MANAGEMENT OF DIFFERENTIATED THYROID CANCER

CURRENT TRENDS

ABCD AUTUMN MEETING

RCP NOV 2012

DTC

- 1INCIDENCE ↑

- SURVIVAL ↑

. **PRE-OP MOLECULAR PROFILING**

- **SURGERY -- Extent-**
  ---TT+ PCCND T1 T2 PTC
  --Robotic Transaxillary ,BABA, MIVAT, Intra

operative Nerve Monitoring ,Per –op RN probe, Sentinel node biopsy etc

DTC

- **Molecular Targeted Radiotherapy-- I131 - Magic Bullet.**

  AT RISK -SPM

  RAI **1.Low (1.1GBq) vs High (3.7) ---HILO TRIAL**

  2. Abl vs No abl ----------ION TRIAL

- **Targeted " Kinome "Inhibition. Iodine Refractory DTC**
- **Re differentiation MEKI-NIS ,HDAC etc.**
- **NIS –Theranostics, Transfection,Reporter Gene in cell trafficking, Cell Motility**

TYPES OF TC

Table 1 | Types of thyroid cancer and their mutational profiles

Characteristics	Papillary carcinoma	Follicular carcinoma	Poorly differentiated carcinoma	Anaplastic (undifferentiated) carcinoma	Medullary carcinoma
Cell type	Follicular	Follicular	Follicular	Follicular	C cell
Main histopathologic variants	Classic papillary type, microcarcinoma, follicular variant, tall-cell variant	Conventional type, oncocytic (Hurthle cell) type	–	–	–
Prevalence (%)	80–85	10–15	<2	1–2	3–5
Frequency of familial forms (%)	5	5	0	0	15–30
Typical route of spread	Local lymph-node metastasis	Hematogenous metastasis, typically to bones and lungs	Invasive local growth, lymph-node and hematogeneous metastases	Invasive local growth, lymph-node and hematogeneous metastases	Lymph-node and hematogeneous metastases
10-year survival (%)	95–98	90–95	~50	<10	60–80
Common mutations and their prevalence (%)	*BRAF* 40–45 *RAS* 10–20 *RET/PTC* 10–20 *TRK* <5	*RAS* 40–50 *PAX8/PPARγ* 30–35 *PIK3CA* <10 *PTEN* <10	*RAS* 20–40 *TP53* 20–30 *BRAF* 10–20 *CTNNB1** 10–20 *PIK3CA* 5–10 *AKT1* 5–10	*TP53* 50–80 *CTNNB1** 5–60 *RAS* 20–40 *BRAF* 20–40 *PIK3CA* 10–20 *PTEN* 5–15 *AKT1* 5–10	Familial forms: *RET* >95 Sporadic: *RET* 40–50 *RAS* 25

*The gene that encodes β-catenin.

INCIDENCE

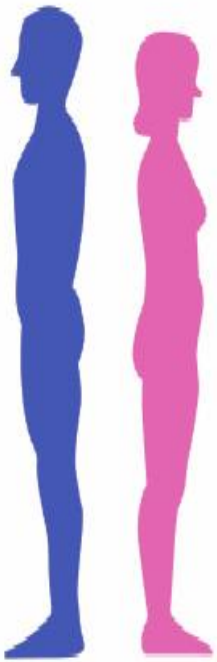
- Fastest rising incidence of any cancer in both men and women- ACS 2011.
- Both US detection and real increase
- From 1970 2.6 times increase in incidence in US
- Most frequently occurring endocrine cancer
- 2100 new cases each year in the UK,
- 48,000 in the United States
- >200,000 worldwide.
- FTC is still common in developing countries,

INCIDENCE

- Low risk ,small,curable PTC , -? Radiation
- Affects all ages with half of patients aged under 50 years.
- F :M about 3 :1
- **The increasing incidence of thyroid cancer and high rates of survival will result in an increasingly large population of survivors and associated health care demands.(Jemal)**
- **AT RISK OF RAI RELATED SPM (IF USED)**

2011 USA -JEMAL

Estimated New Cases*

Males				Females		
Prostate	240,890	29%		Breast	230,480	30%
Lung & bronchus	115,060	14%		Lung & bronchus	106,070	14%
Colon & rectum	71,850	9%		Colon & rectum	69,360	9%
Urinary bladder	52,020	6%		Uterine corpus	46,470	6%
Melanoma of the skin	40,010	5%		Thyroid	36,550	5%
Kidney & renal pelvis	37,120	5%		Non-Hodgkin lymphoma	30,300	4%
Non-Hodgkin lymphoma	36,060	4%		Melanoma of the skin	30,220	4%
Oral cavity & pharynx	27,710	3%		Kidney & renal pelvis	23,800	3%
Leukemia	25,320	3%		Ovary	21,990	3%
Pancreas	22,050	3%		Pancreas	21,980	3%
All Sites	**822,300**	**100%**		**All Sites**	**774,370**	**100%**

CANCER DEATHS

Estimated Deaths

Males			Females		
Lung & bronchus	85,600	28%	Lung & bronchus	71,340	26%
Prostate	33,720	11%	Breast	39,520	15%
Colon & rectum	25,250	8%	Colon & rectum	24,130	9%
Pancreas	19,360	6%	Pancreas	18,300	7%
Liver & intrahepatic bile duct	13,260	4%	Ovary	15,460	6%
Leukemia	12,740	4%	Non-Hodgkin lymphoma	9,570	4%
Esophagus	11,910	4%	Leukemia	9,040	3%
Urinary bladder	10,670	4%	Uterine Corpus	8,120	3%
Non-Hodgkin lymphoma	9,750	3%	Liver & intrahepatic bile duct	6,330	2%
Kidney & renal pelvis	8,270	3%	Brain & other nervous system	5,670	2%
All Sites	**300,430**	**100%**	**All Sites**	**271,520**	**100%**

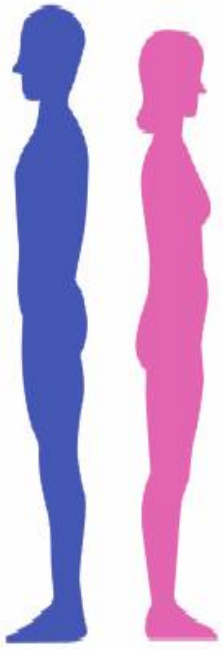
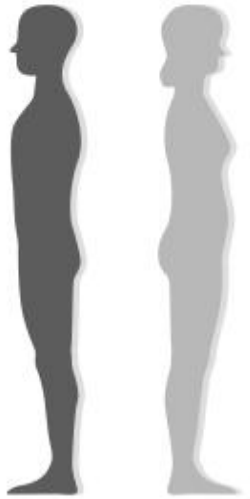


FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths By Sex, United States, 2011.
*Estimates are rounded to the nearest 10 and exclude basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

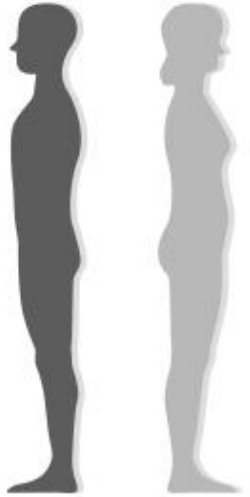
SOUTH KOREA

A



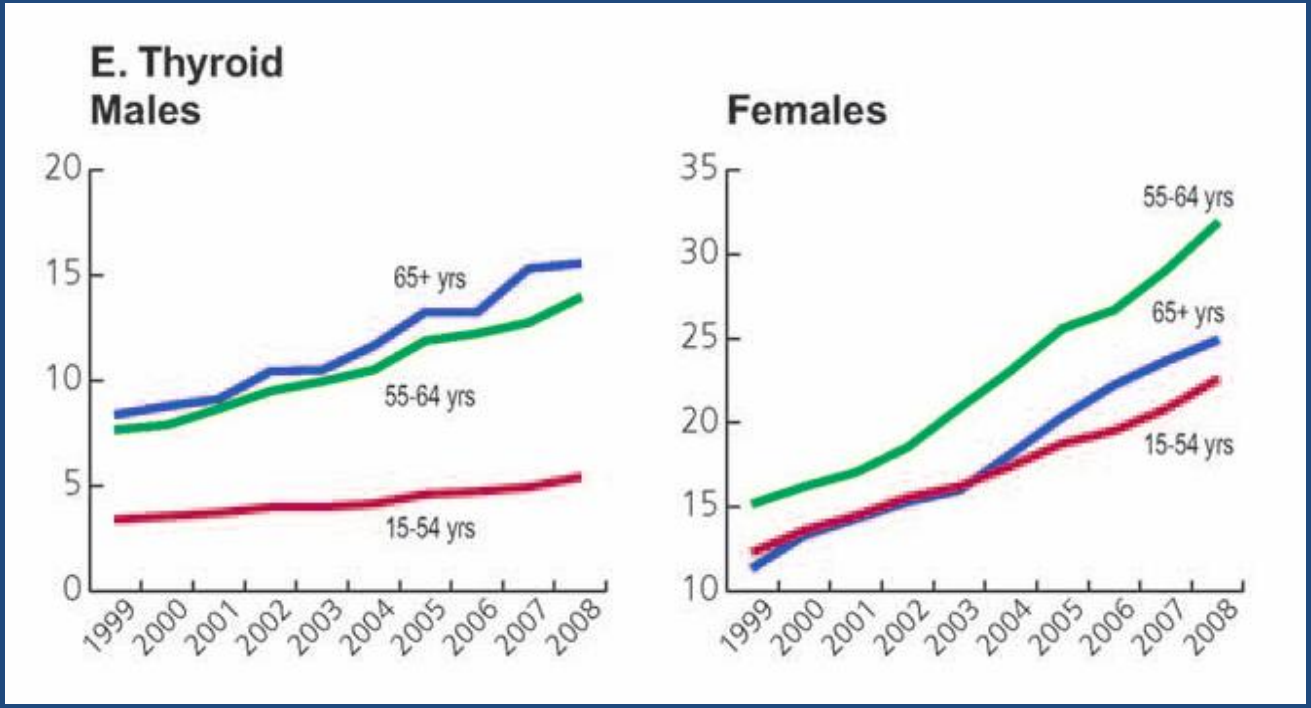
	(%)		(%)	
Stomach	19.0		30.5	Thyroid
Colon and rectum	16.3		14.5	Breast
Lung	14.0		11.0	Colon and rectum
Liver	11.2		9.4	Stomach
Prostate	8.6		6.0	Lung
Thyroid	5.2		4.0	Liver
Bladder	2.8		3.2	Cervix uteri
Pancreas	2.5		2.5	Gallbladder etc.
Kidney	2.5		2.2	Pancreas
Gallbladder etc.	2.3		2.0	Ovary
All sites	**100.0**		**100.0**	**All sites**

B

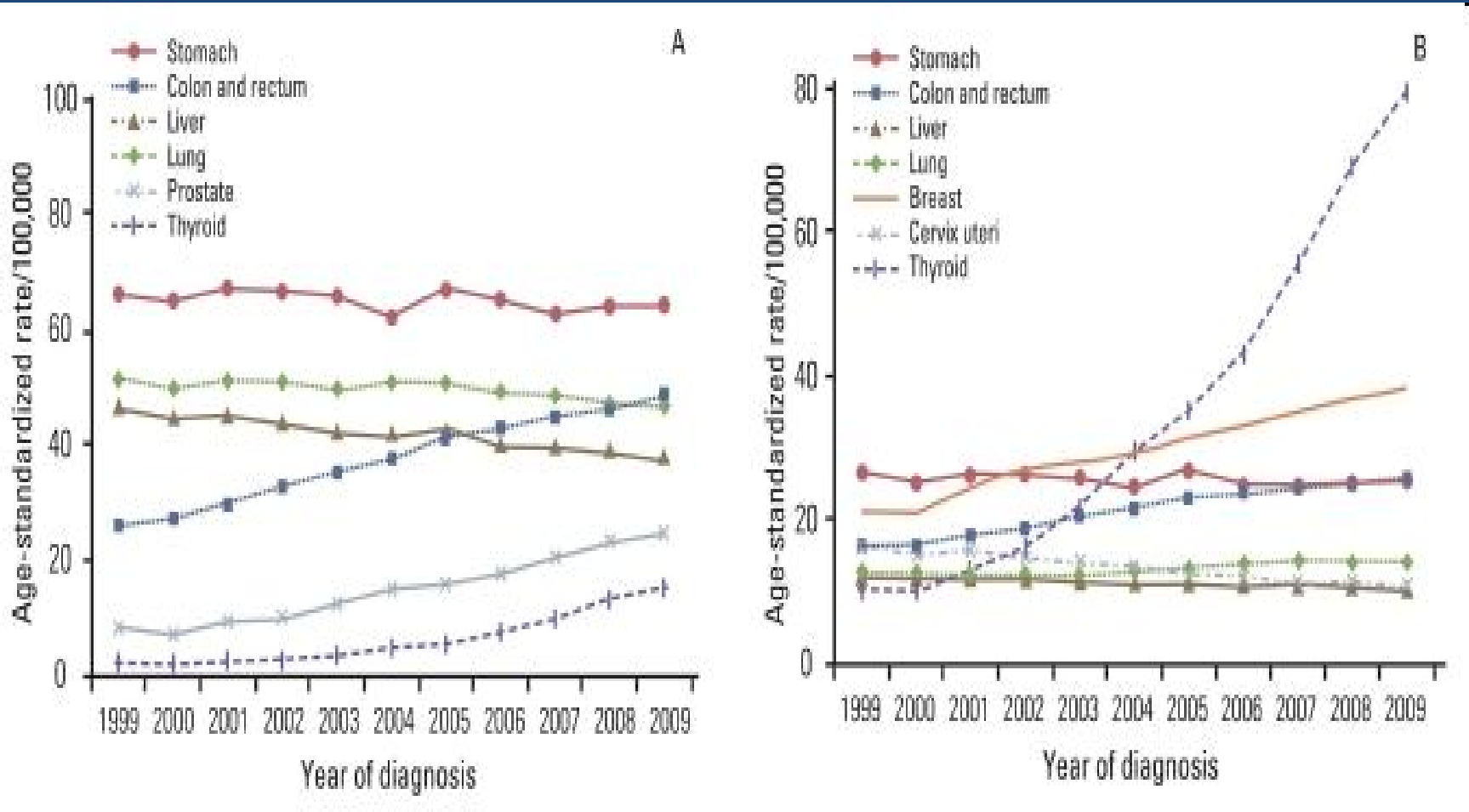


	(%)		(%)	
Lung	26.0		15.8	Lung
Liver	18.5		12.8	Colon and rectum
Stomach	13.1		11.7	Stomach
Colon and rectum	9.8		10.4	Liver
Pancreas	5.2		7.9	Pancreas
Gallbladder etc.	4.1		7.8	Breast
Prostate	3.3		7.5	Gallbladder etc.
Esophagus	2.6		3.6	Ovary
Leukemia	2.1		3.2	Cervix uteri
Non-Hodgkin lymphoma	1.9		2.6	Leukemia
All sites	**100.0**		**100.0**	**All sites**

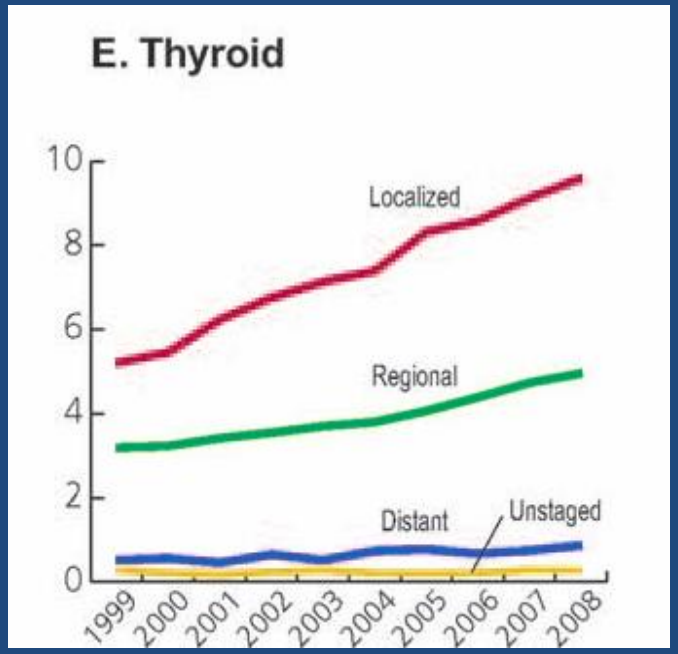
RATES /100,000-JEMAL 2012



RISING INCIDENCE-KOREA



Incidence rates increased for tumors of all stages, although the greatest increase was in the incidence of localized disease (from 5.2 in 1999 to 9.6 in 2008)



