Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Socio Sanitario Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

5th Milan NET Conference

A live and web multimodal meeting among active Italian NET Centers

Wednesday June 12th, 2019
Milan

Circulating tumor cells, DNA and MicroRNAs as prognostic markers for NETs - **M. C. Zatelli**

Section of Endocrinology & Internal Medicine
Dept of Medical Sciences
University of Ferrara

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NEN PROGNOSIS

Depends on
- disease extent
- histological grade
- site of the primary tumor

5-year survival rates

60-90% in patients with localized NENs following surgery
50-75% in patients with regional lymph node involvement
25–40% of patients with distant metastases

Modlin et al. Cancer 2003;97: 934

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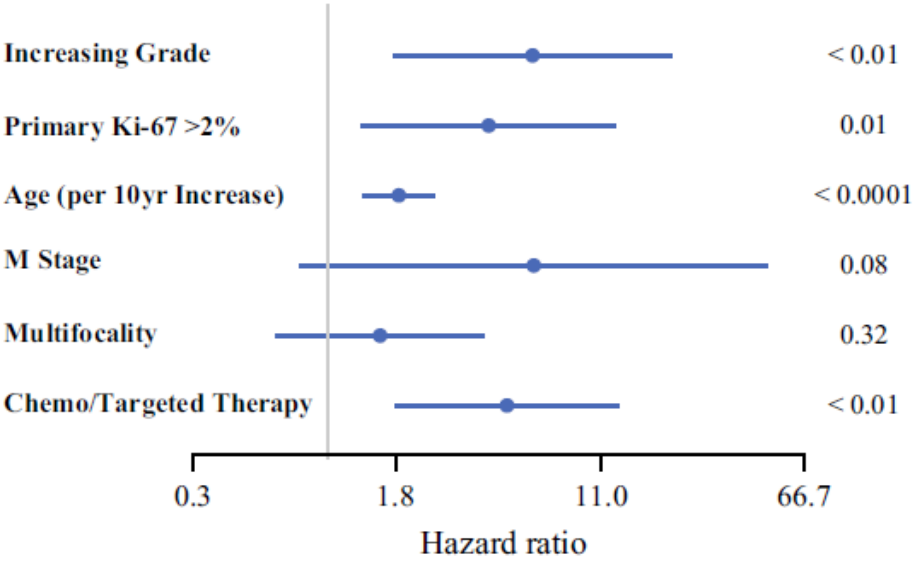
PROGNOSTIC MARKERS



Keck et al. Ann Surg Oncol (2017) 24:2206-2212

Multivariate analysis of factors affecting overall survival

- AGE
- Ki-67
- grading

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PROGNOSTIC MARKERS

Ki-67

Ki-67 index and mitotic count

markers of cell proliferation

strong indicator of aggressive phenotype

TECHNICAL ISSUES

HETEROGENEITY

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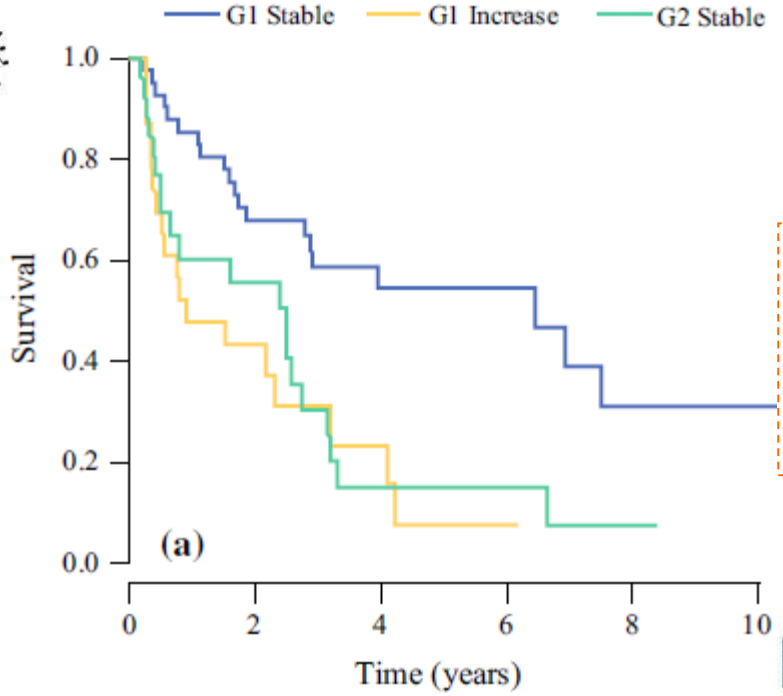
PROGNOSTIC MARKERS

grading



Keck et al. Ann Surg Oncol (2017) 24:2206-2212

30% of GEP-NEN patients had M with a different grade than their primary

When grade increased, PFS and OS significantly decreased.

Determining the grade in both the primary tumor and a metastasis is important for estimating prognosis and to help inform decisions regarding additional therapies

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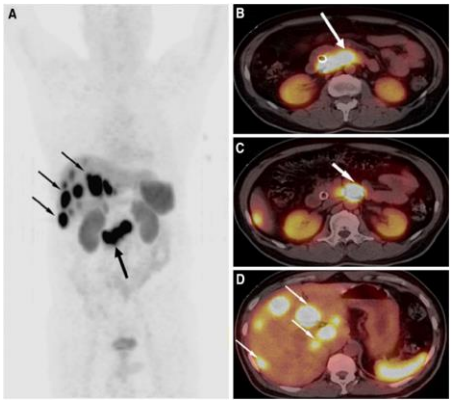
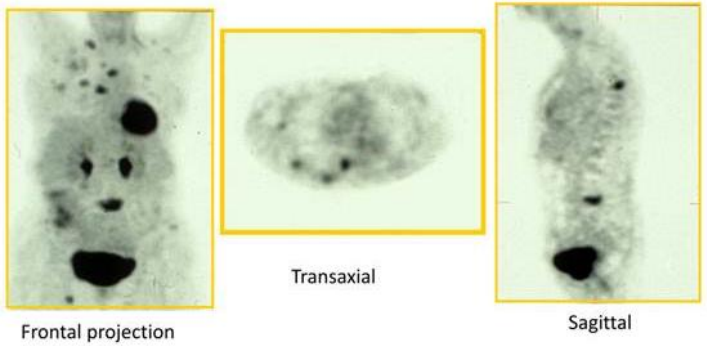
PROGNOSTIC MARKERS

