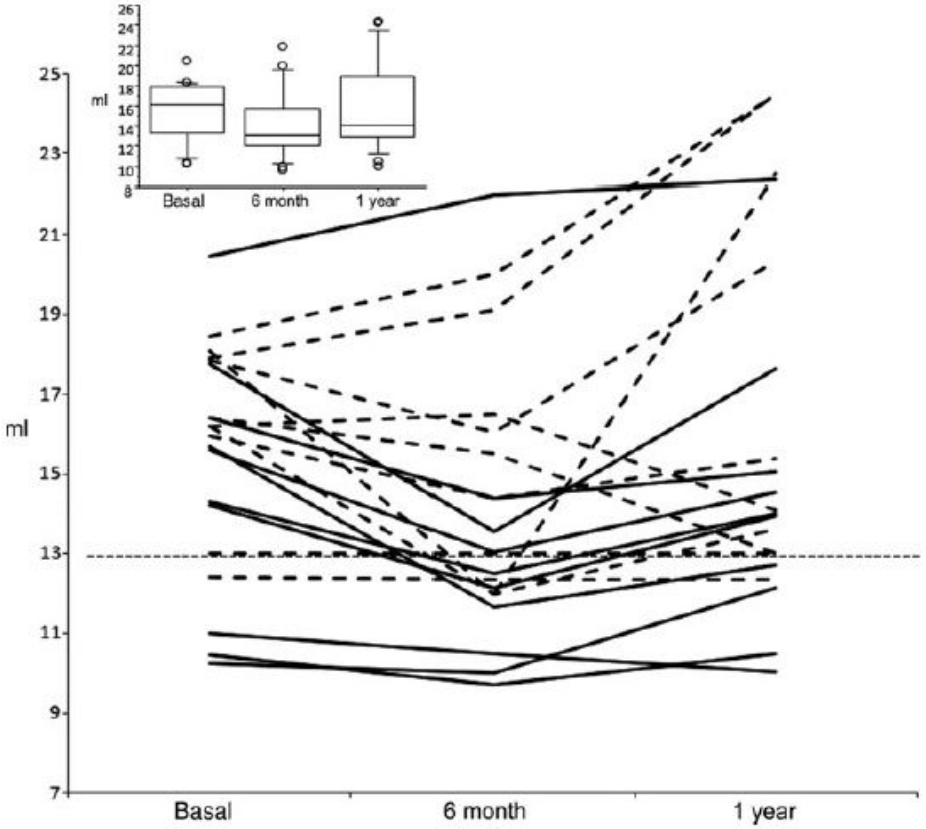
Canale D. et al (2015)

Terapia con radiodiodio e fertilità maschile: terapia del CTD- VOLUME TESTICOLARE

Upper left: Box plot representation of **mean testis volume** (sum of the two testes/2) assessed by ultrasounds in the **whole population: 6 month vs. basal p <0.005; 1 year vs. basal NS.**

Main figure: Individual testis volume before RAI, at 6-month and 1-year post-RAI:

- dotted lines: single treatment group
- continuous lines: multiple treatments group
- the horizontal line indicates the cutoff point (13 ml) of the normal fertile population.