INCREASING INCIDENCE

- Increased detection of small neoplasms, and True increase of mainly PTC (Cramer ,Jemal)
- DTC patients diagnosed after 1990 have smaller tumors , less advanced stage and a better prognosis (Elisei)

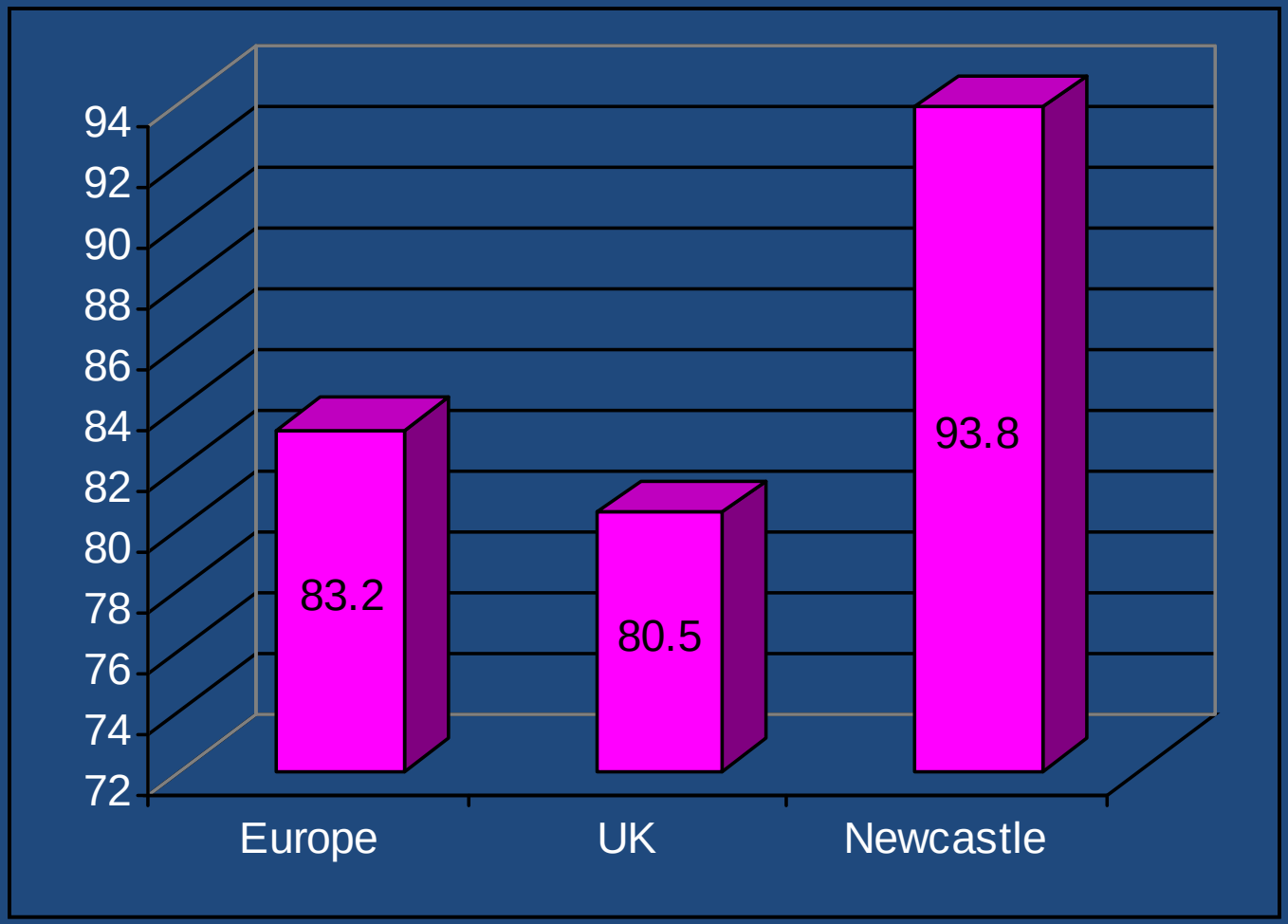
EUROCARE 4

Verdecchia A, et al

EUROCARE-4 Working Group. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *The Lancet* 2007; Vol. 8.

- The European mean age-adjusted 5-year survival calculated by the period method for 2000-02
- Thyroid cancer (83.2% [80.9-85.6]).

Five Year Relative Survival Rates: REGISTRY vs Institutional data



DTC

- 1INCIDENCE ↑
- SURVIVAL ↑
- PRE-OP MOLECULAR PROFILING
- SURGERY -- Extent-
  ---TT+ PCCND T1 T2 PTC

  --Robotic Transaxillary ,BABA, MIVAT, Intra operative Nerve Monitoring ,Per –

op RN probe, Sentinel node biopsy etc

DTC

- **Molecular Targeted Radiotherapy-- I131 - Magic Bullet.**

  AT RISK -SPM

  RAI 1.Low (1.1GBq) vs High (3.7) (surgical variation) –---------- --HILO TRIAL

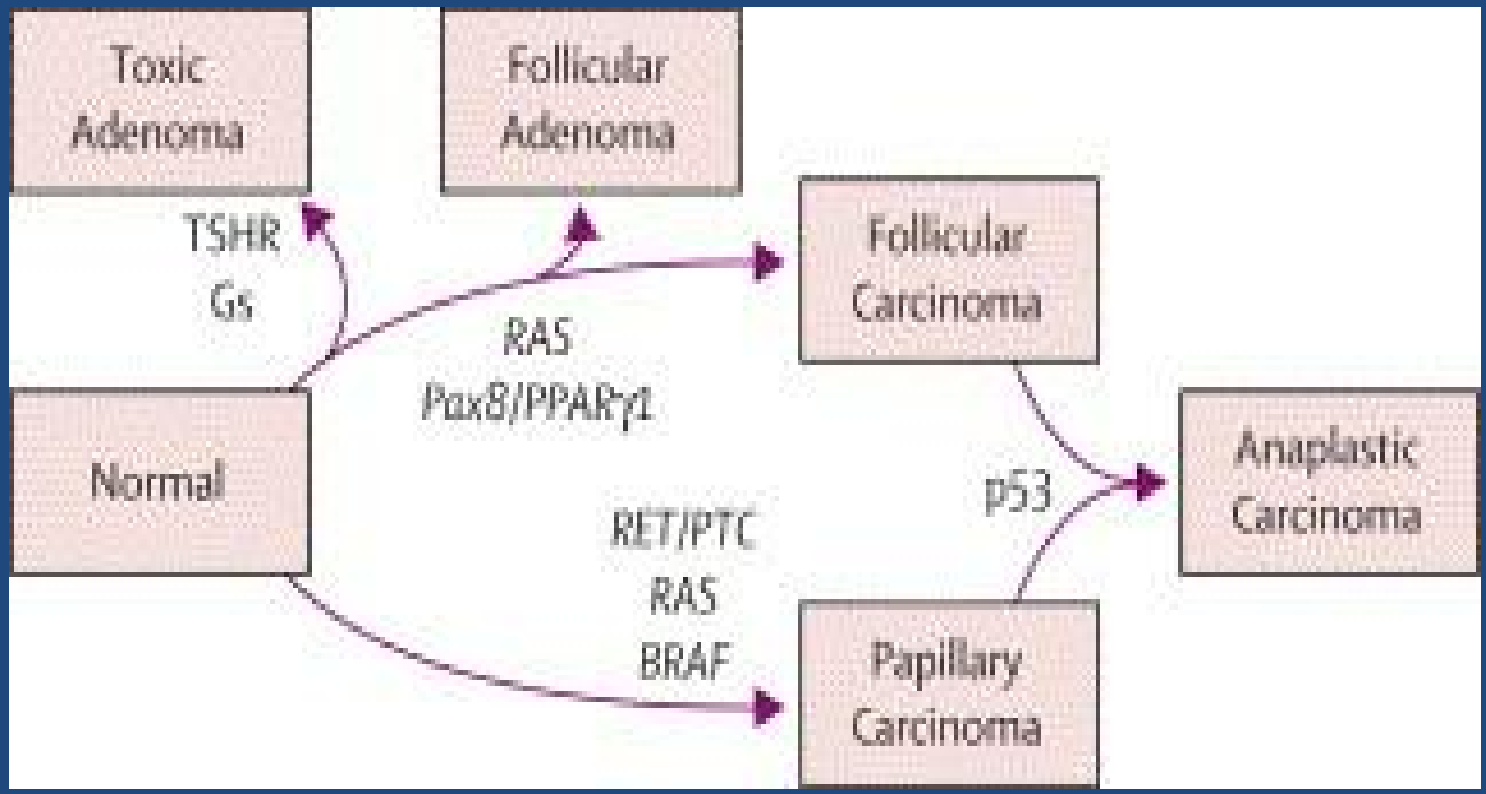
  2. Abl vs No abl ---ION TRIAL

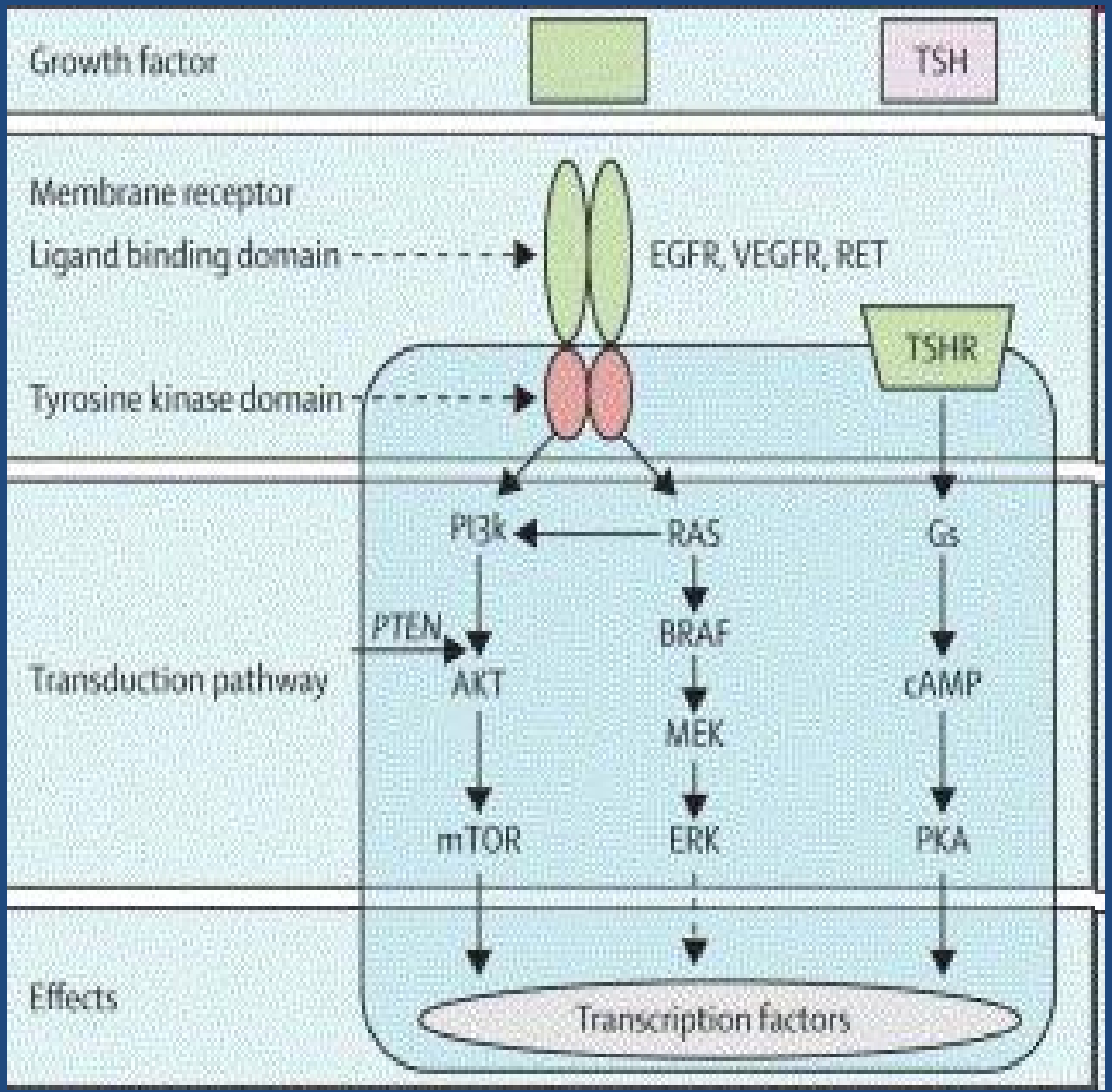
- **Targeted " Kinome "Inhibition. Iodine Refractory DTC**

- **Re differentiation MEKI-NIS ,HDAC etc.**

- **NIS –Theranostics, Transfection,Reporter Gene in cell trafficking, Cell Motility**

GENES IMPLICATED




Growth factor
TSH
Membrane receptor
Ligand binding domain
EGFR, VEGFR, RET
TSHR
Tyrosine kinase domain
PI3k
RAS
Gs
PTEN
BRAF
AKT
cAMP
MEK
mTOR
ERK
PKA
Transduction pathway
Effects
Transcription factors