Nuclear imaging

^{68}Ga-DOTATOC PET





^{18}F-FDG PET

Chan et al. Critical Reviews in Oncology/Hematology 113 (2017) 268–282

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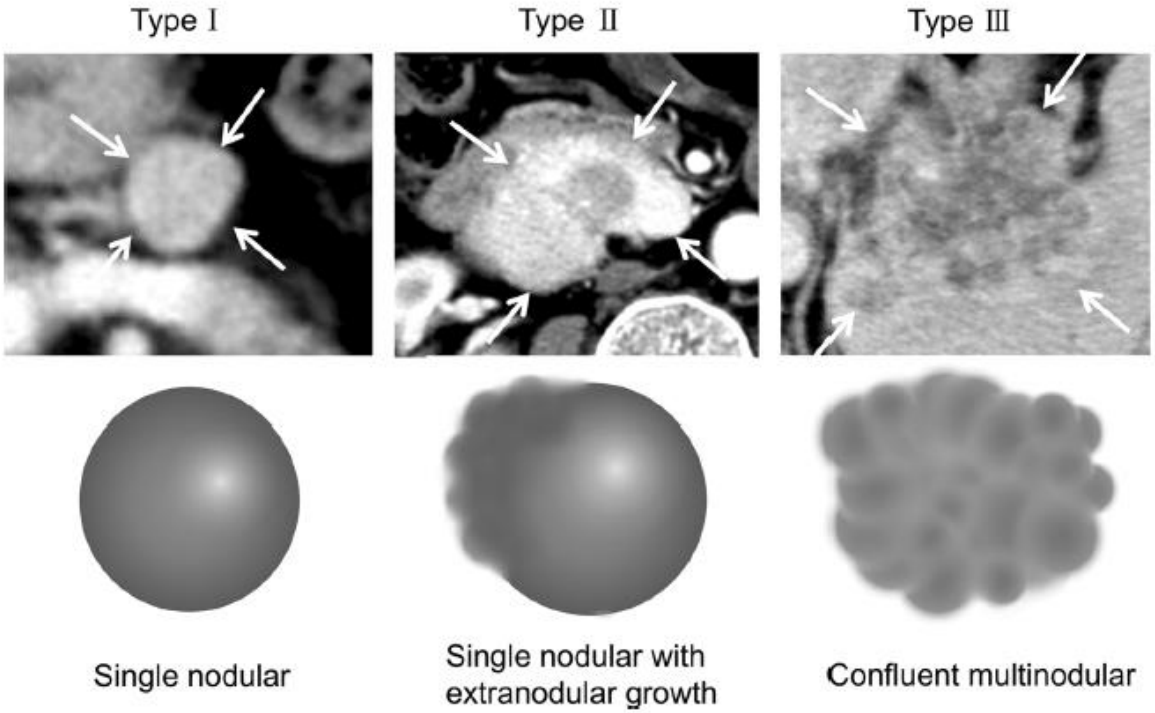
PROGNOSTIC MARKERS

…SHAPE?



Oba et al J Gastroenterol, 2017 DOI 10.1007/s00535-017-1349-7

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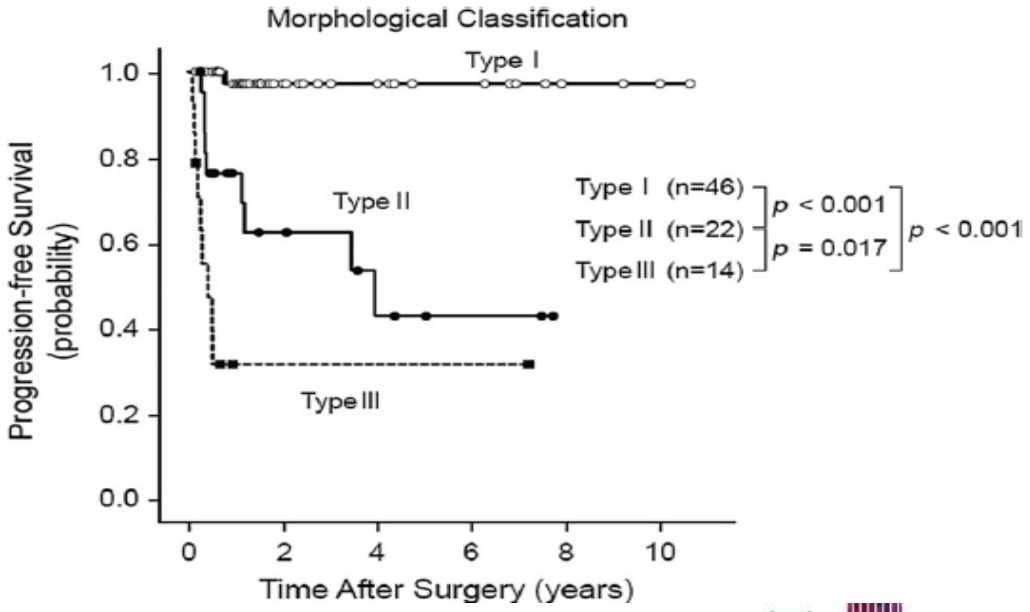
PROGNOSTIC MARKERS

SHAPE



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PROGNOSTIC MARKERS

GENETICS

Gene mutations

DAXX
ATRX

Protein expression

DAXX
ATRX

mainly G2 tumors
advanced stage

Jiao et al. 2011 Science 331:1199–1203
Gross et al. 2006 Endocr Relat Cancer 13:535–540.
Marinoni et al. 2014 Gastroenterology 146: 453-460e5.
deWilde et al. 2012 Mod Pathol 25:1033–1039.
Singhi et al.2017 Clin Cancer Res 23:600–609.

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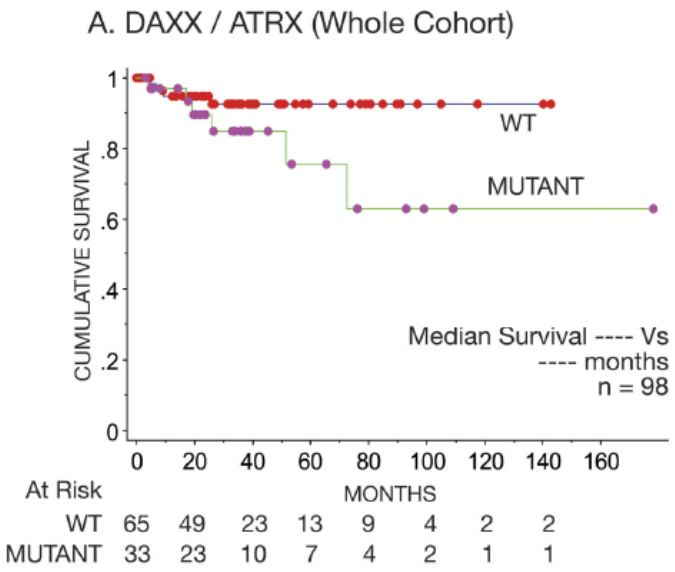
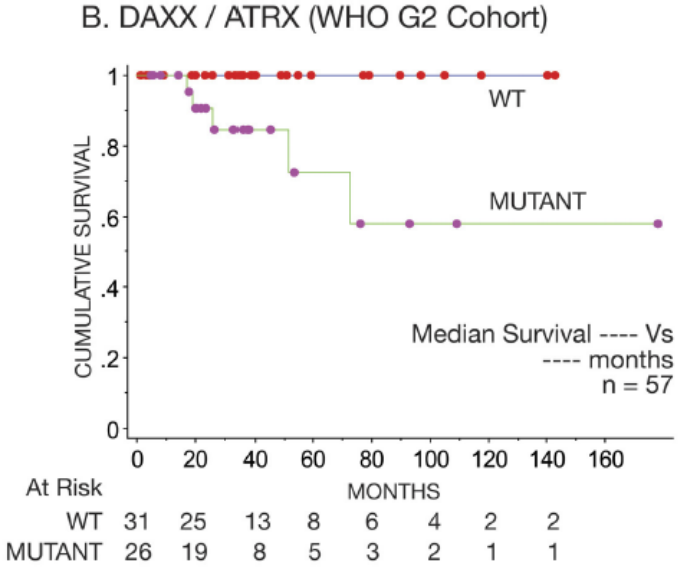
PROGNOSTIC MARKERS

