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## Radiotherapy in non functioning pituitary adenomas

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## Disclosures

- None relevant to the current presentation

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## Agenda

- Natural history of NFPA
- Can we identify which NFPA will recur?
- RT to all patients or should we wait
- Long term adverse events of RT
- Is there any difference between RT modalities?
- Guidelines

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## Natural history: metanalysis

	No detectable postoperative residual tumor	Residual tumor
Recurrence rate	12% (6-19)	46% (36-56)
Tumor growth free survival rate at 5 years	96 (89-99)	56% (41-71)
Tumor growth free survival rate at 10 years	82 (65-94)	40% (27-53%)

19 studies with 1614 patients  
Only NFPA  
No postoperative radiotherapy

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Chen Y. Neuroendocrinology. 2012;96:333

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## Natural history: metanalysis

### Tumor volume doubling time

Study reference	TVDT	P-TVDT	95% CI
Hsu C.Y., 2010 [65]	3.0	3.00	[2.10; 4.00]
Honegger J., 2008 [66]	3.0	3.00	[2.10; 4.00]
Tanaka Y., 2003 [61]	5.0	5.00	[4.00; 6.00]
Ekramullah S.M., 1996 [62]	2.5	2.50	[1.70; 3.50]
<b>Summary</b>	<b>3.4</b>	<b>3.40</b>	<b>[2.40; 4.50]</b>

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## WHEN IS RADIOTHERAPY INDICATED?

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### Indications

- If patient has surgical contraindications
- Patient's preferences
- Immediately after surgery
- After tumor recurrence
- After remnant regrowth

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### Goals of radiation therapy

- Arrest tumor growth
- Preserve pituitary function
- Minimize adverse events
- Partial shrinkage or complete resolution as secondary goals

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Loeffler JS. J Clin Endocrinol Metab. 2011;96:1992



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### CAN WE PREDICT TUMOR RECURRENCE?

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### Risk factors for recurrence

- Silent pituitary adenomas (positive immunolabeling for one or more hormones)
  - Not in the Mexican series
- Presence of remnants after surgery
- Giant adenomas (>4 cm)
- Cavernous sinus invasion
- Ki67?

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Losa M. J Endocrinol Invest. 2011;34:623

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### Histologic risk factors (French consensus)

- Silent corticotroph adenoma
  - Higher rate of cavernous sinus invasion
  - Recurrence similar to other NFPA but earlier and more aggressive
- Ki67?
- p53?
- SST2 and SST5?

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Cortet-Rudelli C. Ann Endocrinol. 2015;76:228

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### EFFICACY

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### Recurrence rate

	Recurrence rate n(%)	Median time to recurrence
Gross total resection (n=308)	19 (6,18%)	
With RT (n=60)	6 (10%)	5.3 years
W/O RT (n=248)	13 (5,24%)	6.9 years
Subtotal resection (n=352)	45 (12,64%)	
With RT (n=277)	24 (8,66%)	8.7 years
Without RT (n=75)	21 (28%)	3.8 years

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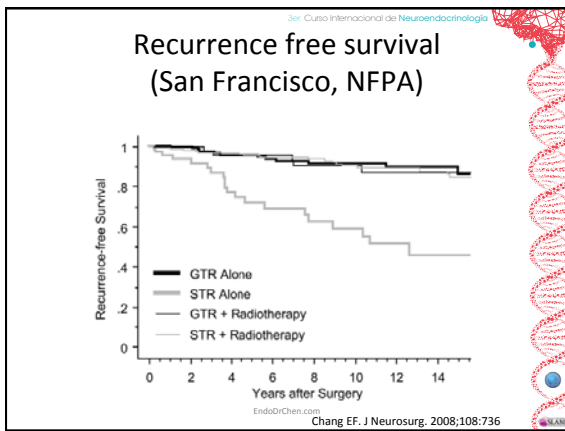
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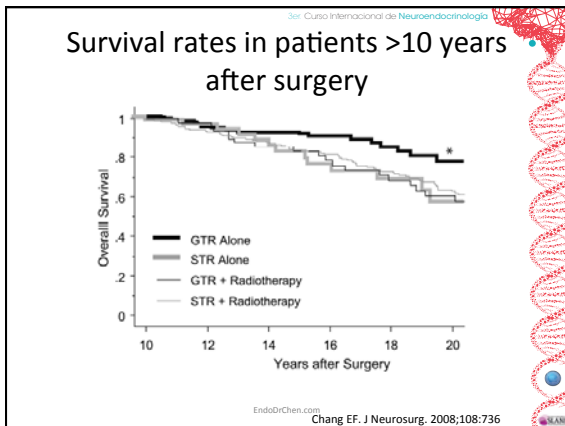
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## Caveats