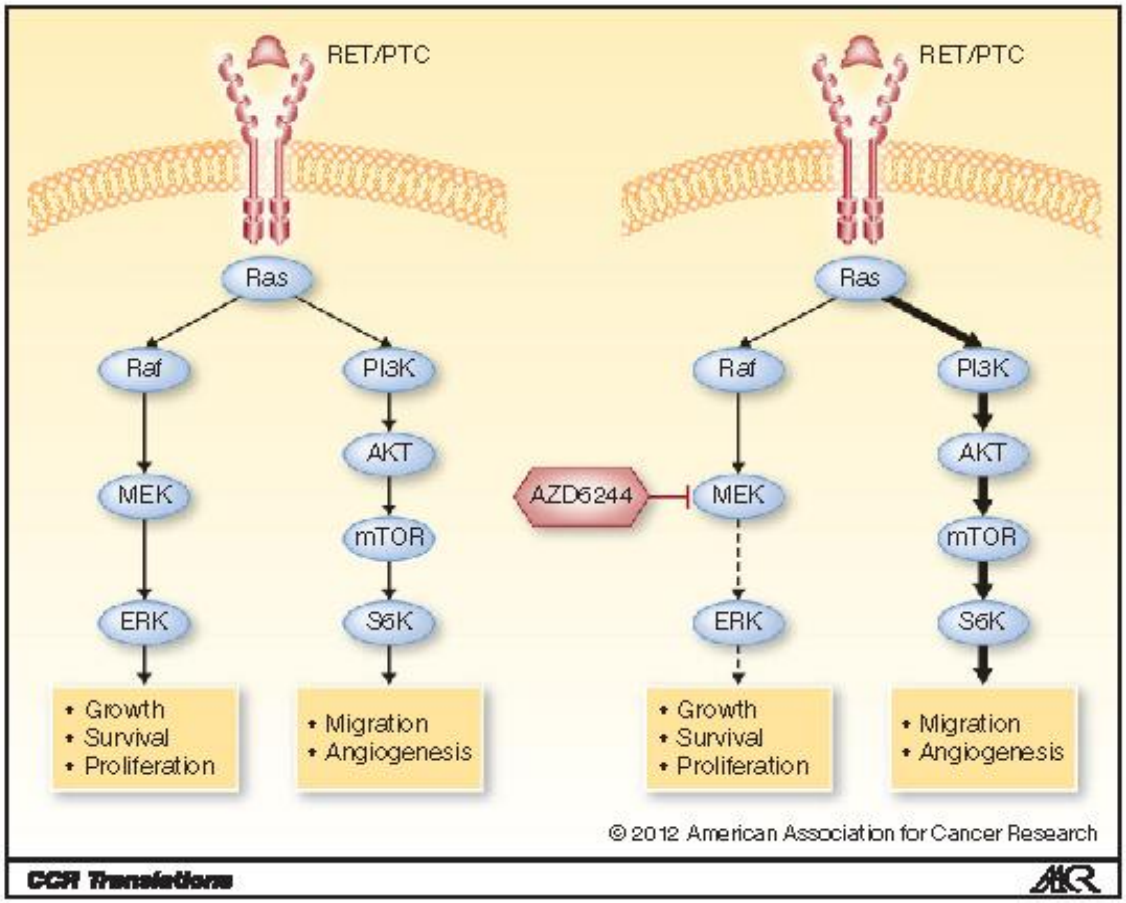
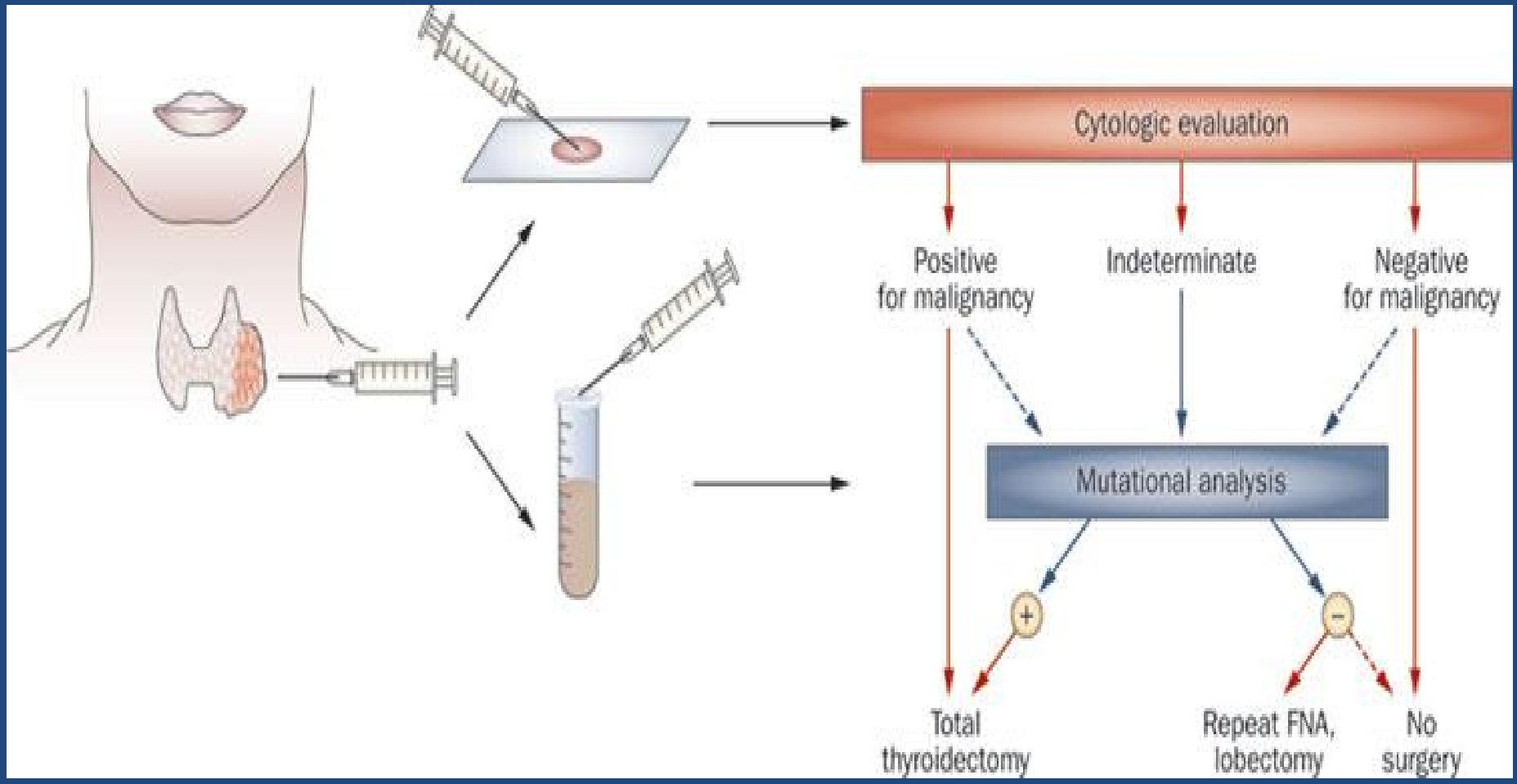


Figure 1. Selective targeting of MEK 1/2 in PTC. Intracellular-signaling pathway aberrancy is critical to the molecular pathophysiology of thyroid cancer tumorigenesis. In tumor cells (left), altered expression and mutation involving B-Raf, Ras, and Akt have been implicated in a wide variety of thyroid cancer cell types. In the tumor microenvironment, angiogenesis is also a critical step in tumor progression and metastasis. Angiogenesis is mediated primarily through VEGFR-2, which also signals through Raf and Akt. Inhibition of VEGFR-2 has proved to be a successful therapeutic strategy in thyroid cancer in which drugs such as bevacizumab, sorafenib, sunitinib, axitinib, and motesanib have activity as single agents. VEGFR-2 has been found to be expressed on tumor cells in thyroid cancer, raising the question of whether multikinase inhibitor therapy might also be exerting an effect on the tumor cells themselves.

MOLECULAR PROFILING



PRE-OP MOLECULAR PROFILING

- 15 - 30% of Thyroid Nodules evaluated by FNA are not clearly benign or malignant (cytologically indeterminate)

- Only 20-30% are Malignant on lobectomy

- Diagnostic tests-

  AGEC (Veracyte)- Confirming benignity

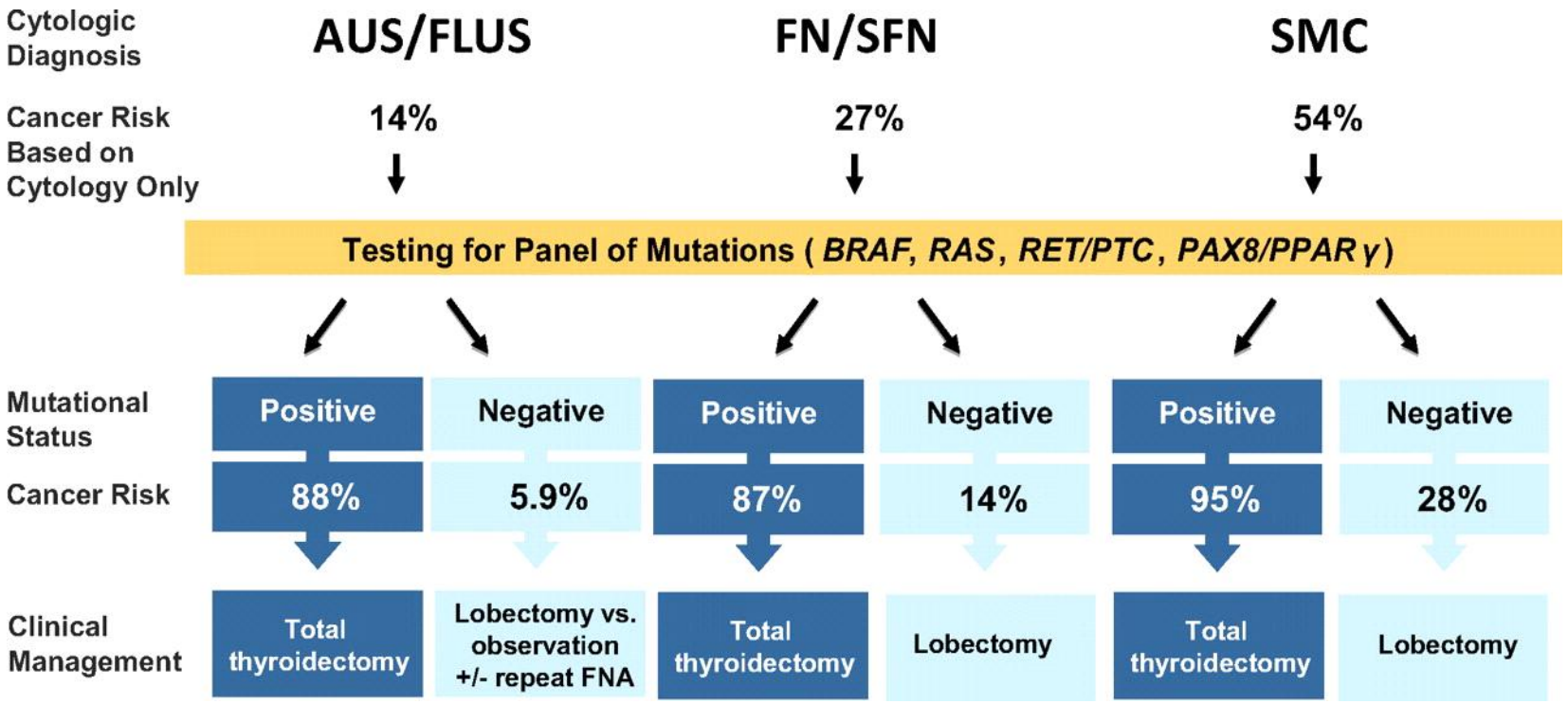
  167 genes has shown promise in improving preoperative risk assessment.

  Assuragen – Confirming malignancy

  PTC BRAF,RET/PTC,

  FTC H-,K-,N –RAS,PAX8,PPAR-G

Proposed clinical algorithm for management of patients with cytologically indeterminate thyroid FNA applying the results of mutational analysis.



Nikiforov Y E et al. JCEM 2011;96:3390-3397

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

J Am Coll Surg.2012 Jul 4.

Intraoperative Pathologic Examination in the Era of Molecular Testing for Differentiated Thyroid Cancer.

McCoy KL, Carty SE, Nikiforov YE

Division of Endocrine Surgery, University of Pittsburgh, Pittsburgh, PA.

STUDY DESIGN:

- In a retrospective, consecutive cohort study, we compared outcomes of 670 patients undergoing thyroidectomy.

CONCLUSIONS:

- Together with the Bethesda cytologic criteria, preoperative MT allows for an increased rate of initial definitive total thyroidectomy
- Eliminates the need for routine intraoperative pathologic examination during diagnostic lobectomy.

N Engl J Med. 2012 Aug 23;367(8):705-15.
Preoperative diagnosis of benign thyroid nodules with indeterminate cytology.
Alexander EK, Kloos RT LiVolsi VA, Rosai J Haugen BR

METHODS:

- 19-month, prospective, multicenter validation study involving 49 clinical sites, 3789 patients, and 4812 fine-needle aspirates from thyroid nodules 1 cm or larger that required evaluation.
- After inclusion criteria were met, a GEC was used to test 265 indeterminate nodules in this analysis, and its performance was assessed.

Alexander EK, Kloos RT LiVolsi VA, Rosai J Haugen BR

- **RESULTS:**
- Of the 265 indeterminate nodules, 85 were malignant.
- The GEC correctly identified 78 of the 85 nodules as suspicious (92% sensitivity; 95% confidence interval [CI], 84 to 97), with a specificity of 52% (95% CI, 44 to 59).
- The negative predictive values for "atypia (or follicular lesion) of undetermined clinical significance," "follicular neoplasm or lesion suspicious for follicular neoplasm," or "suspicious cytologic findings" were 95%, 94%, and 85%, respectively.

- **CONCLUSIONS:**
- These data suggest consideration of a more conservative approach for most patients with thyroid nodules that are cytologically indeterminate on fine-needle aspiration and benign according to gene-expression classifier results. (Funded by Veracyte.)

Alexander et al

- AGEC Designed to identify benign, rather than malignant.
- NPV was 95% for aspirates classified as atypia (or follicular lesions) of undetermined significance and 94% for aspirates classified as follicular neoplasms or lesions suspicious for follicular neoplasm,
- Although the NPV for aspirates with features suspicious for malignancy was lower, at 85%, ascertainment of a 15% risk of cancer may be useful in deciding whether to perform hemi-thyroidectomy or total thyroidectomy.
- The observed sensitivity of 100% for cytologically benign and cytologically malignant lesions provides strong independent evidence of the performance of the GEC.
- This test should not be used in the analysis of samples with benign cytologic features.
- can be useful in making important management decisions, such as recommending watchful waiting in lieu of diagnostic surgery, in the case of nodules with indeterminate cytologic features and benign findings on subsequent testing with the gene-expression classifier.

Alexander et al 2012

- **AGEC Designed to identify benign, rather than malignant.**
- **NPV was 95% for aspirates classified as atypia (or follicular lesions) of undetermined significance**
- **The observed sensitivity of 100% for cytologically benign and cytologically malignant lesions provides strong independent evidence of the performance of the GEC.**

Thyroid. 2012 Oct;22(10):996-1001..

The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology.

Duick DS McIver B

Conclusions:

Striking reduction in the rate of diagnostic thyroidectomy.

Approximately, 1 surgery was avoided for every 2 AGEC tests run on thyroid FNAs with indeterminate cytology.

- The four primary reasons for operating on nodules with a benign AGEC reading :

- large nodule size (46.4%),
- symptomatic nodules (25.0%)
- rapidly growing nodules (10.7%),
- second suspicious or malignant nodule in the same patient (10.7%).
- those typically given for operation on cytologically benign nodules.

DTC

- 1INCIDENCE ↑
- SURVIVAL ↑

. **PRE-OP MOLECULAR PROFILING**

- **SURGERY -- Extent-**
  ---TT+ PCCND T1 T2 PTC
  --Robotic Transaxillary ,BABA, MIVAT, Intra operative Nerve Monitoring ,Per – op RN probe, Sentinel node biopsy etc