GENETICS





Scarpa et al. 2017 Nature 543: 65

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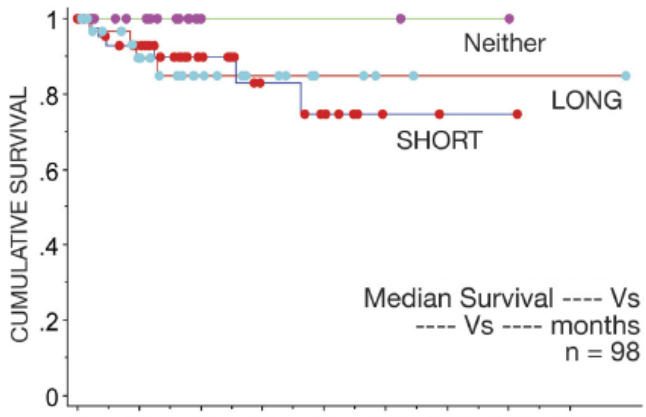
PROGNOSTIC MARKERS

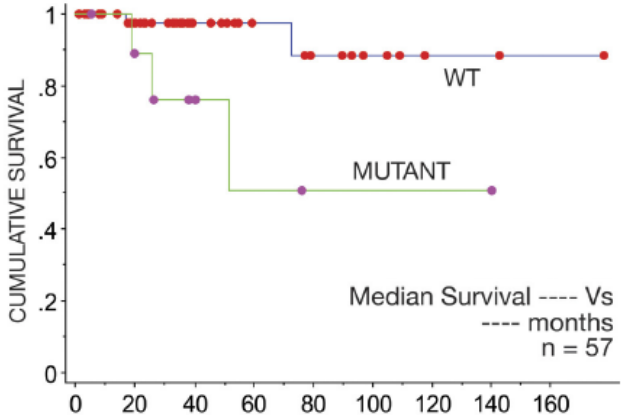
GENETICS

C. Telomere Length (Whole Cohort)



At Risk								
Neither	18	14	3	2	2	2	1	1
LONG	34	23	12	8	4	2	1	1
SHORT	46	35	18	10	7	2	1	1

D. mTOR Pathway (WHO G2 Cohort)



At Risk								
WT	47	36	17	11	8	5	2	2
MUTANT	10	8	4	2	1	1	1	1

Scarpa et al. 2017 Nature 543: 65

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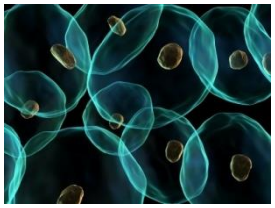
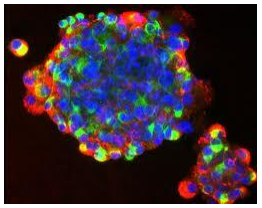
PROGNOSTIC MARKERS

CELL-FREE TUMOR DNA



normal cells

DNA shedding



neoplastic cells

cell-free DNA in blood and serum

potential biomarker

Tsang et al. 2007 Pathology 39:197
Valenti et al. 2009 Cancer Lett 273:122
Dalle Carbonare et al. 2011 Urol Oncol

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PROGNOSTIC MARKERS

CELL-FREE TUMOR DNA

plasma DNA vs. metastasis biopsies

(34 patients covering 18 different tumor types)

46 genes and >6800 COSMIC mutations

97% mutations identified in metastasis biopsies were detected in matched ctDNA

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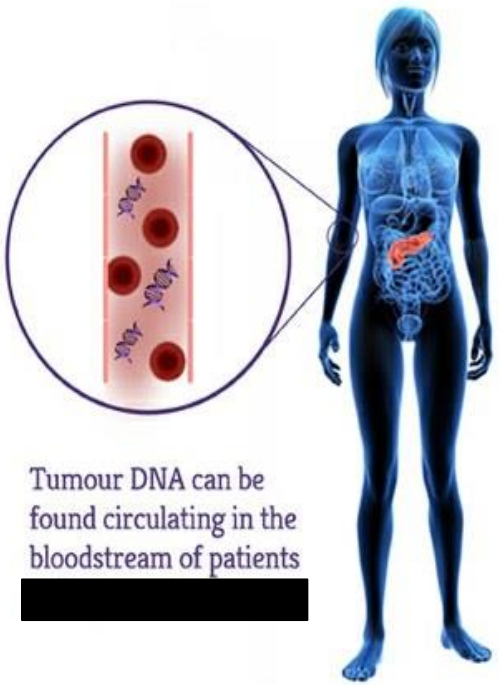
PROGNOSTIC MARKERS

CELL-FREE TUMOR DNA



- potential alternative and/or replacement to tissue biopsies
- irrespective of cancer type and metastatic site
- multiplexed mutation detection
- useful in selecting personalized therapies

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PROGNOSTIC MARKERS

CELL-FREE TUMOR DNA

challenge

Relative lack of recurrent mutations in NENs as compared to other tumors

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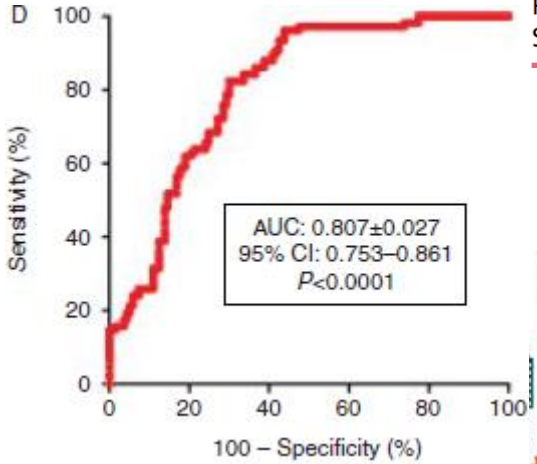
PROGNOSTIC MARKERS