- There may be some bias in most observational studies
  - Patient selection not very clear
    - Risk of recurrence
    - Histological characteristics
    - Patient's choice
    - Logistical constraints
  - Time of follow up may differ with different techniques (more prolonged with CRT)

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## Tumor recurrence with CRT

Author	Year	N	Median FU	PFS at 10 years (%)
Brada	1993	252	11	97
Hughes	1993	121	NA	82
Tsang	1994	128	8	91
Breen	1998	120	9	87
Gittoes	1998	63	8	93
Woollons	2000	50	5	NA
Park	2004	44	6	98
Van den Bergh	2007	76	8	95

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## Progression free survival GK

Author	Year	N	Median FU	PFS at 5 years
Wovra	2002	45	55	93
Petrovich	2003	56	36	94
Losa	2004	54	41	88
Iwai	2005	31	60	93
Liscak	2007	79	60	100
Pollock	2008	62	64	95

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### Impact in tumor recurrence

- Mexico:
  - 51 patients with XRT (LINAC)
    - 50% decrease in tumor volume at 5 years
    - Tumor progression 4%
  - 61 patients (matched by age, gender, remnant size, cavernous sinus invasion)
    - 29% tumor progression rate
  - No cerebrovascular events, optic neuritis, secondary tumors or deaths with XRT

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Vargas G. Int J Endocrinol. 2015 <http://dx.doi.org/10.1155/2015/756069>

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### Efficacy summary

- Although limitations of case series and observational studies, it seems to be quite clear that RT prevents regrowth of NFPA
- However, if tumor recurrence is slow and not 100%
- Risk of adverse events must be weighed in

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### RADIOTHERAPY AND ADVERSE EVENTS

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## Complications

- Optic nerve pathway
- Vascular
- Second tumor
- Hypopituitarism
- Cognitive defects

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## Optic pathway damage

- Less than 1-2%
- Depends largely of administered dose and localization
- With modern planning and techniques it has become less frequent
- In one of the largest series, rate of radiation induced optic neuropathy was 0.8% at 10 years
  - A patient had visual deterioration after 15 years

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## Cerebrovascular events

- Edinburg series
  - 74/385 patients with cerebrovascular events
  - Mean age 70 years
  - Male RR 1.45 (1.05-1.96) and females 2.22 (1.56-3.08)
  - 40% fatal
  - Does not differentiate event rates in NFPA vs functioning adenomas

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Erridge SC. Radiotherapy Oncol. 2009;93:597



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## Cerebrovascular

- Ionizing radiation leads to prothrombotic state and vascular inflammatory reaction
- In the medium to long term may lead to or aggravate atherosclerosis
- Hypopituitarism may increase vascular risk
- Specially associated with conventional RT

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Cortet-Rudelli C. Ann Endocrinol. 2015;76:228




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## Secondary tumors

- Edinburg series
  - 20 year actuarial risk of second intracranial tumor 1.9% (0-2.6)
  - Male RR 5.65 (n=2) and females 9.94 (n=2)
  - Cerebral lymphoma, brain stem glioma, glioblastoma multiforme, sphenoid wing meningioma

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## Secondary tumor

- Royal Marsden Hospital
  - 11/426 of all pituitary adenomas: 2.58%
    - 7/263 of NFPA: 2.66%
    - 4/163 of FPA: 2.45%
  - Meningioma (5), high grade astrocytoma (4), sarcoma (1), primitive neuroectodermal tumor (1)
  - Cumulative incidence
    - 2% (0.9-4.4) at 10 years
    - 2.4% (1.2-5.0) at 20 years
    - 8.5% (3.1-21.8) at 30 years
  - RR 10.5 (4.3-16.7)

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Minniti G. J Clin Endocrinol Metab. 2005;90:800




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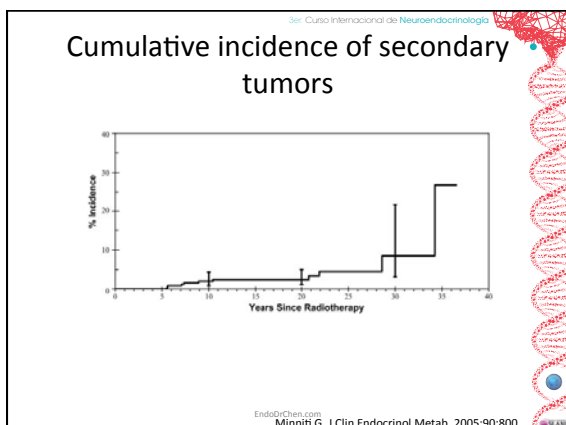
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- ### Causal relationship?
- Benign asymptomatic small meningioma prevalence may be underestimated in general population
  - Increased incidence of brain tumors in patients with NFPA??
    - Not demonstrated
  - SRS have a lower risk??
    - Not demonstrated, not enough patients and not enough follow up time
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### Hypopituitarism