- **Molecular Targeted Radiotherapy-- I131 - Magic Bullet.**

  AT RISK -SPM

RAI **1.Low (1.1GBq) vs High (3.7) (surgical variation) –----------HILO TRIAL**

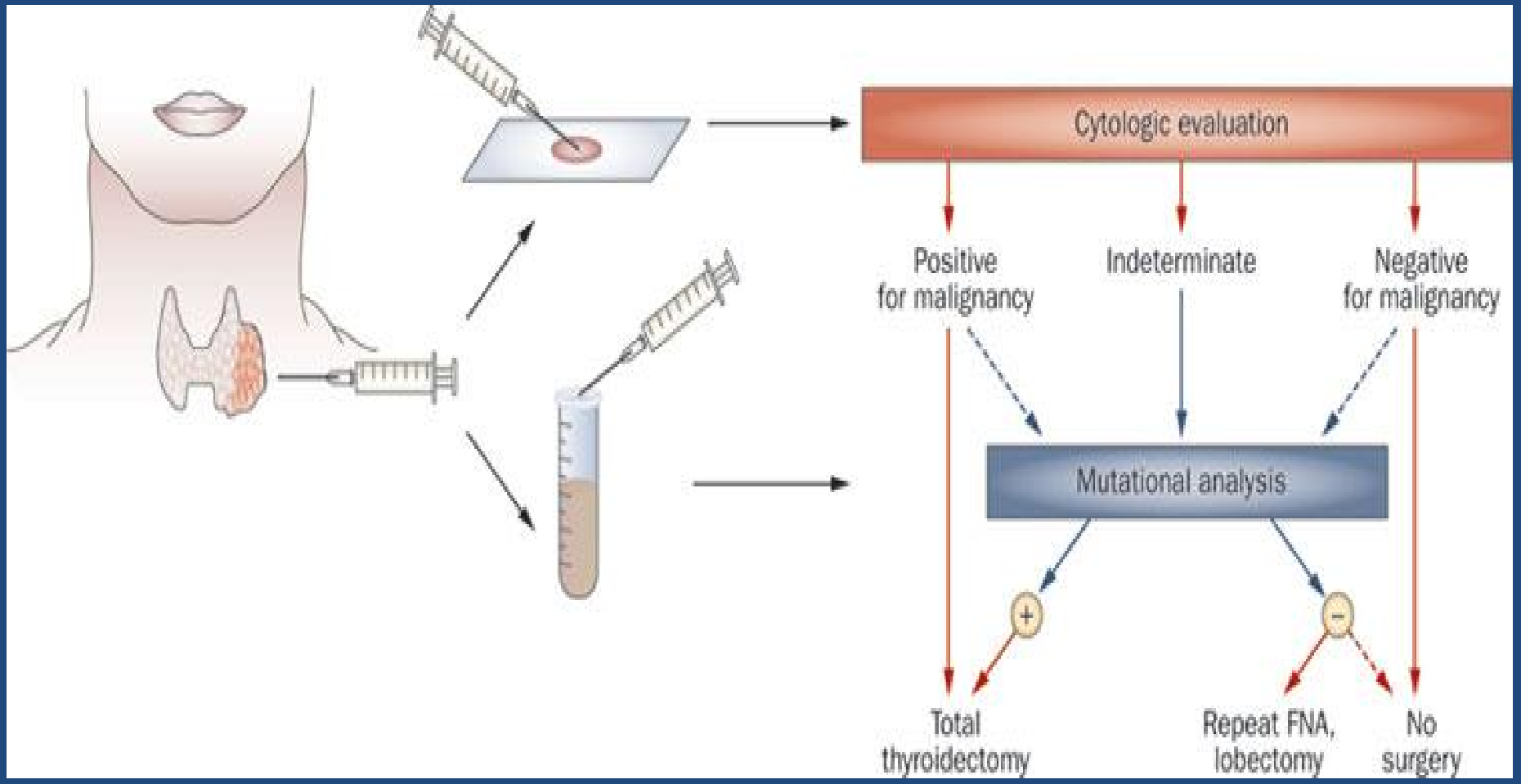
2. Abl vs No abl ---ION TRIAL

- **Targeted " Kinome "Inhibition. Iodine Refractory DTC**

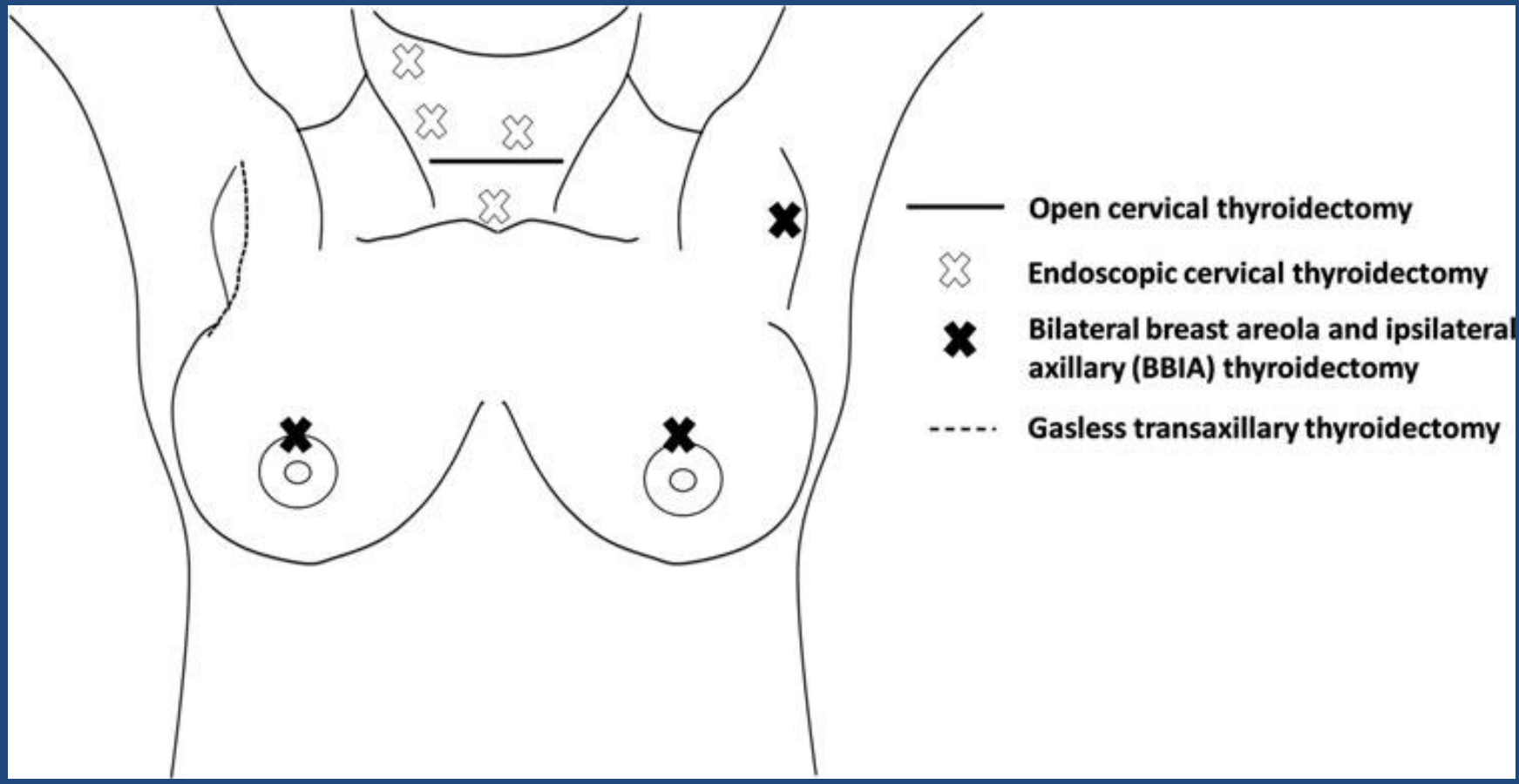
- **Re differentiation MEKI-NIS ,HDAC etc.**

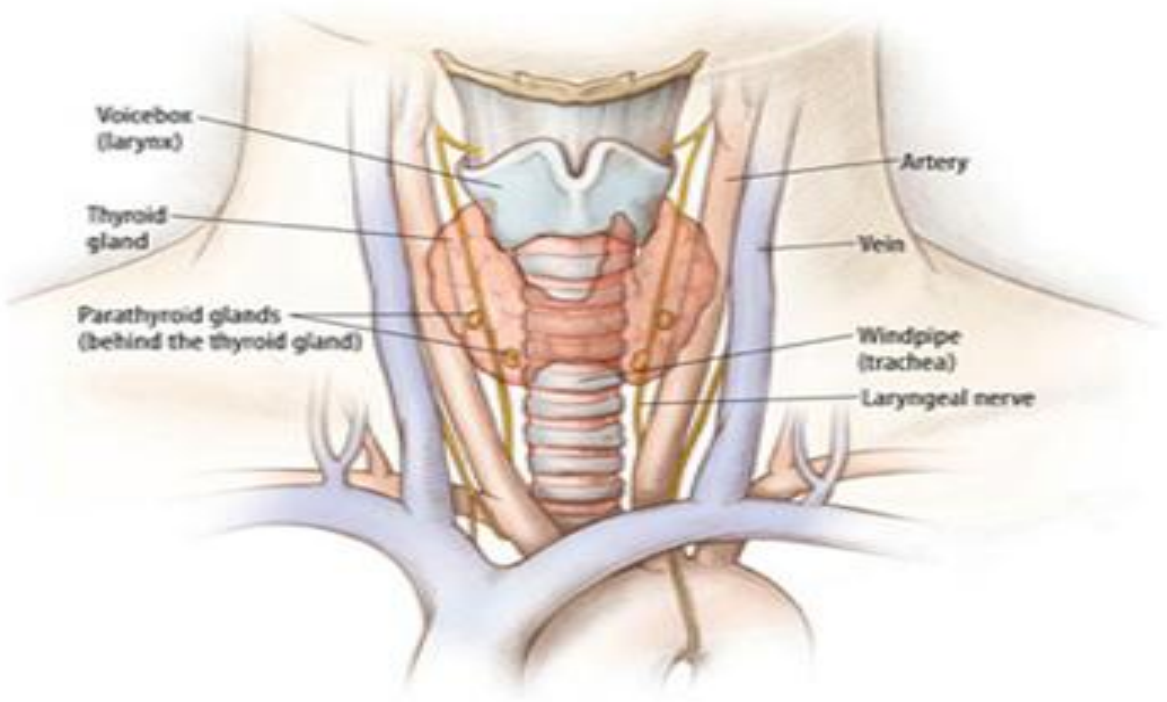
- **NIS –Theranostics, Transfection,Reporter Gene in cell trafficking, Cell Motility**

MOLECULAR PROFILING



TYPES OF SURGERY – RT




Voicebox
(larynx)
Thyroid
gland
Parathyroid glands
(behind the thyroid gland)
Artery
Vein
Windpipe
(trachea)
Laryngeal nerve

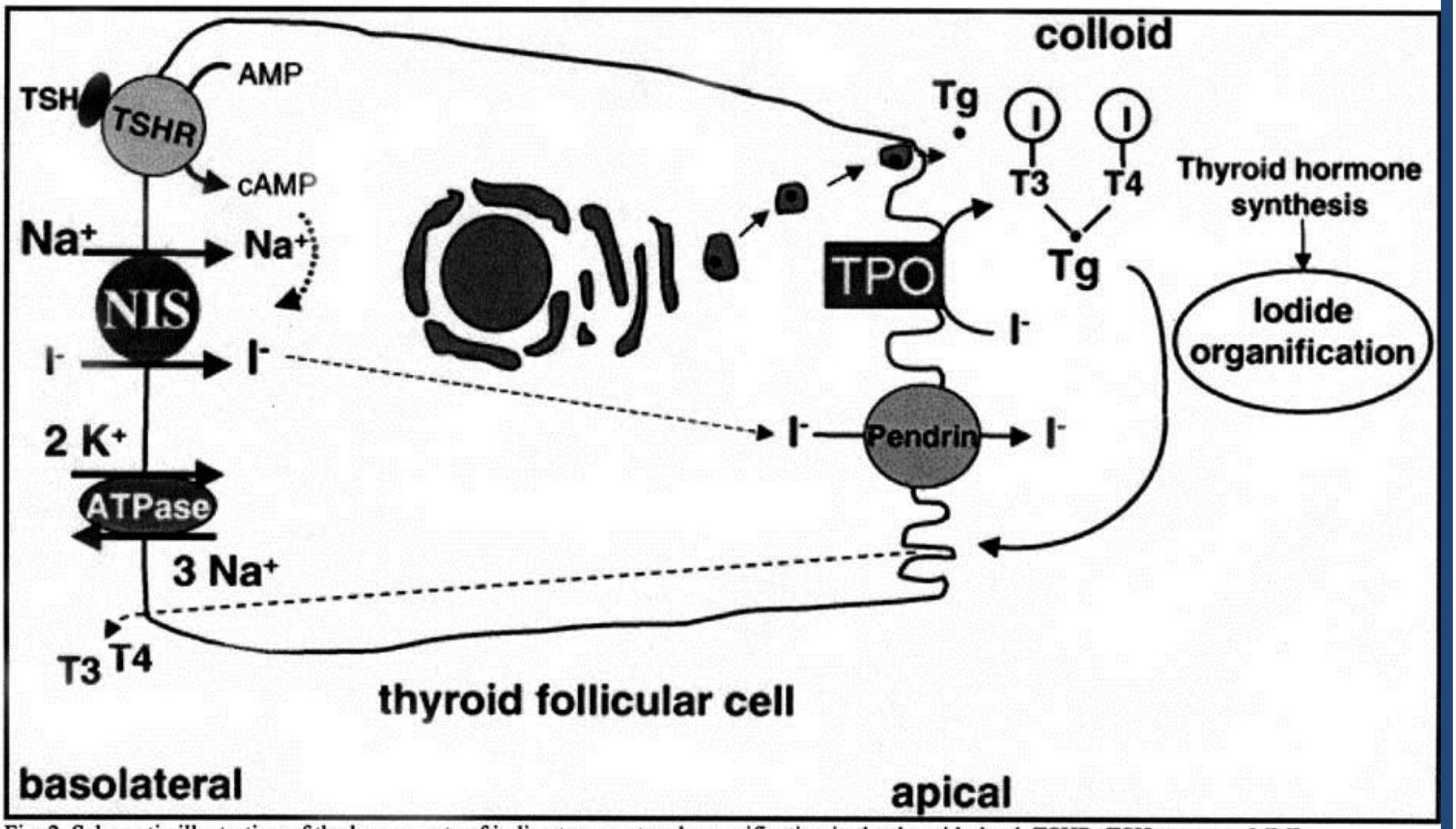
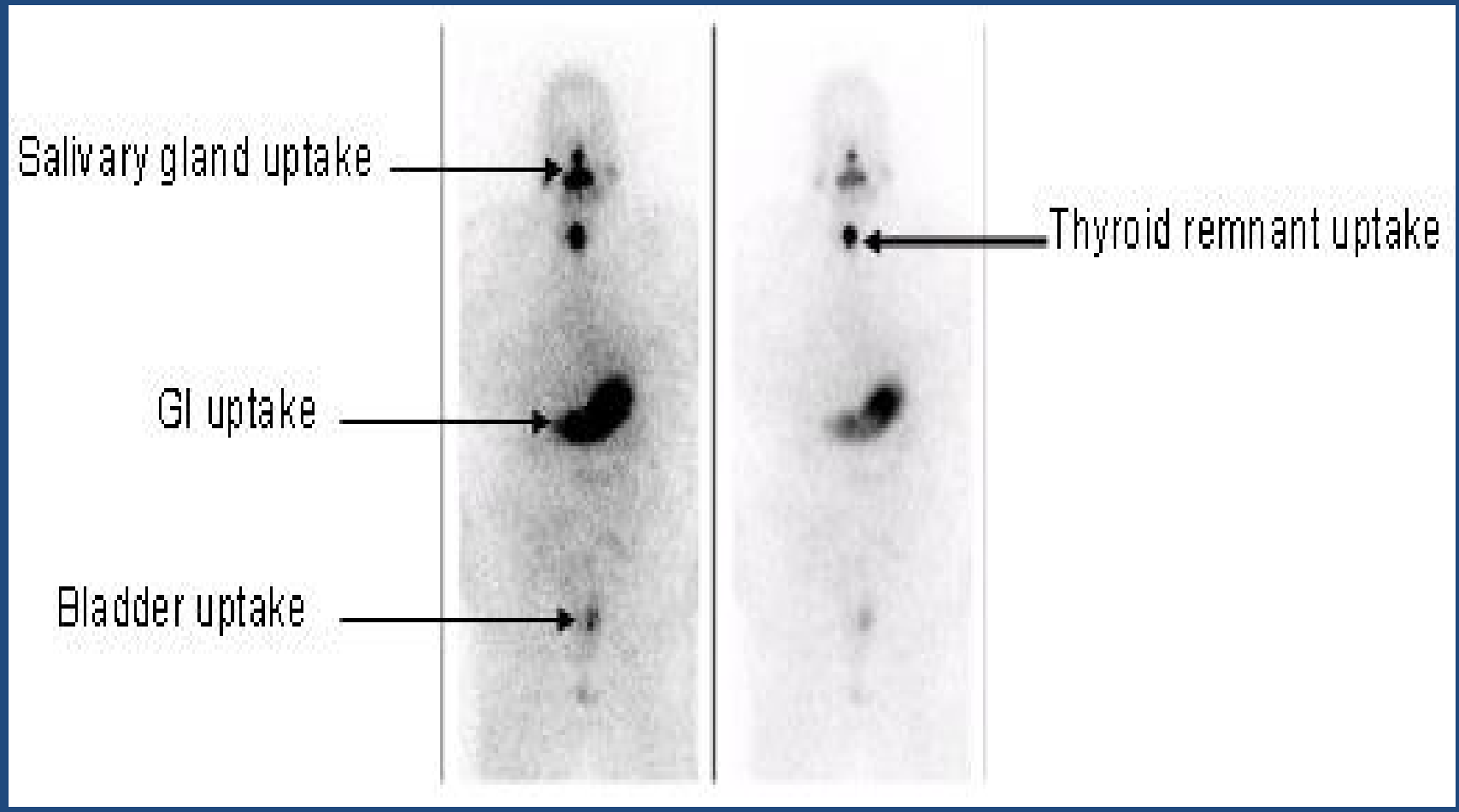
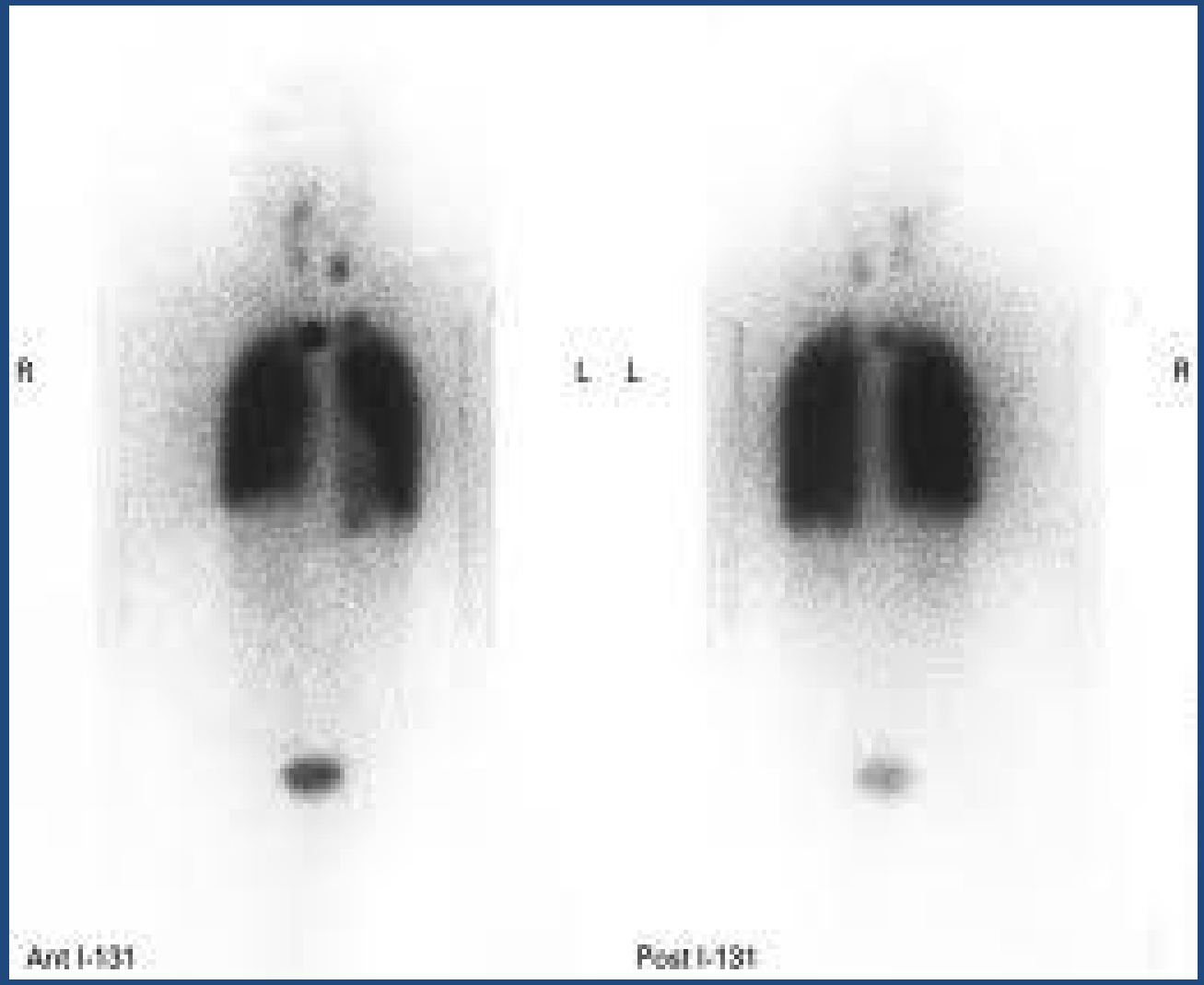