NET TEST

Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status

Proliferome	*Ki67, NAP1L1, NOL3, TECPR2*
Growth factor signalome	*ARAF1, BRAF, KRAS, RAF1*
Metabolome	*ATP6V1H, OAZ2, PANK2, PLD3*
Secretome I (general)	*PNMA2, VMAT2*
Secretome II (progressive)	*PQB1, TPH1*
Epigenome	*MORF4L2, NAP1L1, PQB1, RNF41, RSF1, SMARCD3, ZFHX3*
Apoptome	*BNIP3L, WDFY3*
Plurome	*COMMD9*
SSTRome	*SSTR1, SSTR3, SSTR4, SSTR5*

Capacity of differentiating progressive disease from stable disease



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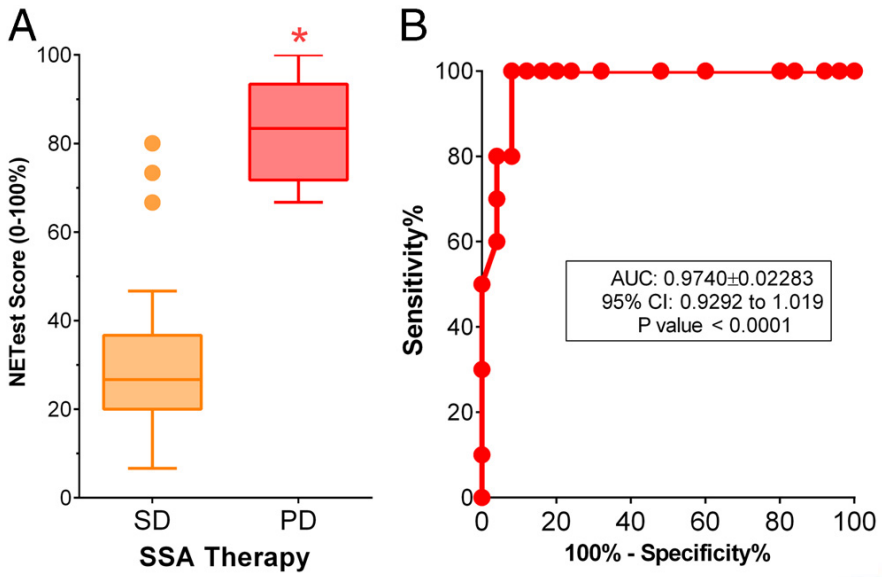
PROGNOSTIC MARKERS

NET TEST

test set = 35 SSA-treated GEP-NEN



NETest significantly increased in the PD (n 10) vs SD (n 25)

Associates with response to medical therapy

C´wikła et al. J Clin Endocrinol Metab 2015, 100:E1437–E1445

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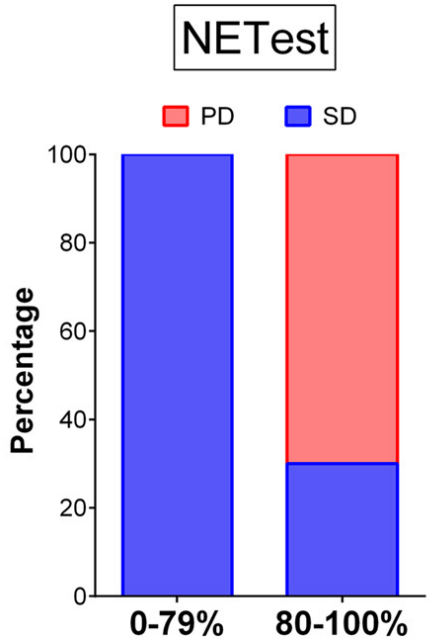
PROGNOSTIC MARKERS

NET TEST

prospective set = 28 SSA-treated G1–G2 GEP-NENs



elevated NETest (80–100% activity; *P* .002, measured anytime during therapy) predicts therapeutic responsiveness

Predicts response to medical therapy

C´wikła et al. J Clin Endocrinol Metab 2015, 100:E1437–E1445

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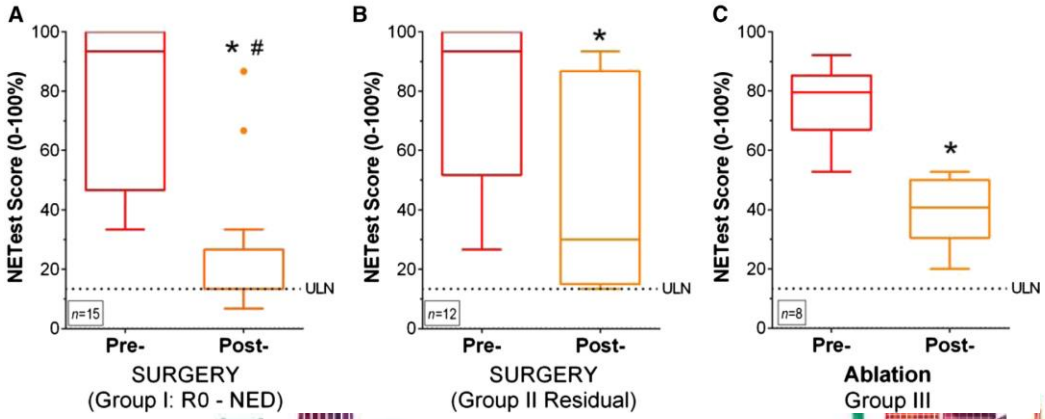
PROGNOSTIC MARKERS

NET TEST

35 GEP-NET
- 27 surgery
  - 15 R0
  - 12 residual
- 8 ablation

Predicts response to surgery



Modlin et al . Surgery 2016;159:336

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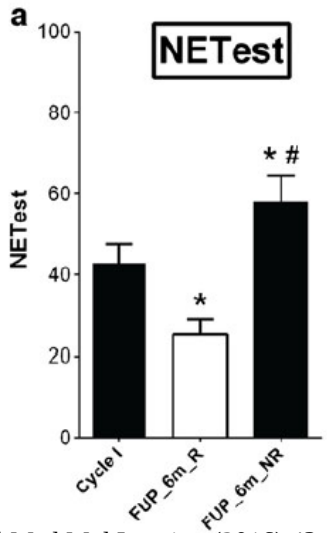
PROGNOSTIC MARKERS	NET TEST

54 NET patients (M: F 37:17)
13 bronchial
35 GEP-NET
6 CUP

→ 177Lu-based-PRRT (6.5-27.8 GBq)