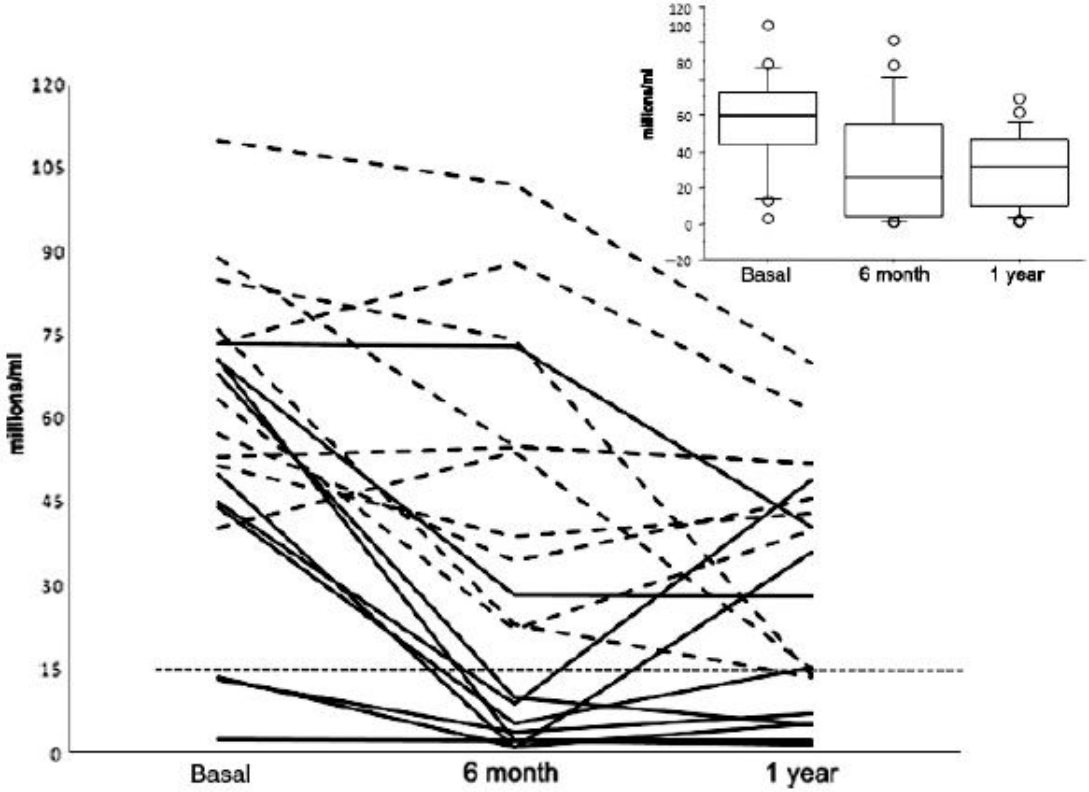
Canale D. et al (2015)

Terapia con radiodiodio e fertilità maschile: terapia del CTD- SPERMATOGENESI

Upper right: Sperm concentrations in basal conditions before RAI and at 6 month and 1 year post-RAI treatment in the **whole population: 6 month vs. basal p<0.005; 1 year vs. basal p<0.001.**

Main figure: Individual sperm concentrations before RAI, a t 6 month and 1 year post-RAI:

- dotted lines: single treatment group
- continuous lines: multiple treatments group
- the horizontal line indicates the 5th percentile of the fertile population, that is 15 mill/ml, according to WHO Lab Manual



Canale D. et al (2015)

Sperm DNA fragmentation after radioiodine treatment for differentiated thyroid cancer

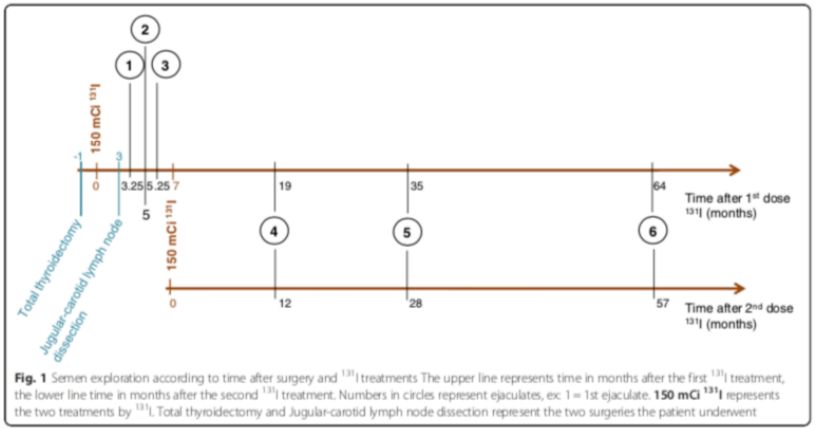


Fig. 1 Semen exploration according to time after surgery and ^{131}I treatments The upper line represents time in months after the first ^{131}I treatment, the lower line time in months after the second ^{131}I treatment. Numbers in circles represent ejaculates, ex: 1 = 1st ejaculate. **150 mCi ^{131}I** represents the two treatments by ^{131}I. Total thyroidectomy and Jugular-carotid lymph node dissection represent the two surgeries the patient underwent