Fig. 2. Schematic illustration of the key aspects of iodine transport and organification in the thyroid gland. TSHR, TSH receptor; MMI, methimazole; PTU, propylthiouracil.

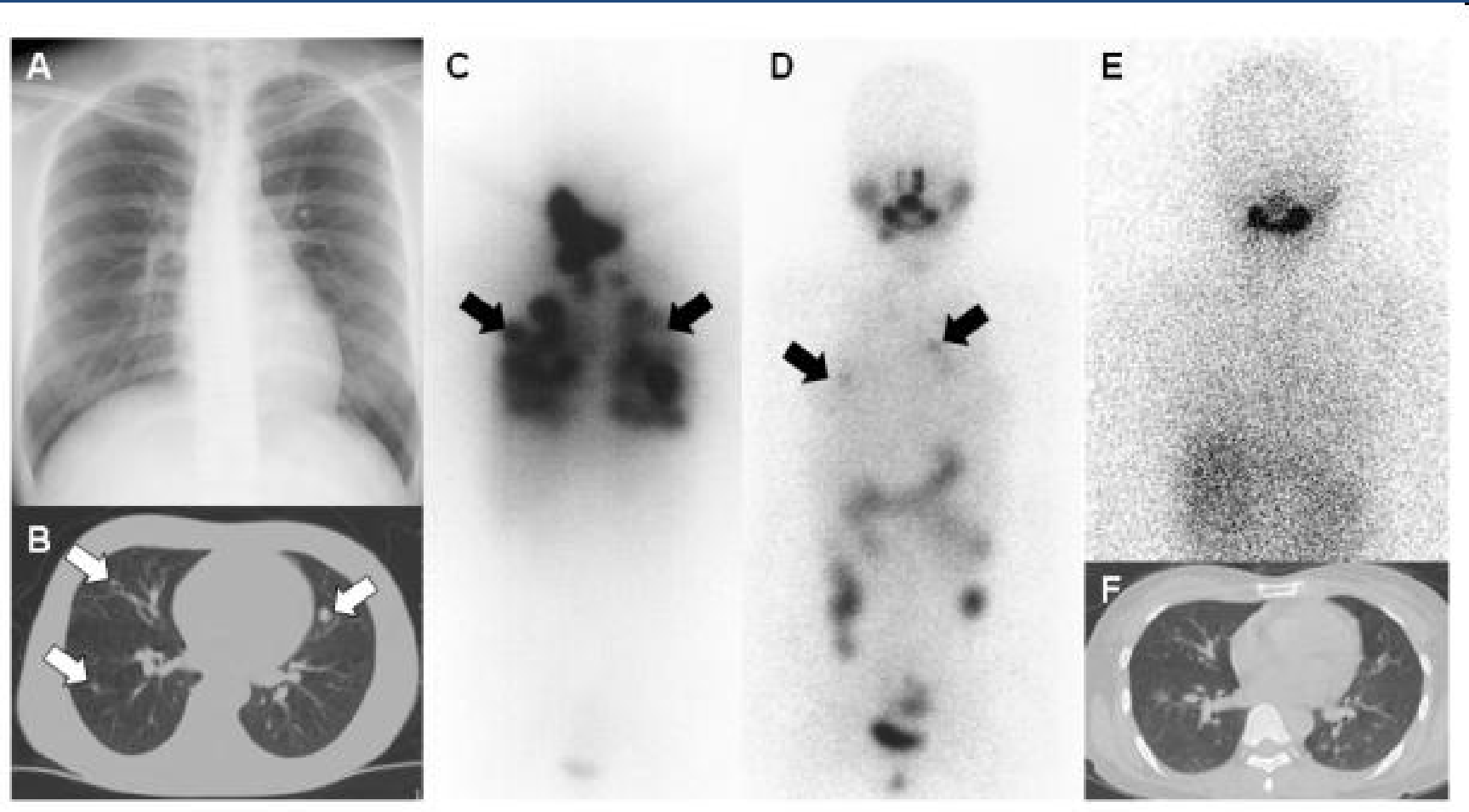
I131 SCAN


Salivary gland uptake
GI uptake
Bladder uptake
Thyroid remnant uptake

I 131 SCAN



131 THERAGNOSTICS



DTC INITIAL MANAGEMENT SCHEMA

- **TT/NTT**(-PT/ST)

↓

RRA 3.7GBq (>25$_{THW/rhTSH}$)

↓

TSHST

↓

TG, US DWBS

↓

- S RAI XT TKI etc
- F UP

TT/NTT

↙ ↘

RRA NO RRA IoN

TT/NTT

↙ ↘

RRA 3.7 RRA1.1 HiLo

↙ ↘ ↙ ↘

THW rh TSH THW rhTSH

HILO

TT/NTT

RRA 3.7

↙ ↘

THW rhTSH

RRA 1.1

↙ ↘

TSH rhTSH

ION

- TT/NTT

RRA NO RRA

Rh-TSH

AVOIDS HYPOTHYROIDISM WITH QOL ,SOCIETAL, HEALTH CARE COST BENEFITS for

- RAI SCAN
- RAI TREATMENT
- STIMULATED TG FOR MONITORING
- RISK ASSESSMENT FOR ABLATION

RRA -the possible consequences

1 NORMAL RA— MAIN UPTAKE
- Tg sensitive /specific----- not absolute/US
- RAI scan more sensitive---- not routine for low risk
- independent clonal origin of tumours---hypothesis

2 ADJUVANT-----? Effective microdosimetry
- R1 disease--- R0
- Residual foci in remnant/Anaplastic change--hypothesis
- N1 disease--- ?

3 THERAPY
- Presumed but unconfirmed metastatic disease---rare

4 STAGING info --- only helpful in rare cases---3% of low risk

? RAI---Anaplastic change in the tumour

RAI USE

- **The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years.**
  Hughes DT

- Wide variation in radioactive iodine use existed
- only 21.1% of this variation was accounted for by patient and tumor characteristics. HAYMART

SAWKA A

- **The RR of SPMs in thyroid cancer survivors treated with RAI was significantly increased at 1.19**
- **The RR of leukemia was also significantly increased in thyroid cancer survivors treated with RAI, with an RR of 2.5 (95% CI 1.13, 5.53, p = 0.024).**

SPM SUMMARY

IYER

- **Between 1973 and 2007, 37,176 patients with WDTC were followed in the SEER Program, equating to 408,750 person-years at risk (PYR).**
- **In total, 14,589 patients received RAI, and SPMs were observed in 3223 patients.**

- **For low-risk patients, the SIR (standardised incidence ratio)of SPM was 1.21 (95% confidence interval [CI], 0.93-1.54).**

- **The EAR (Excess Absolute risk)was 4.6 excess cases per 10,000 PYR.**
- **SPM with significantly elevated risk because of RAI were salivary gland malignancies (SIR = 11.13; 95% CI, 1.35-40.2)**
- **Leukemia (SIR = 5.68; 95% CI, 2.09-12.37).**

HiLo

Multicentre randomised phase III clinical trial of high(3.7GBq) vs low dose(1.1GBq) radioiodine, with or without recombinant human thyroid stimulating hormone (rhTSH), for remnant ablation for differentiated thyroid cancer

Dr Ujjal Mallick

Dr Clive Harmer

Allan Hackshaw

ON BEHALF OF THE HILO TRIAL TMG

CANCER RESEARCH UK

Background

- More than 2100 new cases of thyroid cancer each year in the UK and >48,000 in the US; rising incidence in many countries
- Advantages of using 1.1 GBq
  - Shorter stay in hospital isolation
  - Reduced risk of second malignancies
  - Reduced risk of other side effects such as dry mouth
  - Reduced body exposure to radioactive substances (less radiation protection restrictions post treatment)

- Advantages of using rhTSH (Thyrogen)
  - Avoid hypothyroidism, and improve quality of life
  - Less blood dose due to rapid renal clearance (impact on second tumours)
  - Less overall societal cost (less time off work)

Current guidelines

- Clinicians can choose between 1.1 and 3.7GBq (but there is no reliable evidence from large randomised studies)
  - American Thyroid Association (2009)
  - US National Comprehensive Cancer Network (2010)
  - European Consensus report (2006)

- 3.7 GBq recommended
  - UK guidelines (2007)

NEJM 3rd May 2012 ;366:1674-85

ORIGINAL ARTICLE

Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer

Ujjal Mallick, F.R.C.R., Clive Harmer, F.R.C.P., Beng Yap, F.R.C.P., Jonathan Wadsley, F.R.C.R., Susan Clarke, F.R.C.P., Laura Moss, F.R.C.P., Alice Nicol, Ph.D., Penelope M. Clark, F.R.C.Path., Kate Farnell, R.C.N., Ralph McCready, D.Sc., James Smellie, M.D., Jayne A. Franklyn, F.Med.Sci., Rhys John, F.R.C.Path., Christopher M. Nutting, M.D., Kate Newbold, F.R.C.R., Catherine Lemon, F.R.C.R., Georgina Gerrard, F.R.C.R., Abdel Abdel-Hamid, F.R.C.R., John Hardman, F.R.C.R., Elena Macias, M.D., Tom Roques, F.R.C.R., Stephen Whitaker, M.D., Rengarajan Vijayan, F.R.C.R., Pablo Alvarez, M.Sc., Sandy Beare, Ph.D., Sharon Forsyth, B.Sc., Latha Kadalayil, Ph.D., and Allan Hackshaw, M.Sc.

NEJM HILO

- **BACKGROUND:**
- It is not known whether low-dose radioiodine (1.1 GBq [30 mCi]) is as effective as high-dose radioiodine (3.7 GBq [100 mCi]) for Ablation in patients with DTC
- Whether the effects of radioiodine (especially with 1.1) are influenced by using either recombinant human thyrotropin (thyrotropin alfa) or THW.

HILO

METHODS:

- 29 UK centres

- A Randomized Non-inferiority Trial comparing 1.1 GBq vs 3.7GBq of radioiodine, each in combination with either thyrotropin alfa or THW before ablation.
- Patients (16 - 80 years) had tumor stage T1 - T3, N0-N1 M0 .

- End points

  rate of success of ablation at 6 to 9 months

  adverse events, quality of life, and length of hospital stay.

HILO-RESULTS

- 438 patients underwent randomization;
- data analyzable for 421.

- Ablation success rates were :

  -85.0% in the low-dose group
  -88.9% in the high dose group

  -87.1% in the thyrotropin alfa group
  -86.7% in the group undergoing thyroid hormone withdrawal.

- - 84.3% in low-dose radioiodine plus thyrotropin alfa
- - 87.6% in high-dose radioiodine plus thyroid hormone withdrawal
- - 90.2% in high-dose radioiodine plus thyrotropin alfa

NEJM HILO

- All 95% confidence intervals for the differences were within ±10 percentage points, indicating non-inferiority.

NEJM HILO

- More patients in the high-dose group than in the low-dose group were hospitalized for at least 3 days (36.3% vs. 13.0%, P<0.001).
- The proportions of patients with adverse events were 21% in the low-dose group versus 33% in the high-dose group (P=0.007)
- and 23% in the thyrotropin alfa group versus 30% in the group undergoing thyroid hormone withdrawal (P=0.11).
- **CONCLUSIONS:**
- Low-dose radioiodine plus thyrotropin alfa was as effective as high-dose radioiodine, with a lower rate of adverse events.