	ACTH	TSH	Gonadotrophin
Deficient at presentation	54 (16%)	53 (16%)	74 (43%)
Deficient post-surgery	84 (24%)	45 (14%)	18 (11%)
Deficient post-radiotherapy	66 (19%)	87 (26%)	48 (28%)
No deficiency	143 (41%)	145 (44%)	31 (18%)
No data/not applicable	35	52	24

- The actuarial deficiency attributable to radiotherapy at 10 years
  - 22% TSH
  - 19% ACTH
  - 25% sex hormones

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## Hypopituitarism

- Older series report pituitary deficiency if dose <12 Gy and doses >20 Gy result in deficit
  - Recommended dose of SRS for NFPA is 18 Gy
    - However there is still long term hypopituitarism
  - Time to onset of hormonal deficiency was shorter with higher doses
- Predictive factors:
  - Larger baseline tumor volume
  - Preexisting pituitary deficiency

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## Dosimetry and cognitive function

	With different RT techniques				P value*
	Three fields	Four fields	Five fields	Without RT	
n	10	15	5	45	
Estimated dosimetric data (RT dose received at 30/50/70% of the volume of)					
Left hippocampus (Gy)	23.0/3.2/2.0	21.8/14.9/13.5	19.6/4.1/2.9		
Right hippocampus (Gy)	28.5/4.4/2.0	29.8/15.2/14.2	19.0/4.8/2.8		
Prefrontal cortex (Gy)	23.0/19.0/3.6	26.5/18.2/17.3	25.6/16.2/4.9		
Memory performance (15 Words Test, mean (s.d.))					
Short-term memory	-0.13 (1.42)	-0.65 (0.90)	-0.39 (1.23)	-0.20 (1.09)	0.536
Total memory	-0.46 (1.66)	-1.33 (1.07)	-0.92 (0.72)	-0.62 (1.15)	0.337
Learning score	-0.23 (1.17)	-0.70 (0.93)	-0.16 (0.90)	-0.22 (1.04)	0.280
Delayed memory	0.00 (1.39)	-0.96 (1.21)	-1.26 (0.67)	-0.86 (1.19)	0.249
Executive functioning (Ruff Figural Fluency Test, mean (s.d.))					
Unique designs	-0.32 (1.08)	-1.19 (1.08)	-0.43 (1.39)	-0.56 (1.13)	0.150
Perservative errors	-0.87 (0.73)	-0.60 (0.89)	-0.61 (0.67)	-0.33 (1.46)	0.618
Error ratio	-0.80 (0.48)	-0.31 (1.40)	-0.59 (0.71)	-0.09 (1.78)	0.732

\*P values by Kruskal-Wallis ANOVA. Cognitive performance data are given as Z-scores.

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Brummelman P. Eur J Endocrinol. 2012;166:171

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## Limitations

- Most series includes several types of adenomas
- Hormonal effect on cognitive functions
- Overall, conclusion is that pituitary adenoma and surgery (specially craniotomy) impacts cognitive function
- Hormone replacement is a key factor in cognitive function

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Murovic J. World Neurosurg. 2012;78:53