Bodei et al . Eur J Nucl Med Mol Imaging (2016) 43:839–851

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PROGNOSTIC MARKERS	NET TEST		
Pre-PRRT (Cycle I) *n*=54		*p*=0.0004	
Responders *n*=39		*p*=0.0002	
Non-Responders *n*=15		*p*=0.0068	

Predicts response to PRRT

Bodei et al . Eur J Nucl Med Mol Imaging (2016) 43:839–851

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PROGNOSTIC MARKERS

NET TEST

NET gene transcript signature may be useful in patients clinical management

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PROGNOSTIC MARKERS

Review | M C Zatelli et al. | CTCs and miRNA as prognostic markers in NENs | 24:6 | R223–R237

Circulating tumor cells and miRNAs as prognostic markers in neuroendocrine neoplasms

Maria Chiara Zatelli[1], Erika Maria Grossrubatscher[2], Ella Guadagno[3], Concetta Sciammarella[4], Antongiulio Faggiano[5] and Annamaria Colao[4]

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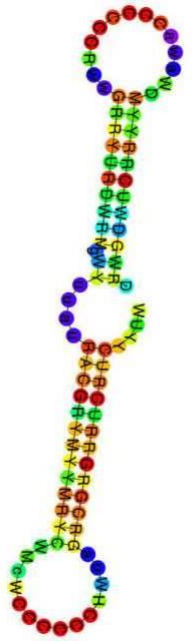
PROGNOSTIC MARKERS

miRNA	De-regulation	NEN histology	Number of cases	Prognostic role	References
miR-92a2*	Up-regulated	SCLC	31	Correlation with chemoresistance and reduced OS	Ranade *et al.* (2010)
miR-150 and miR-886-3p	Down-regulated	SCLC	82	Correlation with reduced OS and PFS	Bi *et al.* (2014)
miR-886-3p	Down-regulated	SCLC	82	Correlation with reduced OS and PFS	Cao *et al.* (2013)
miR-7	Up-regulated	SCLC	44	Correlation with chemoresistance and reduced OS	Liu *et al.* (2015)
miR-192, miR-200c, miR-205	Down-regulated	SCLC	50	Correlation with increased OS	Mancuso *et al.* (2016)
miR-21	Up-regulated	Lung NENs	63 (19 TC, 6 AC, 19 LCNEC, 19 SCLC)	Correlation with presence of lymph node metastases in TC and AC	Lee *et al.* (2012)
let-7d, miR-19, miR576-5p, miR-340*, miR-1286	Up-regulated	Lung NENs	12 (3 TC, 3 AC, 3 SCLC, 3 LCNEC)	Correlation with OS	Mairinger *et al.* (2014)
miR-409-3p, miR 409-5p, miR431-5p	Down-regulated	Lung NENs	37 (22 TC, 15 AC)	Correlation with presence of lymph node metastases	Rapa *et al.* (2015)
miR-21	Up-regulated	Pancreatic NEN	40	Correlation with Ki-67 index and liver metastases	Roldo *et al.* (2006)
miR-642, miR-210	Up-regulated	Pancreatic NEN	37	Correlation with Ki-67 index (miR-642) and with metastatic spread (miR-210)	Thorns *et al.* (2014)



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PROGNOSTIC MARKERS

miRNA	De-regulation	NEN histology	Number of cases	Prognostic role	References
miR 196a	Up-regulated	Pancreatic NEN	37	Correlation with advanced stage, lymph node metastases, higher mitotic count, higher Ki67 index, reduced OS and DFS	Lee *et al.* (2015)
miR-183, miR-375	Up-regulated	MTC	45	Correlation with lymph node, residual disease after surgery, distant metastases and survival	Abraham *et al.* (2011)
miR-224	Up-regulated	MTC	40	Correlation with the absence of node metastases, lower stage at diagnosis and biochemical cure during follow up	Mian *et al.* (2012)
miR-21	Up-regulated	MTC	64	Correlation with basal calcitonin levels, lymph node metastases and advanced disease at the end of follow up	Pennelli *et al.* (2015)
miR-1225-3p	Up-regulated	PC	34	Correlation with recurrence in sporadic PC	Tombol *et al.* (2010)
miR483-5p	Up-regulated	PC	24	Correlation with metastatic spread and shorter DFS	Meyer-Rochow *et al.* (2010)

Circulating tumor cells, DNA and microRNAs as prognostic markers for NETs

PROGNOSTIC MARKERS

Conclusions

The available literature data clearly show that tissue miRNA profiling may potentially represent a prognostic biomarker in NENs. However, the role of circulating miRNAs in these settings is far to be consolidated.

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PROGNOSTIC MARKERS

Studies prospectively evaluating circulating miRNA in different NEN types (and stages) and their levels after the different available therapeutic approaches are still lacking. On the contrary, studies employing CTC count as a marker of NEN prognosis report very promising results that need to be validated in further clinical trials. Studies on selected validation cohorts with long-term clinical follow-up are necessary to further qualify CTC as biomarkers in NENs.

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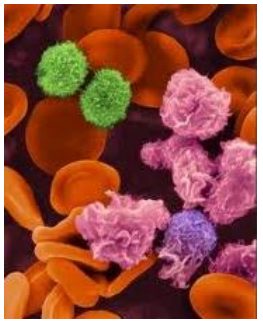
PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS



circulating tumor cells can be used as sentinels

blood can be proposed as a surrogate of tissues for diagnostic analyses

Liew et al. 2006 J Lab Clin Med 147:126

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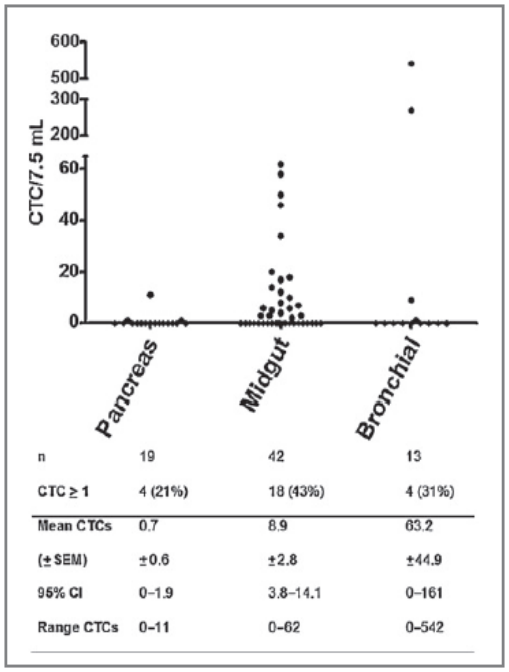
PROGNOSTIC MARKERS



n	19	42	13
CTC ≥ 1	4 (21%)	18 (43%)	4 (31%)
Mean CTCs	0.7	8.9	63.2
(± SEM)	±0.6	±2.8	±44.9
95% CI	0–1.9	3.8–14.1	0–161
Range CTCs	0–11	0–62	0–542