Ablation success using both diagnostic scan and Tg

	1.1 GBq N=214	3.7 GBq N=207	Thyrogen N=210	Hormone withdrawal N=211
% ablation success	**85.1**	**88.9**	**87.1**	**86.7**
Difference	**-3.8**		**+0.4**	
95% CI	**-10.2 to +2.6**		**-6.0 to +6.8**	
P-value	**P=0.24**		**P=0.90**	
Risk diffrence on sensitivity analysis	**-4.9(-11.2 to1.4)**		**0.4**	

All comparisons are within ± 10%, so
(i) 1.1 considered equivalent to 3.7 GBq
(ii) Thyrogen considered equivalent to hormone withdrawal

Ablation success using both diagnostic scan and Tg

	1.1 GBq Thyrogen N=108	**3.7 GBq Hormone withdrawal N=105**	**1.1 GBq Thyrogen N=108**	**3.7 GBq Thyrogen N=105**
% ablation success	**84.3**	**87.6**	**84.3**	**90.2**
Difference	**-3.3**		**-5.9**	
95% CI*	**-12.7 to +6.0**		**-14.9 to +3.0**	
P-value	**P=0.48**		**P=0.20**	

*wider confidence intervals because trial was not powered for these comparisons

Ablation success using diagnostic scan & Tg: Patients with T3 disease

1.1 GBq N=47	3.7 GBq N=49
80.9%	81.6%
Difference : -0.7%	

Thyrogen N=48	Hormone withdrawal N=48
83.3%	79.2%
Difference: +4.1%	

1.1 GBq Thyrogen N=25	3.7 GBq Hormone withdrawal N=26
80.0%	76.9%
Difference: +3.1%	

1.1 GBq Thyrogen N=25	3.7 GBq Thyrogen N=23
80.0%	87.0%
Difference: -7.0%	

Ablation success using diagnostic scan & Tg: Patients with N1 disease

1.1 GBq N=30	3.7 GBq N=33
86.7%	81.8%
Difference : +4.9%	

Thyrogen N=33	Hormone withdrawal N=30
81.8%	86.7%
Difference: -4.9%	

1.1 GBq Thyrogen N=17	3.7 GBq Hormone withdrawal N=17
82.4%	82.4%
Difference: 0%	

1.1 GBq Thyrogen N=17	3.7 GBq Thyrogen N=16
82.4%	81.3%
Difference: +1.1%	

Quality of Life during 4 weeks immediately prior to radioiodine ablation 15 specific thyroid cancer specific symptoms examined

% of patients whose symptoms were 'moderate' or 'a lot'	Thyrogen N=219 %	Hormone withdrawal N=219 %	P-value
1 symptom	15.5	9.3	0.04
2	8.7	11.4	0.34
≥ 3	29.7	51.1	<0.001

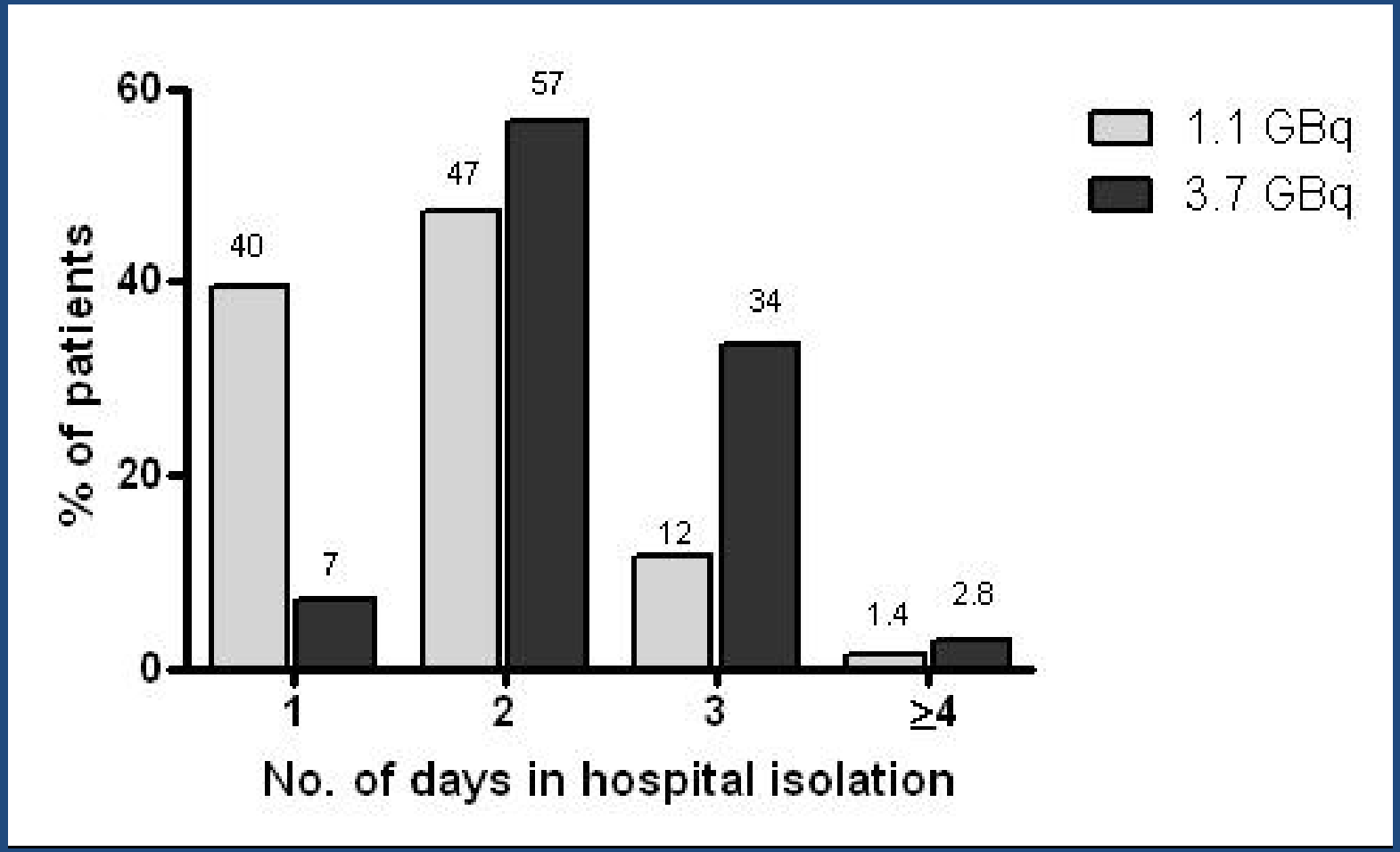
Quality of Life during 4 weeks immediately prior to radioiodine ablation

% of patients whose symptoms were 'moderate' or 'a lot'	Thyrogen N=219 %	Hormone withdrawal N=219 %	P-value
Fatigue	29.7	48.9	<0.001
Puffy face & hands	4.1	21.9	<0.001
Sleep disturbance	19.2	40.2	<0.001
Difficult to concentrate	18.3	36.5	<0.001
Difficult to perform usual activities at home	13.2	19.2	0.09
Difficult to take care of children at home (those with dependent children)	8.1	14.5	0.19
Difficult to perform usual activities at work (median no. days off work)	9.4 (1)	22.1 (5)	0.004 (0.17)

Hospital stay with and without Thyrogen

	% of patients ≥3 days in hospital		Difference
	Thyrogen	Hormone withdrawal	
1.1 GBq	10.4%	15.8%	-5.4%
3.7 GBq	33.3%	39.2%	-5.9%

Number of days in hospital isolation



Adverse events summary

	% of patients with any adverse event		P-value
	1.1 GBq	3.7 GBq	
Up to 1 week post ablation	21%	33%	0.007
3 months post ablation	27%	24%	0.55
	Thyrogen	Hormone withdrawal	
Up to 1 week post ablation	23%	30%	0.11
3 months post ablation	27%	24%	0.34

Financial costs

	Estimated total cost for the 438 trial patients (£443 per patient per day in hospital)
3.7 GBq	£222K
1.1 GBq	£169K (a 24% reduction)
	Mean cost per patient (£443 per patient per day in hospital, £583 for Thyrogen per patient)
1.1 GBq, hormone withdrawal	£776
1.1 GBq, Thyrogen	£1356
3.7 GBq, hormone withdrawal	£1056
3.7 GBq, Thyrogen	£1582

During the 4 weeks before ablation, 44.6% (Thyrogen) vs. 28.7% (hormone withdrawal) continued to work without taking time off

Key conclusions-HILO

Among patients with T1-3 N0-1 M0 DTC, and favourable histology, treated by TT and R0 resection by specialist surgeons:

- 1.1 GBq has a similar ablation success rate as 3.7 GBq
- Thyrogen has similar success rates as THW
- Patients had better quality of life before ablation; they were able to perform better at home and work
- 1.1GBq+Thyrogen had fewer Early side effects
- 1.1GBq + Thyrogen has similar results to 3.7GBq with/without Thyrogen
- Evidence of similar success rates in patients with T3 and N1 cancers
- Fewer days in hospital with 1.1GBq
- 1.1GBq+Thyrogen is a safe, cost-effective and convenient treatment

SPECIAL POTENTIAL BENEFITS

- ***1.1GBq +Thyrogen (renal clearance of ^{131}I is faster with Thyrogen) compared to 3.7GBq +THW , will potentially reduce risk of radiation-induced second cancers, which might be less curable than the primary DTC itself due to less body dose.***

- ***I.IGBq +Thyrogen (renal clearance of ^{131}I is faster with Thyrogen) more suitable for OP ablation (less cost)***

On-going Analyses

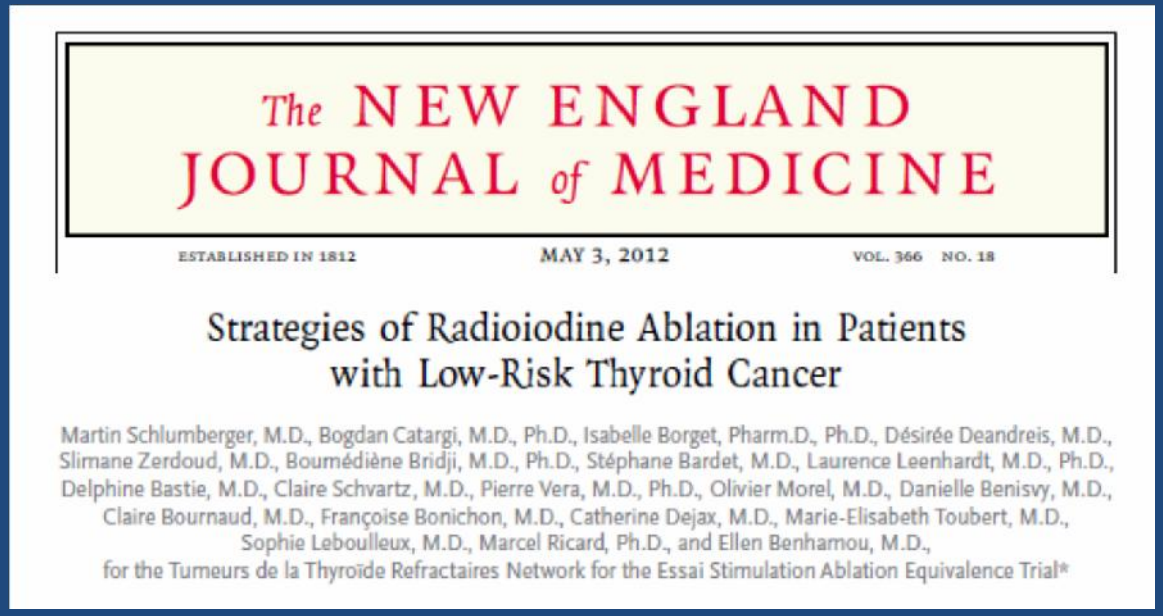
- Recurrence rates (after median follow up of 20 ms ; 21% of patients followed for >2 years) .
- Examining more sensitive Tg assays (eg Beckman)
- Trans Hilo - Translational research (tissue blocks collected from all patients):

  - PTTG) ,PBF and genetic instability in normal and tumour tissue

  - Relationship of Tumour Normal Biomarker Difference (TNBD) to overall ablation success, and its impact on 1.1, 3.7GBq and rhTSH outcomes.

  -BRAF assay.

Schlumberger-Estimabl



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 3, 2012 VOL. 366 NO. 18

Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer

Martin Schlumberger, M.D., Bogdan Catargi, M.D., Ph.D., Isabelle Borget, Pharm.D., Ph.D., Désirée Deandreis, M.D., Slimane Zerdoud, M.D., Boumédiène Bridji, M.D., Ph.D., Stéphane Bardet, M.D., Laurence Leenhardt, M.D., Ph.D., Delphine Bastie, M.D., Claire Schvartz, M.D., Pierre Vera, M.D., Ph.D., Olivier Morel, M.D., Danielle Benisvy, M.D., Claire Bournaud, M.D., Françoise Bonichon, M.D., Catherine Dejax, M.D., Marie-Elisabeth Toubert, M.D., Sophie Leboulleux, M.D., Marcel Ricard, Ph.D., and Ellen Benhamou, M.D., for the Tumeurs de la Thyroïde Refractaires Network for the Essai Stimulation Ablation Equivalence Trial*

Combination of 2 large recent trials

	Difference in ablation success rates	
	1.1 vs 3.7 GBq	Thyrogen vs hormone withdrawal
HiLo (UK); n=421	-3.8% (-10.2 to +2.6)	+0.4% (-6.0 to +6.8)
ESTIMABL (France); n=687* (excluded pT3 & T2/N1)	-2.1% (-5.4 to +1.3)	1.5% (-4.9 to +1.9)
Combined (n=1108)	-2.5% (-5.5 to +0.5)	-0.3% (-3.3 to +2.7)

*ablation success determined using neck ultrasound and Thyrogen-stimulated Tg

What next?

- Differentiated thyroid cancer has high cure rates, therefore main aim is to reduce treatment without affecting outcomes
- HiLo shows that we can reduce the administered activity

J Clin Endocrinol Metab. 2012 May;97(5):1526-35. Epub 2012 Feb 16.

Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients.

Schvartz C

- . Design: 1298 DTC patients at low risk treated between 1975 and 2005.
- **. Results: 911 patients received RAI after surgery vs. 387 patients without RAI after surgery**.
- **Conclusion: With a long-term follow-up of 10.3 yr, we failed to prove any survival benefit of RAI after surgery in a large cohort of low-risk DTC patients.**

CONTEXT

- HAY
- SAWKA
- MSKCC
- SCHVARTZ
- HAYMART
- IYER

MAYO –Some N1b disease “optimal surgery”

TABLE I. Lack of Influence of RRA on Outcome in 1,163 MACIS Low-Risk (Scores <6) Patients (Without Distant Metastases) Treated During 1970–2000 at Mayo by Near-Total (NT) or Total Thyroidectomy (TT)

Low-risk (MACIS <6) 1970–2000	20-year mortality		20-year recurrence	
	NT/T alone	NT/TT and RRA	NT/T alone	NT/TT and RRA
All patients (1,163)	0.4%	0.6%	8.7%	13.6%
P-value	$P=0.64$		$P=0.008$	
Node-negative (636)	0%	0%	3.4%	4.3%
P-value	N/A		$P=0.80$	
Node-positive (527)	1.2%	0.9%	19.5%	19.9%
P-value	$P=0.99$		$P=0.66$	

SAWKA UPDATED-REVIEW

OF OBSERVATIONAL STUDIES

- RRA NO CONSISTENT ,SIGNIFICANT BENEFIT IN CSM OR REC
- DECREASED RISK OF DM---- ~ -2%(2 ADJUSTED AND POOLED UNADJUSTED ANALYSES RARE IN PTC

  CONFLICTING AND UNCERTAIN DATA
- 10 YR CSM FOR ESWDTC ~ 1.7% VIRTUALLY IMPOSSIBLE TO PROVE A TREATMENT BENEFIT

SAWKA UPDATED-REVIEW

OF OBSERVATIONAL STUDIES

- BLR ESWDTC
- 10 YR ABSOLUTE REC ~ 10%
- LR REC ~ 7.3%
- DM ~1.3%

Clin Endocrinol (Oxf). 2011 Feb 8
Vaisman F, Shaha A Fish S Tuttle R
MSKCC

Retrospective review. 289 patients

- Lobectomy (n=72)
- T Thyroidectomy (n=217) without RRA
- F UP with modern detection tests
- PTC (89%), cN0 (91%).
- 55% patients primary tumors > 1 cm,
- 10% minor ETE .

MSKCC

5 year median follow up

- Structural disease recurrence was detected in

  -2.3% (5/217) of patients treated with TT without RRA,

  -4.2% (3/72) of patients treated with lobectomy.

  --- Size of the primary tumor,
  --- the presence of cervical lymph node metastases,
  --- ATA risk category were all statistically significant predictors of recurrence.
  ---- Changes in serum TG were not helpful in identifying the presence of persistent/recurrent structural disease.

- **Importantly, 88% (7/8) of the patients that had recurrent disease were rendered clinically disease free with additional therapies**.

MSKCC

Conclusions: very low risk of structural disease recurrence following treatment with either thyroid lobectomy or total thyroidectomy without RRA.

Our data strongly support a selective approach to the initial management of thyroid cancer.

IoN Trial

Is radioiodine remnant ablation Necessary for low risk differentiated thyroid cancer patients

TT +RAI+TSHST

vs

TT+TSHST

ION

- Eligible patients are those with R0 total thyroidectomy and
- include:
- papillary thyroid cancer with non-aggressive histological
- features, stages pT1b (1-2 cm), pT2 (2-4 cm), pT3
- intrathyroidal only, multifocal microcarcinoma and
- pN0, pN1a, pNX.
- follicular thyroid/Hurthle cell cancer (minimally invasive
- with capsular invasion only) stages pT1b (1-2 cm)
- or pT2 (2-4 cm).