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**RADIOTHERAPY MODALITY**

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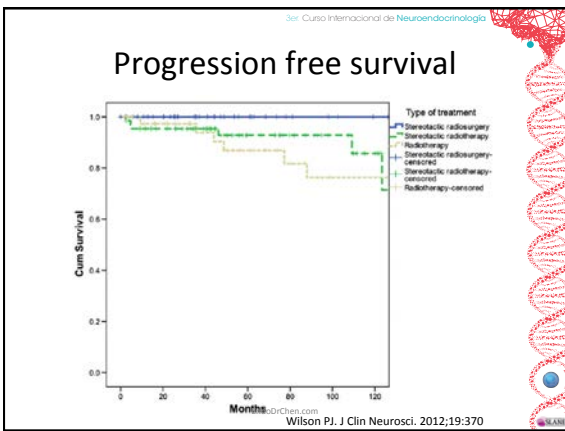
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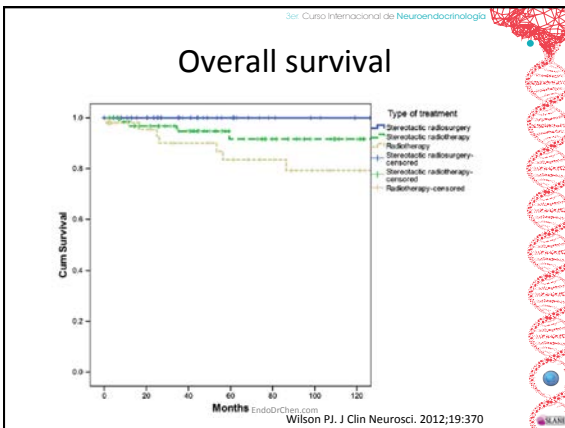
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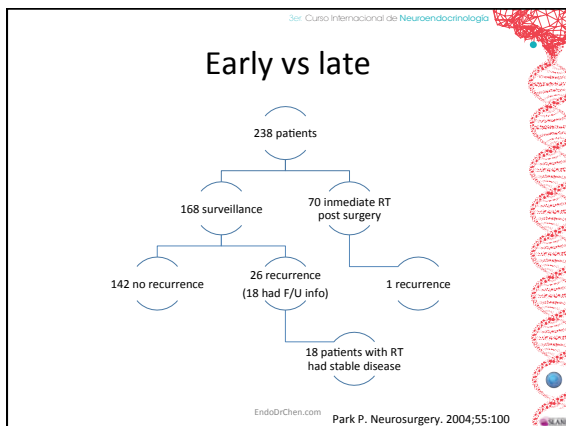
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	Control tumoral	Hypopituitarism	Ophtalmologic complications
Conventional radiotherapy	70-100% 70-90% (20 years)	50-80% >10 years	<1%
Fractionated stereotactic	93-100%	5-35%	<1%
Cyber Knife	93-98%	0-20%	0-1%
LINAC	93-98%	0-9.8%	<2%
Gamma knife	89.9-100%	7-40%	0-13.7%

EndoDrChen.com Cortet-Rudelli C. Ann Endocrinol. 2015;76:228

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	Secondary tumor	Radionecrosis	Vascular
Conventional radiotherapy	1.9-2.7% at 20 years	↓↓↓	RR 1.5-4
Fractionated stereotactic	?	↓↓↓	Not reported
Cyber Knife	?	?	Not reported
LINAC	?	Reported	Intracavernous carotid stenosis
Gamma knife	Rare glioblastoma, sarcoma	?	Intracavernous carotid stenosis

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**NON FUNCTIONING PITUITARY ADENOMA GUIDELINES**

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**French Endocrinology Society Guidelines**

- Various types of RT show comparable efficacy in terms of tumoral control
- Which technique?
  - Size, delineation and relation to adjacent neural structures
  - Particular center’s technical experience
  - Patient’s availability for follow up

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Chanson P et al. Ann Endocrinol (Paris). 2015.

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**French Endocrinology Society Guidelines**

- Systematic postoperative RT is not indicated following complete resection
- Significant residual tumor, RT should be considered, taking account of risk factors for regrowth, patient age and history and presence of hypopituitarism

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Chanson P et al. Ann Endocrinol (Paris). 2015.

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## French Endocrinology Society Guidelines

- In most cases, first line can be regular surveillance postponing RT until recurrence is confirmed
- First line RT may be indicated in case of high regrowth potential and if the risk of hypopituitarism is no longer a major problem

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Chanson P et al. Ann Endocrinol (Paris). 2015.

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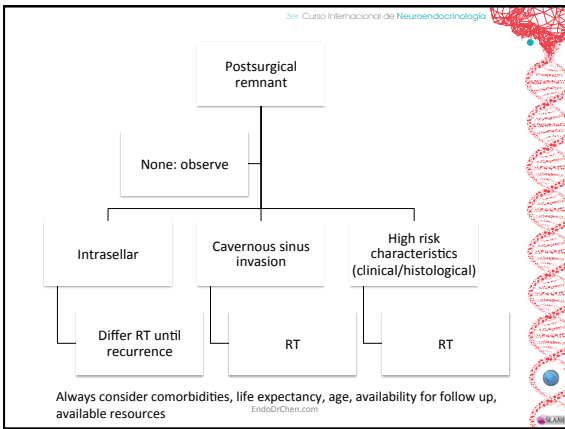
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## Conclusion

- Residual tumor after surgical resection has a high recurrence rate
- Risk factors for recurrence include residual tumor, cavernous sinus invasion, giant adenomas
- Radiotherapy is very effective preventing recurrence
- Selective use of radiotherapy
- Side effects include hypopituitarism, it is not that clear with secondary tumor or vascular events

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Questions...

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