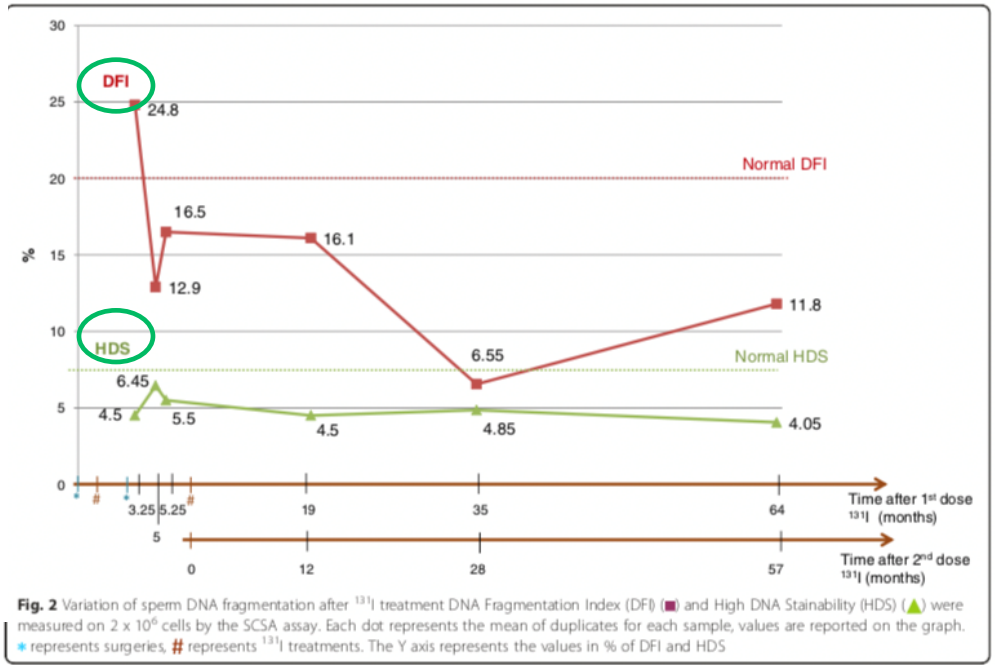


Fig. 2 Variation of sperm DNA fragmentation after ^{131}I treatment DNA Fragmentation Index (DFI) (■) and High DNA Stainability (HDS) (▲) were measured on 2 x 10^6 cells by the SCSA assay. Each dot represents the mean of duplicates for each sample, values are reported on the graph. * represents surgeries, # represents ^{131}I treatments. The Y axis represents the values in % of DFI and HDS

Camille Esquerré-Lamare et al.
(Basic and Clinical Andrology 2015)


LADIES

Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer

- Arruolate 496 donne < 40 anni di età alla diagnosi di DTC
- 322 pz dose ablativa singola di 3000 MBq (81 mCi)
- 174 pz trattamenti multipli per persistenza/recidiva/metastasi: dose cumulativa di 8.500–59.000 MBq (229-1594 mCi)
- Dopo follow-up mediano di 18 anni dati raccolti per 409/496 pz

Learning points

- Temporary amenorrhoea lasting for up to 10 months occurs in about 8% of patients after ablative radioiodine.
- Permanent ovarian failure is rare after radioiodine treatment and fertility does not appear to be reduced.
- Patients receiving large doses of radioiodine should drink plenty of fluids and avoid constipation to avoid unnecessary radiation to the ovaries.

L Vini, S Hyer, A Al-Saadi, B Pratt, C Harmer
(Postgrad Med J 2002;78:92–93)