Khan et al. Clin Cancer Res 2011, 17: 337

CIRCULATING TUMOR CELLS

No CTCs → stable disease

CTC levels correlate with
- ➔ urinary 5-HIAA levels
- ➔ burden of liver metastases

but not with
- ➔ Ki-67
- ➔ serum CgA

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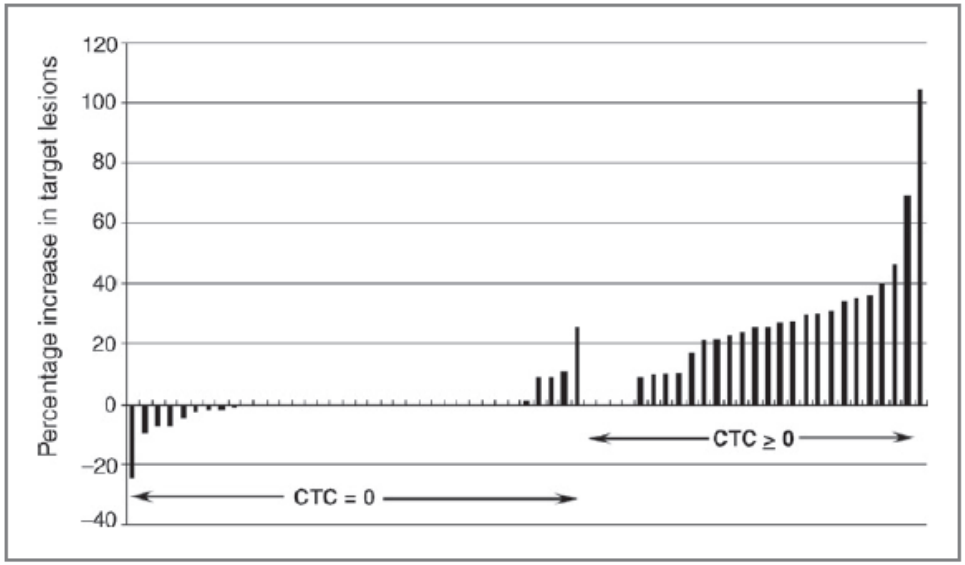
PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS



Khan et al. Clin Cancer Res 2011, 17: 337

CTCs seem to be associated with progressive disease and may provide useful prognostic information given the variable survival rates

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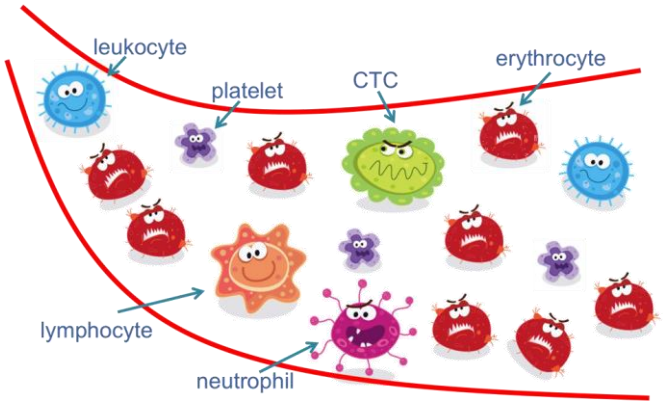
PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS

single-center prospective study, 176 patients with metastatic NETs

Presence of CTCs was associated with

- ➔ increased burden
- ➔ increased tumor grade
- ➔ elevated serum CgA



Khan et al. J Clin Oncol 2012,31:365-372

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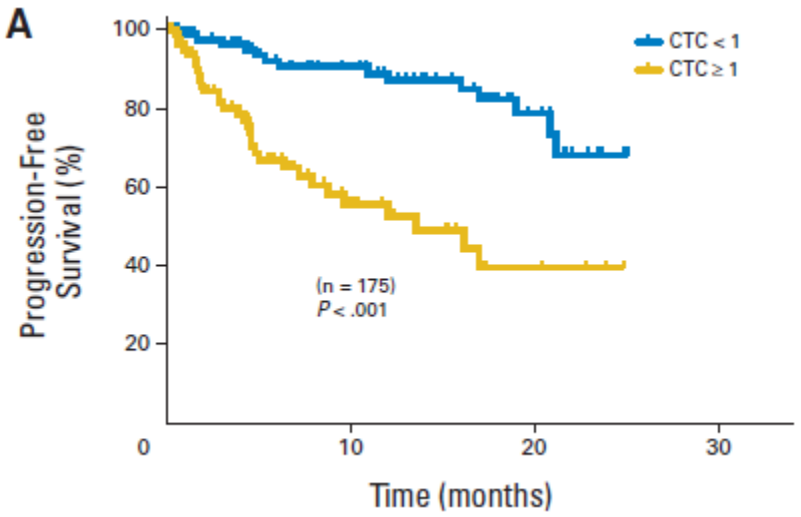
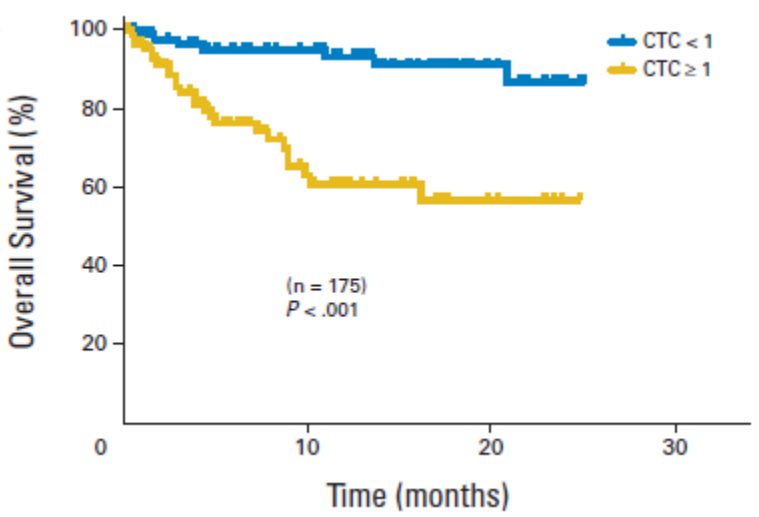
PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS





CTCs correlate with progression-free survival independently of grade, tumor burden, and CgA