ION

- IoN (Iodine or Not) trial, will show whether radioiodine ablation can be avoided completely in low-risk patients
- Primary outcome: 5-year disease-free survival rate (95% with ablation, and should be no lower than 90% without ablation)
- Feasibility study started in the UK (funded by Cancer Research UK)
- Ultimate target 570 patients

ION CHART

- LOW- RISK DTC TT –R0
-
-

NO RAI (TSHS) RAI (TSHS)

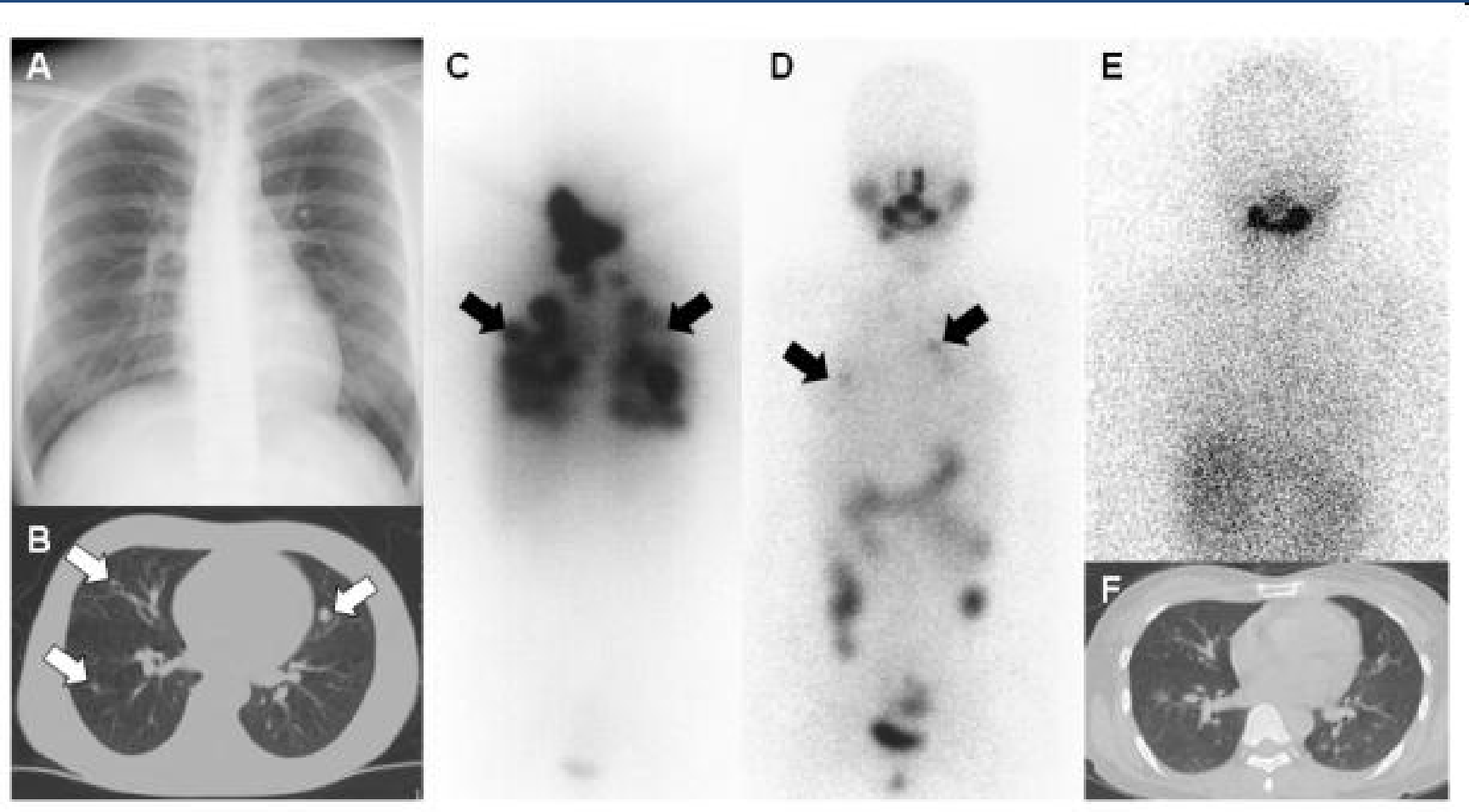
CE, US,TG , 6-12 MS

5YR L-R RECURRENCE, DFS

Trans -IoN

- Beckman TG
- BRAF V600 E Mutations and residual/recurrent disease
- Serum and Tissue proteomics

131 THERAGNOSTICS



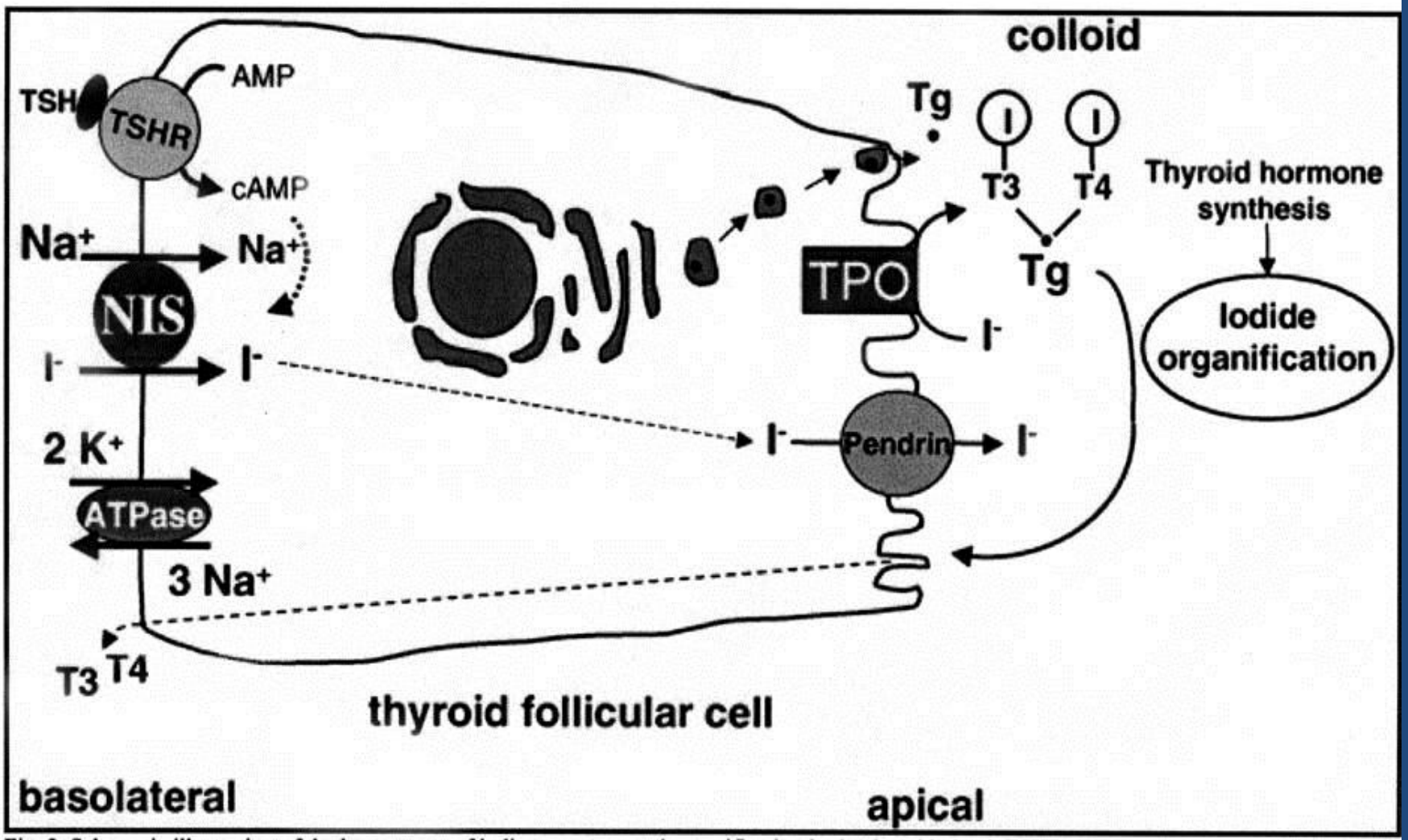
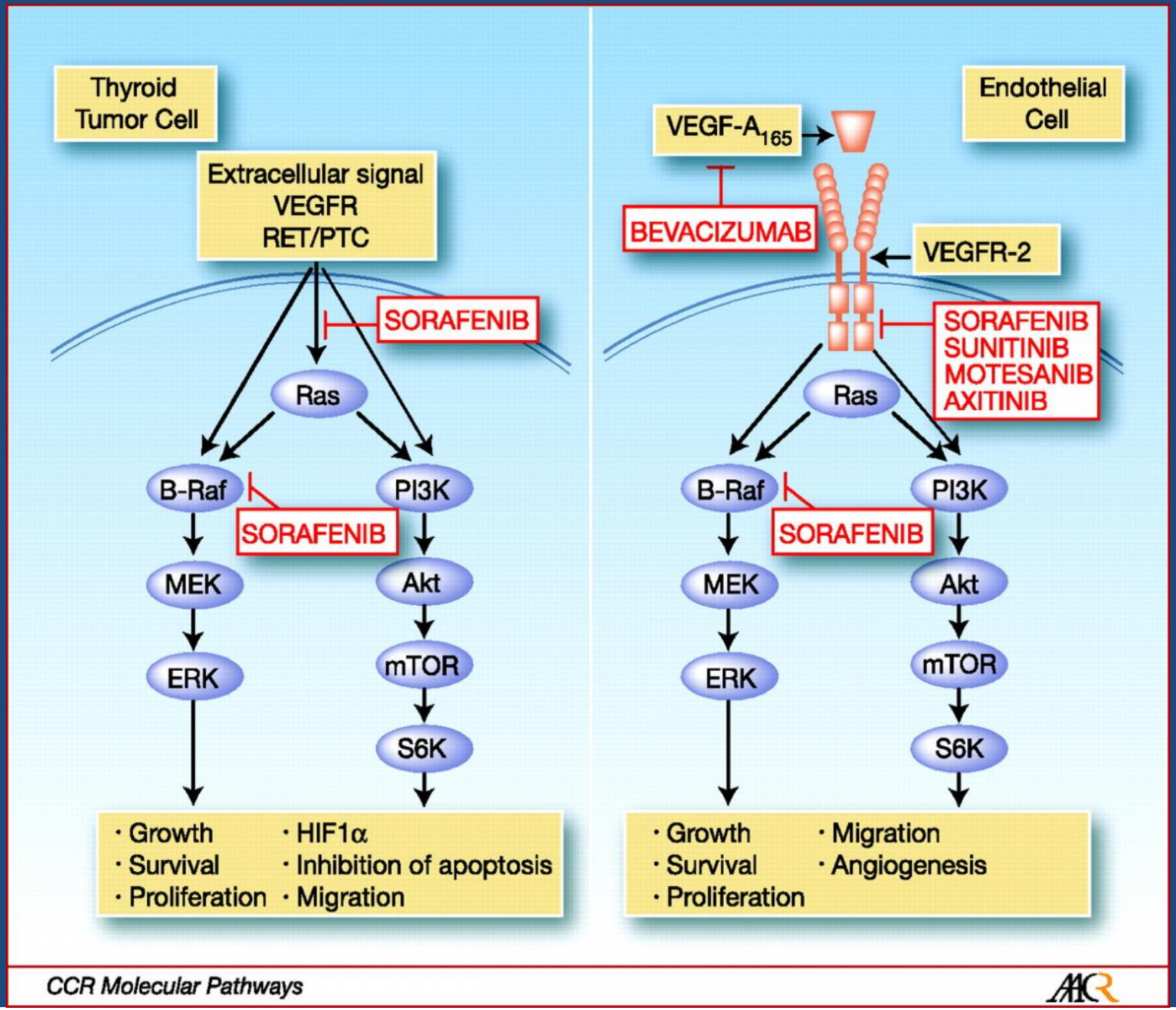


Fig. 2. Schematic illustration of the key aspects of iodine transport and organification in the thyroid gland. TSHR, TSH receptor; MMI, methimazole; PTU, propylthiouracil.


Thyroid Tumor Cell
Extracellular signal
VEGFR
RET/PTC
SORAFENIB
Ras
B-Raf
SORAFENIB
PI3K
MEK
Akt
ERK
mTOR
S6K
· Growth
· Survival
· Proliferation
· HIF1α
· Inhibition of apoptosis
· Migration
Endothelial Cell
VEGF-A165
BEVACIZUMAB
VEGFR-2
SORAFENIB
SUNITINIB
MOTESANIB
AXITINIB
Ras
B-Raf
SORAFENIB
PI3K
MEK
Akt
ERK
mTOR
S6K
· Growth
· Survival
· Proliferation
· Migration
· Angiogenesis
CCR Molecular Pathways
AACR

"Drugging the KINOME" in thyroid carcinomas.

Schlumberger M et al.CLINICS 2012;67(S1):125-129

126

	VEGFR1	VEGFR2	VEGFR3	RET	BRAF	OTHER
• Axitinib	1.2	0.25	0.29			
• Sunitinib	2	9	17	41		
• Motesanib	2	3	6	59		PDGFR,CKIT
• **Sorafenib**		**90**	**20**	**49**	**6**	
• **Vandetanib**		**40**	**110**	**100**		**EGFR**
• Pazopanib	10	30	47			PDGFR, C-KIT
• Cabozantinib		0.035		4		C-MET, C-KIT
• Lenvatinib	22	4	5	35		PDGFR, FGFR

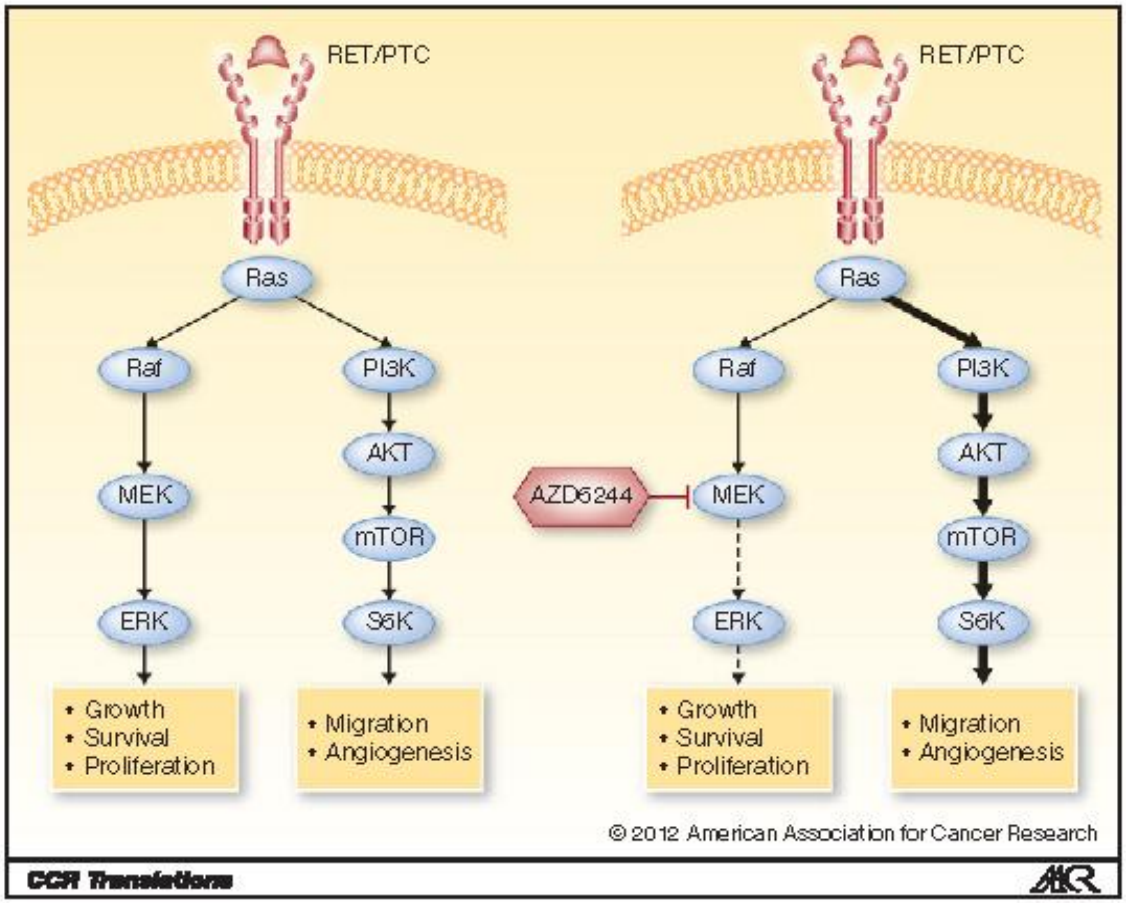


Figure 1. Selective targeting of MEK 1/2 in PTC. Intracellular-signaling pathway aberrancy is critical to the molecular pathophysiology of thyroid cancer tumorigenesis. In tumor cells (left), altered expression and mutation involving B-Raf, Ras, and Akt have been implicated in a wide variety of thyroid cancer cell types. In the tumor microenvironment, angiogenesis is also a critical step in tumor progression and metastasis. Angiogenesis is mediated primarily through VEGFR-2, which also signals through Raf and Akt. Inhibition of VEGFR-2 has proved to be a successful therapeutic strategy in thyroid cancer in which drugs such as bevacizumab, sorafenib, sunitinib, axitinib, and motesanib have activity as single agents. VEGFR-2 has been found to be expressed on tumor cells in thyroid cancer, raising the question of whether multikinase inhibitor therapy might also be exerting an effect on the tumor cells themselves.