Ovarian function after radioiodine therapy in patients with thyroid cancer

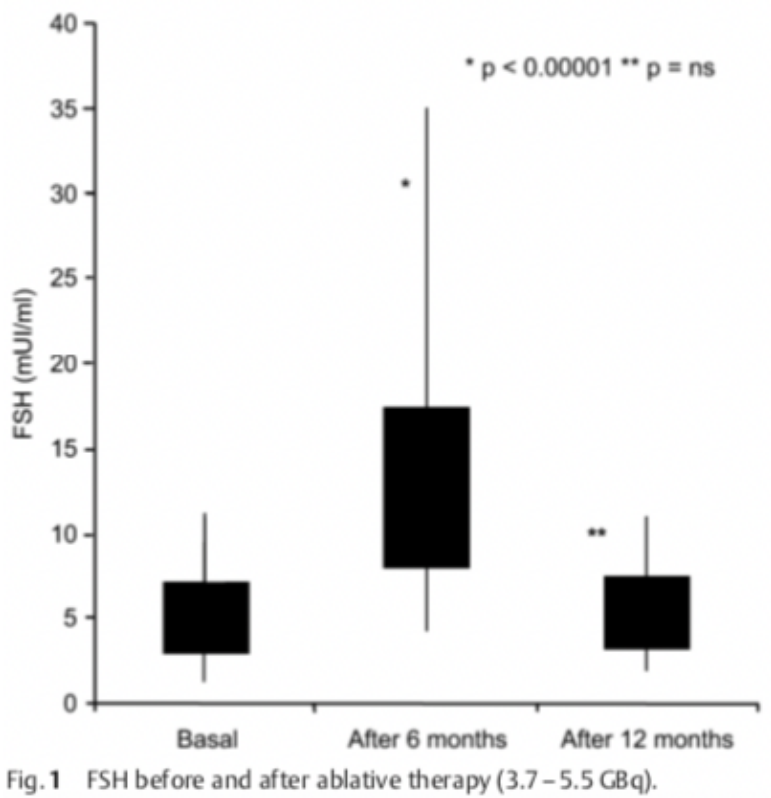


Fig. 1 FSH before and after ablative therapy (3.7 – 5.5 GBq).

50 donne	**19-37 (29.8) aa**
Attività ^{131}I *	**3.7-5.5 GBq (100-149 mCi)**
Dose ovaio	**0.38-0.56 Gy**
Amenorrea	**10/50 (20%)**
FSH	**14/50 (28%)**

*

1.5 Gy	sterilità transitoria
> 3.2 Gy	sterilità permanente

P.W. Spuza Rosàrio
(Exp Clin Endocrinological Diabetes 2005; 113-333)

Evaluation of Ovarian Reserve with AMH Level in Patients with Well-Differentiated Thyroid Cancer Receiving Radioactive Iodine Ablation Treatment

Table 2 Laboratory findings of the patient and control groups.

3.7 – 5.5 GBq : 100 -150 mCi)	PATIENT (n=45)				CONTROL (n=40)				
	Min	Max	Median	M±SD	Min	Max	Median	M±SD	P
AMH (µg/l)	0.80	8.40	2.50	2.82±1.88	1	9.78	2.92	3.35±1.84	0.038
FSH (mIU/ml)	1.55	14.66	5.45	5.81±2.66	3.63	10.12	5.91	6.21±1.38	0.028
LH (mIU/ml)	1.39	20.46	6.53	6.62±3.52	1.44	16.13	5.42	5.79±3.01	0.228
E2 (pg/ml)	11.82	81.84	36.70	38.98±14.01	10.61	88	31.04	36.93±19.62	0.174
TSH (mIU/ml)	0.01	3.27	0.05	0.49±0.87	0.69	4.98	1.62	1.91±1.01	0.001
CR (mg/dl)	0.55	0.82		0.67±0.07	0.62	0.81		0.70±0.04	0.072

AMH: Anti-Müllerian hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, TSH: Thyroid stimulating hormone, CR: creatinine, Min: Minimum, Max: Maximum, M: Mean, SD: Standard Deviation

Oligomenorrea	7/45 (15.6%)	3 – 5 mesi
Gravidanze	8/45 (17.8%)	tutte le gravidanze desiderate hanno avuto successo

F. Acıbucu, D. O. Acıbucu, Ö. B. Akkar, H. S. Dokmetas (Exp Clin Endocrinol Diabetes , 2016)

A Single Radioactive Iodine Treatment Has a Deleterious Effect on Ovarian Reserve in Women with Thyroid Cancer: Results of a Prospective Pilot Study

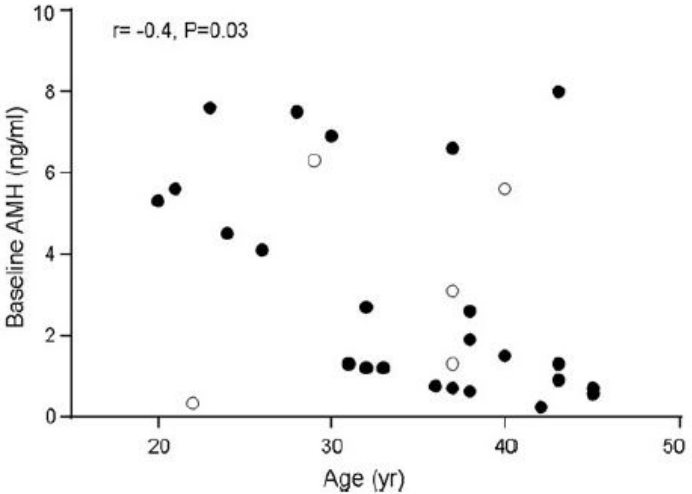


FIG. 1. Baseline serum anti-Müllerian hormone (AMH) levels are inversely correlated with the women's age. All 35 women (30 with differentiated thyroid cancer [solid circles] and five with Graves' disease [empty circles]) are included in this analysis.