Khan et al. J Clin Oncol 2012,31:365-372

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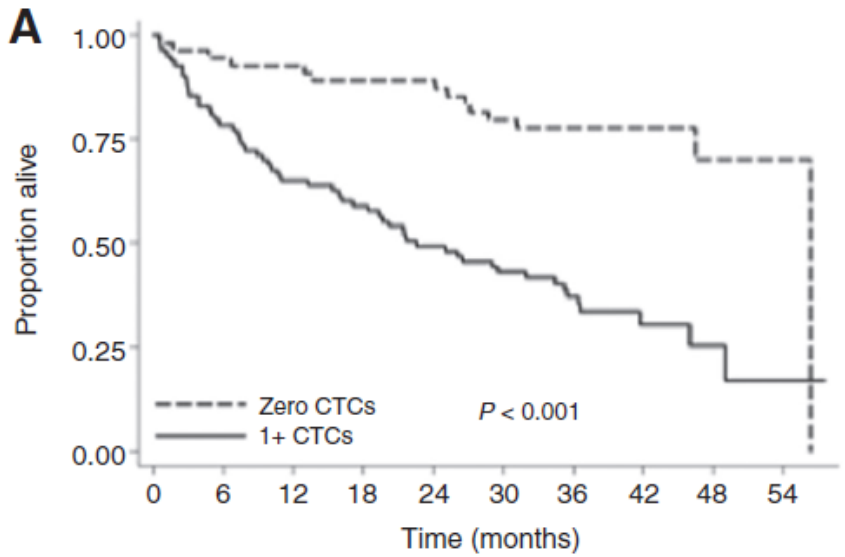
Circulating tumor cells, DNA and microRNAs as prognostic markers for NETs

PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS

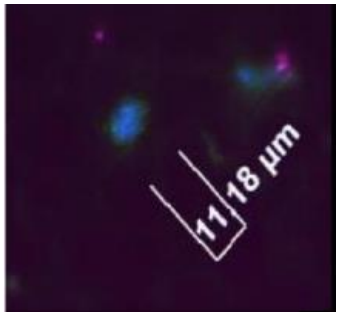
138 patients with metastatic NENs



Number at risk

Zero CTCs	55	52	51	49	47	42	30	16	5	1
1+ CTCs	83	65	54	48	40	35	23	10	3	1

At diagnosis



Khan et al. Clin Cancer Res 2016; 22(1); 79–85

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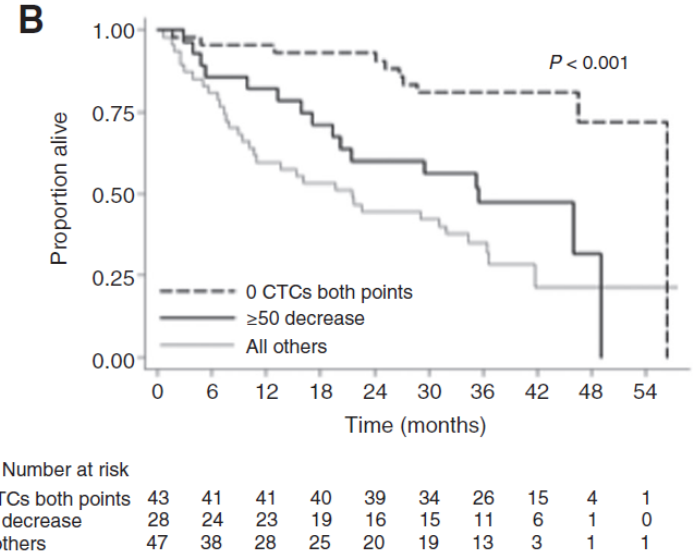

Number at risk										
0 CTCs both points	43	41	41	40	39	34	26	15	4	1
≥50 decrease	28	24	23	19	16	15	11	6	1	0
All others	47	38	28	25	20	19	13	3	1	1

Changes in CTCs at first posttreatment time (3 – 5 weeks)

Khan et al. Clin Cancer Res 2016; 22(1); 79–85

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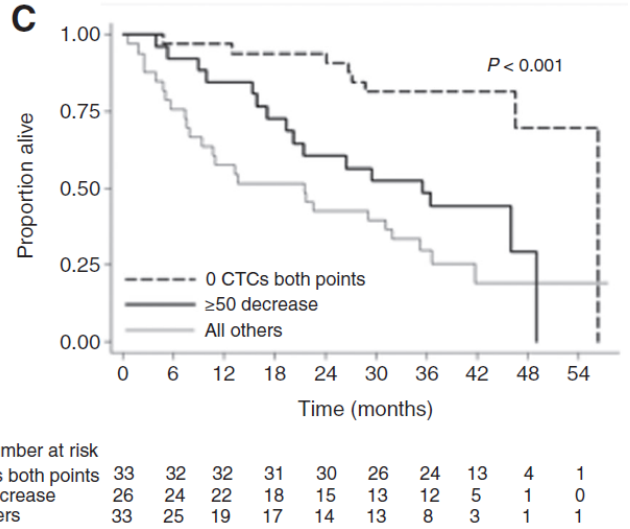

Changes in CTCs at second posttreatment time point (10–15 weeks)

Khan et al. Clin Cancer Res 2016; 22(1); 79–85

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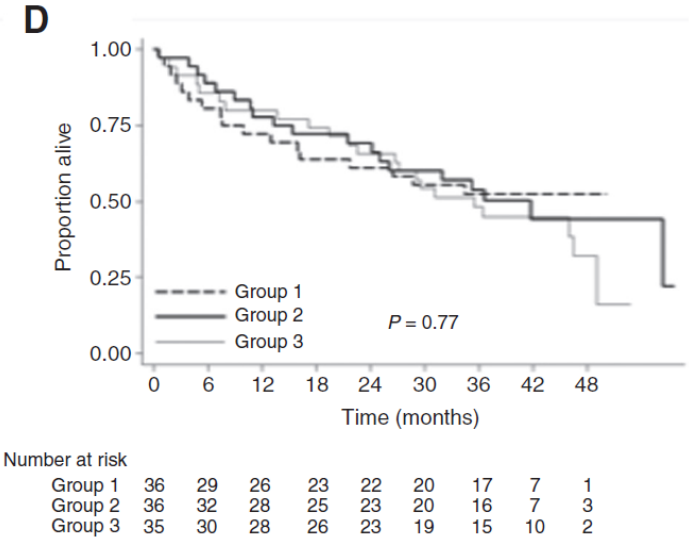

OS dependent on changes in CgA at first posttreatment time point

Khan et al. Clin Cancer Res 2016; 22(1); 79–85

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CIRCULATING TUMOR CELLS

Translational Relevance

There is an increasing range of therapeutic options available for patients with neuroendocrine neoplasms (NEN) but no validated predictive biomarkers to direct treatment selection or sequence. Having previously demonstrated the prognostic relevance of circulating tumor cells (CTC) in NENs, we have evaluated their role as predictive biomarkers in response to therapy. We show that a poor outcome group can be defined by the presence of >8 CTCs at 3 to 5 weeks after therapy, or by a <50% fall or a rise in CTC number at the same time point compared with baseline. The association of change in CTC number is an independent prognostic variable and allows serial monitoring of response to therapy. These findings will require further external validation but may present the opportunity for adaptive trials in NENs, in which evidence-based sequencing strategies can be defined.