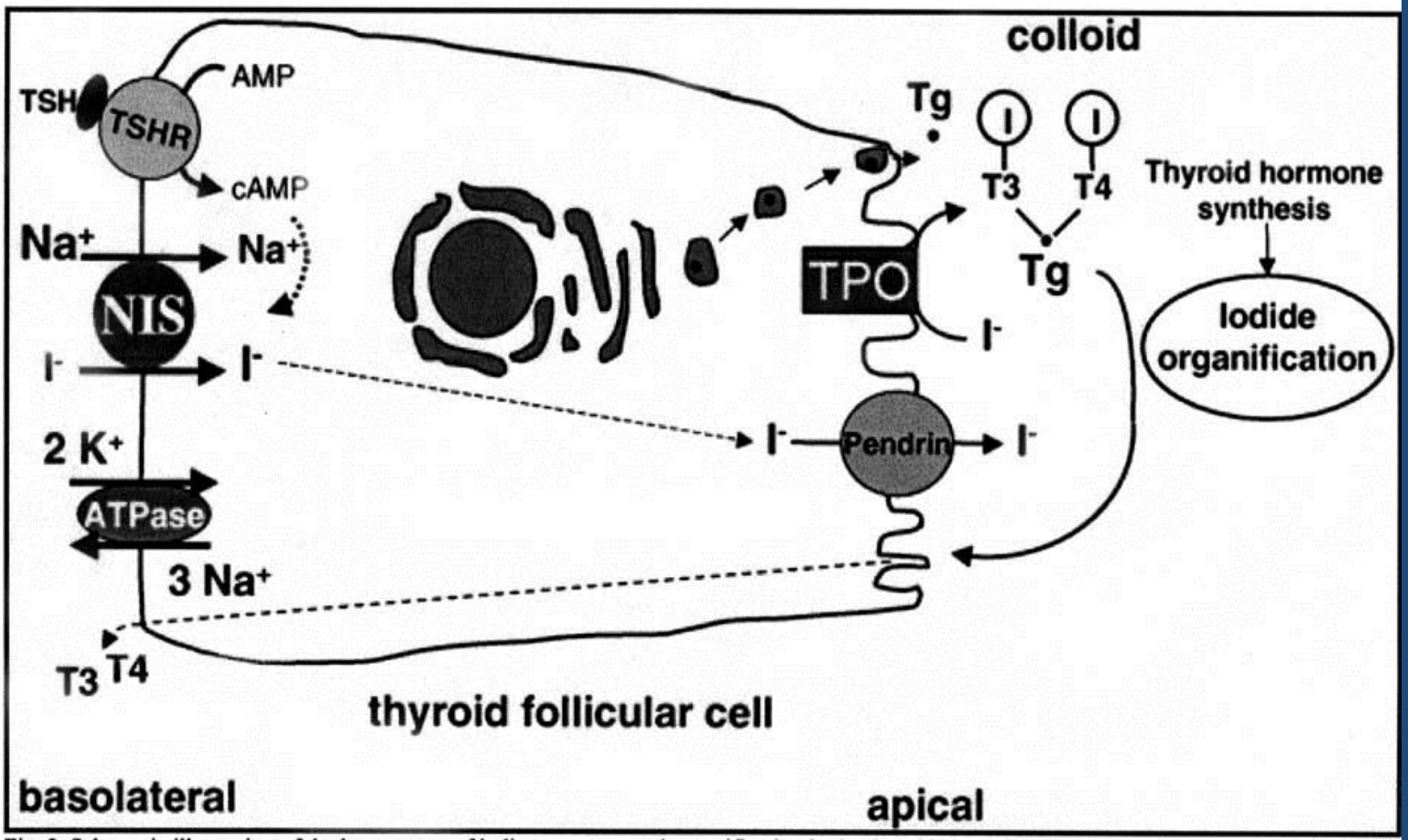


Fig. 2. Schematic illustration of the key aspects of iodine transport and organification in the thyroid gland. TSHR, TSH receptor; MMI, methimazole; PTU, propylthiouracil.

MEKI-RAI-MSKCC -J FAGIN

- Genetic alterations in differentiated thyroid cancer cause activation of RAF/MEK/ERK signalling.
- Expression of the NIS is suppressed by RAF/MEK/ERK activation
- MEK inhibition by AZD6244 should reverse this and re-establish iodine uptake into thyroid cancer cells.
- “Reacquisition Of RAI Uptake Of RAI-Refractory Metastatic Thyroid Cancers By Pre-treatment With The Selective MEK Inhibitor Selumetinib: A Pilot Study” (Ho et al).

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty,
N Engl J Med 2012; 367:1694-1703 November 1, 2012

Oncogene-Targeted Therapy
CML
GIST
BREAST CA SUBTYPES
NSCLC SUBTYPES

Acquired resistance.

Combined Targeted Therapies in an Oncogene-defined patient population.

DTC

- INCIDENCE ↑
- SURVIVAL ↑

. **PRE-OP MOLECULAR PROFILING**

- **SURGERY -- Extent-**
  ---TT+ PCCND T1 T2 PTC
  --Robotic Transaxillary ,BABA, MIVAT, Intra operative Nerve Monitoring ,Per – op RN probe, Sentinel node biopsy etc

- **Molecular Targeted Radiotherapy-- I131 - Magic Bullet.**

AT RISK -SPM

RAI 1.Low (1.1GBq) vs High (3.7) (surgical variation) –----------HILO TRIAL

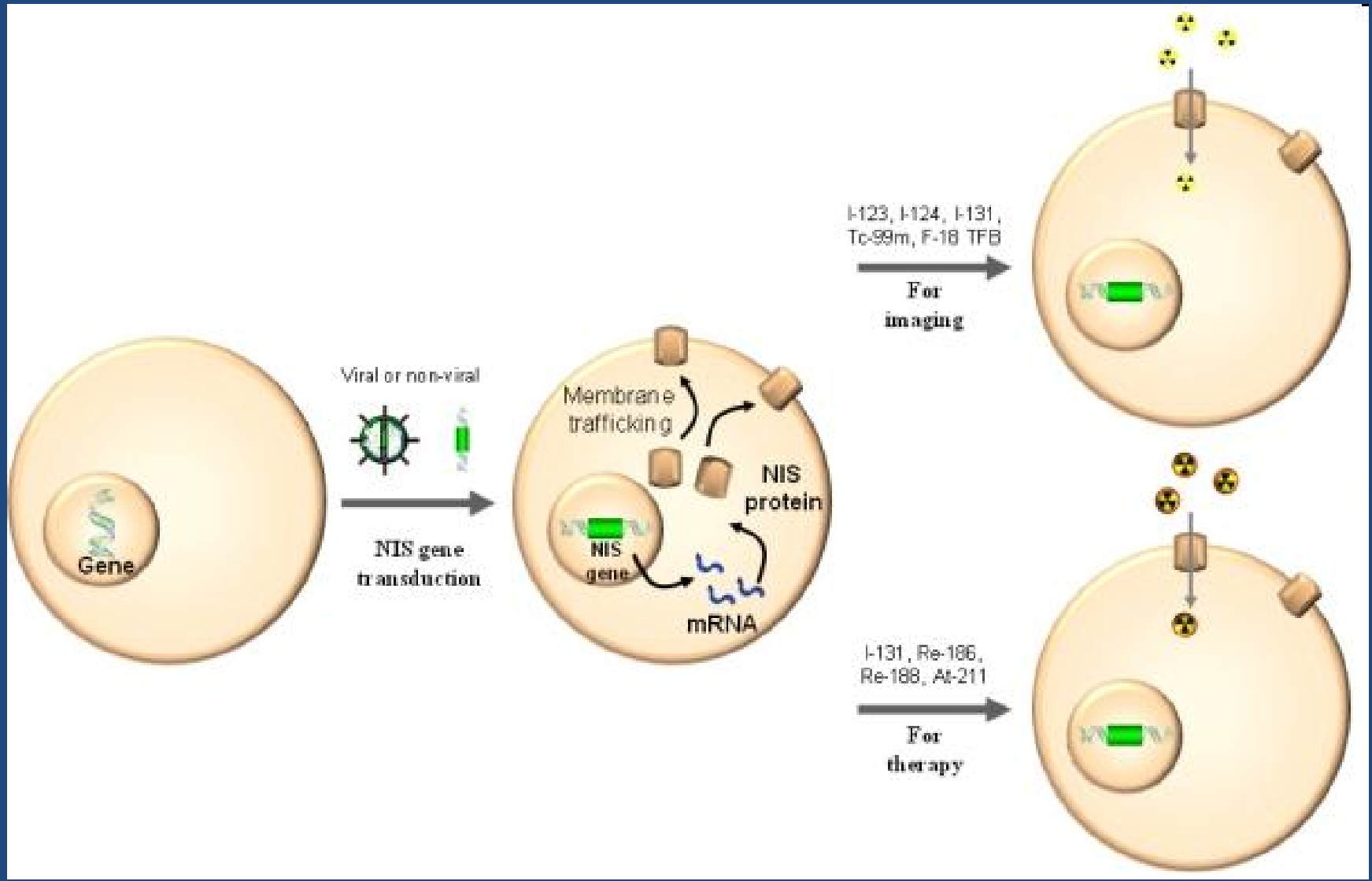
2. Abl vs No abl ---ION TRIAL

- **Targeted " Kinome "Inhibition. Iodine Refractory DTC**

- **Re differentiation MEKI-NIS ,HDAC etc.**

- **NIS –Theranostics, Transfection,Reporter Gene in cell trafficking, Cell Motility**

NIS TRANSFECTION



Acknowledgements

- All the patients who kindly agreed to participate
- All the recruiting centres; clinicians and research nurses
- Genzyme Corporation (for providing free Thyrogen)

- Funding: Cancer Research UK (no. C18243/A5802)

Trial Management Group and Recruiting Clinicians

Ujjal Mallick, Clive Harmer, Sue Clarke, Laura Moss, Alice Nicol, Penelope Clarke, James Smellie, Ralph McCready, Kate Farnell, Jayne Franklyn, Rhys John, Chris Nutting, Pablo Alvarez, Latha Kadalayil, Allan Hackshaw

Abdel Abdel-Hamid, Matthew Beasley, Caroline Brammer, Anna Cassoni, Perric Crellin, Georgina Gerrard, Simon Gollins, Andrew Goodman, John Hardman, Mohan Hosahalli, Arshad Jamil, Sarah Jeffries, Catherine Lemon, Roy Matthews, Kate Newbold, Irene Peat, Roger Owen, Tom Roques, Nick Rowell, Joanna Simpson, Jonathan Wadsley, Elena Macias, Christopher Scrase, Rengarajan Vijayan, Stephen Whitaker, Michael Williams, Beng Yap

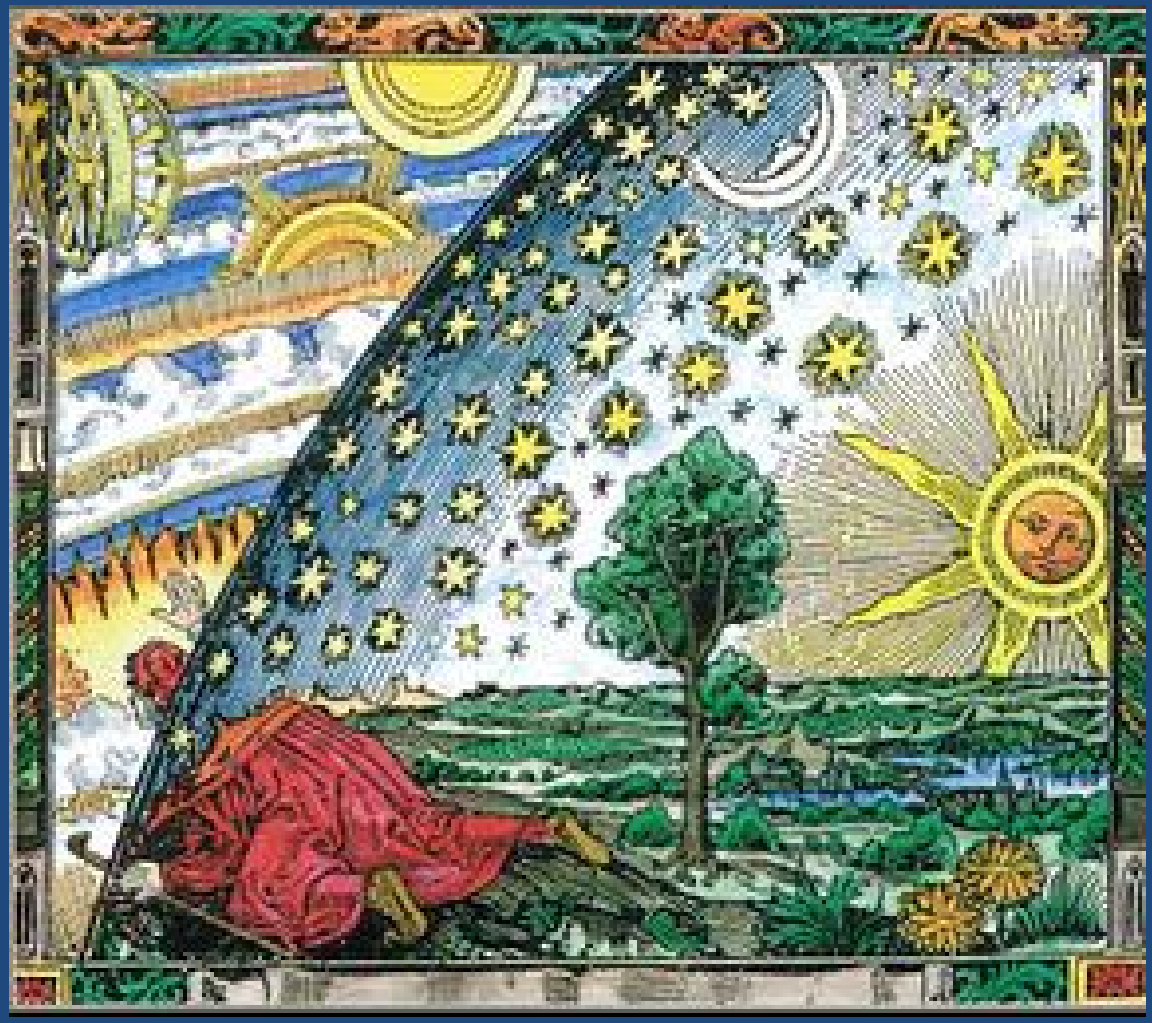
RICHARD FEYNMAN

SCIENTIFIC KNOWLEDGE IS A BODY OF STATEMENTS OF VARYING DEGREES OF CERTAINTY –SOME MOST UNSURE ,SOME NEARLY SURE , BUT NONE ABSOLUTELY CERTAIN

WE MUST LEAVE A BLIND ALLEY AND FIND THE OPEN CHANNEL OF DOUBT , A TRIAL--AND –ERROR SYSTEM AND DISCUSSION TO MAKE PROGRESS INTO THE UNKNOWN.

UNENDED QUEST

- FLAMMARION ENGRAVING



THANK YOU FOR YOUR ATTENTION