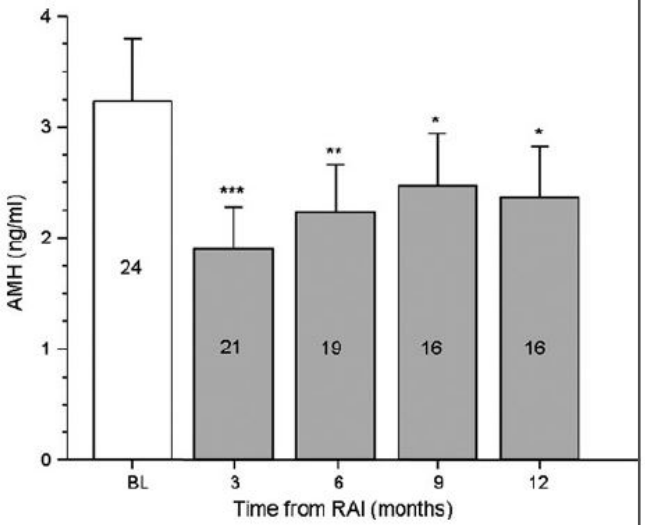


FIG. 2. AMH levels in women with differentiated thyroid cancer in relation to the time elapsed since radioiodine ablation. The number of subjects assessed at each time point is indicated in the box. The bars show the means with standard errors. Significance for paired comparisons relative to baseline is indicated by the asterisks. ***$p<0.005$; **$p<0.01$; *$p<0.05$.

Iris Yaish et al.
(Thyroid, Vol 28, Number 4, 2018)

- **Arruolate**:
  - 24 pz con DTC (stadio I) (età: 20-45 aa)
  - 5 pz con Graves (età: 22-40 aa)
- **Dose di 131I:**
  - pz con DTC: range 1110-5.550 MBq (30 – 150 mCi)
  - pz con Graves: range 370-814 MBq (10 – 22mCi)
- **Dosaggi ormonali**: FSH, LH, E2, AMH (tempo 0' – 3 – 6 – 12 mesi)

Mediana AMH: ng/mL

Basale	3.25 (0.32–17.42)
3 mesi	1 (0.01–3.93)
6 mesi	1.13 (0.08–6.12)
12 mesi	1.37 (0.09–6.1)

A Single Radioactive Iodine Treatment Has a Deleterious Effect on Ovarian Reserve in Women with Thyroid Cancer: Results of a Prospective Pilot Study

Meanwhile, in an era of declining human fertility, **RAI treatment in young women with low-risk DTC should be given with careful thought, particularly in those >35 years** of age who still desire to have a child.

Until further data are available, it is speculated that the **measurement of AMH may be useful as an adjunct decision-making** tool when contemplating RAI ablation in women of reproductive age.

Conclusioni

- La terapia con ^{131}I per l'ipertiroidismo appare sicura
- La terapia con ^{131}I del CDT , in particolare a dosi multiple, rappresenta un rischio di infertilità (transitoria/permanente) sia nel maschio che nella femmina

Elementi da valutare:

- Età
- Stadio del CTD
- Storia di infertilità certa o presunta
- Counselling
- Consulenza endocrinologica
- Crioconservazione del seme

- ✓ *91.36.3 CRIOCONSERVAZIONE IN AZOTO LIQUIDO DI CELLULE E TESSUTI C.U.R. C00459800*
- ✓ *90.31.4 LIQUIDO SEMINALE ESAME MORFOLOGICO E INDICE DI FERTILITA' C.U.R. C0028010*
- ✓ *Ricevuta di pagamento di un ticket di € 46,15, di cui 36,15 euro per la prestazione e 10 euro di quota fissa regionale sulla richiesta, a meno di esenzione. A partire dal secondo anno di crioconservazione il Paziente è tenuto al pagamento di una quota annua di € 60,00*

Grazie per l'attenzione

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