Changes in CTCs are associated with response to treatment and OS in metastatic NENs, suggesting CTCs may be useful as surrogate markers to direct clinical decision making

Khan et al. Clin Cancer Res 2016; 22(1); 79–85

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CIRCULATING TUMOR CELLS

SSTR expression

→ tumor heterogeneity

→ tracking expression over time and during therapy

skeletal involvement

Rizzo et al. Endocrinol Metab Clin N Am (2018) doi.org/10.1016/j.ecl.2018.04.002

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PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS

Series	Findings	Reference
79 metastatic NENs: – 19 pancreatic – 42 midgut – 13 bronchopulmonary – 5 unknown primary	• Moderate correlation ($r=0.5$, $P=0.007$) between CTCs count and urinary 5-HIAA in midgut and unknown primary NENs • Significant association between CTCs count and tumor burden of liver metastase ($B=8.91$, 95% CI=4.3–13.5, $P<0.001$) • No correlation between CTCs count and Ki67 ($r=0.08$, $P=0.59$) and low correlation between CTCs count and serum CgA ($r=0.246$, $P=0.03$) • 0 CTCs associated with stable disease ($P<0.001$)	Khan *et al.* (2011)
175 metastatic NENs: – 42 pancreatic – 101 midgut – 17 bronchopulmonary – 12 unknown primary – 3 hindgut	• Significant association between CTCs count (≥1) and grade ($P=0.036$), tumor burden >25% ($P<0.001$) and serum chromogranin A >120 pmol/L ($P<0.001$), respectively • CTCs count ≥1 related with worse PFS (HRs: 6.6, $P<0.001$) and OS (HRs: 8.0, $P<0.001$) • Within grade 1, two CTCs-based subgroups: HRs=5.0 for PFS ($P=0.017$) and HRs=7.2 for OS ($P=0.023$) • Within grade 2, two CTCs-based subgroups: HRs=3.5 for PFS ($P=0.018$) and HRs=5.2 for OS ($P=0.036$)	Khan *et al.* (2013)
138 metastatic NENs: – 31 pancreatic – 81 midgut – 12 bronchopulmonary – 11 unknown primary – 3 hindgut	• Significant association ($P<0.001$) between the first post-treatment (after 3–5 weeks) CTCs count and progressive disease (PD): PD in 8% of patients with 'favorable count' (0 CTCs at baseline and after treatment, or ≥50% CTCs reduction after treatment) vs 60% in unfavorable group (<50% CTCs reduction or increase) • Changes in CTCs count at the first post-treatment time (after 3–5 weeks) strongly associated with OS ($P<0.001$): the best outcome in group with 0 CTCs count at baseline, followed by the group with ≥50% CTCs reduction after treatment (HRs=3.31; 95% CI=1.50–7.32) and then the group with <50% CTCs reduction or increase (HRs=5.07; 95% CI=2.48–10.38) • In multivariate analysis changes from baseline CTCs count ($P=0.0002$) and grade ($P=0.0046$) resulted independent prognostic factors	Khan *et al.* (2016)

Zatelli et al. Endocrine-Relat Can (2017) 24: R223

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PROGNOSTIC MARKERS

CIRCULATING TUMOR CELLS

Series	Findings	Reference
34 Merkel cell carcinomas	• Correlation between CTCs positivity (≥1 CTCs) and extent of disease ($P=0.004$) • Statistically significant difference in median OS between CTCs positive and CTCs negative samples ($P=0.0003$), also in case of regional node metastases ($P=0.015$)	Blom *et al.* (2014)
30 Merkel cell carcinomas	• Significantly higher CTCs count in patients with active disease • Increasing CTCs count associated with development of new metastases	Gaiser *et al.* (2015)
59 Small cell lung cancers	• Association between CTCs count <2 and prolonged OS and PFS ($P\leq0.001$) • CTCs count decrease after the first cycle of therapy correlated with longer OS and PFS ($P\leq0.001$) • CTCs count decrease after four cycles of therapy correlated with longer OS ($P=0.05$) and PFS ($P=0.007$) • CTCs count <2 after the first cycle of therapy is an independent prognostic factor for OS in multivariate analysis (HRs=3.5, $P=0.09$)	Hiltermann *et al.* (2012)
31 Small cell lung cancers	• Identification of chemosensitive and chemorefractory patients by CTCs copy-number aberrations profile and observation of significant difference ($P=0.0166$) in PFS between these two groups • Difference in CTCs copy-number aberrations profile between initial and acquired chemoresistance	Carter *et al.* (2017)

Zatelli et al. Endocrine-Relat Can (2017) 24: R223

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"CTCs are a promising prognostic markers for patients with NETs and should be assessed in the context of clinical trials with defined tumor subtypes and therapy"

Khan et al. J Clin Oncol 2012,31:365-372

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PROGNOSTIC MARKERS

Despite the identification of CTCs, ctDNA and miRNAs as circulating biomarkers capable of providing prognostic and predictive information in patients with NET, they have not been incorporated into routine clinical practice. This is due in part to technological limitations hampering routine analysis, as well as limited data regarding the implications of clinical decision making based on these biomarkers.

Rizzo et al. Endocrinol Metab Clin N Am (2018) doi.org/10.1016/j.ecl.2018.04.002

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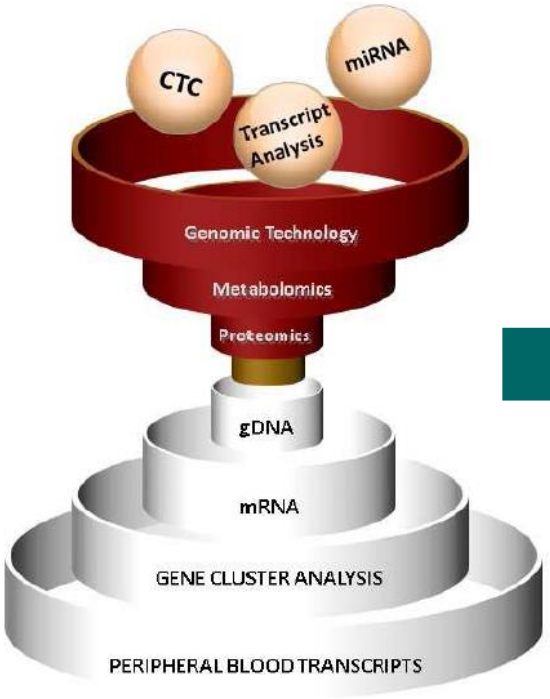

PERSONALIZED MEDICINE

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PROGNOSTIC MARKERS

THERE ARE A LOT OF ZEBRAS

NOT ALL ZEBRAS ARE THE SAME

ENEA

6th workshop

ParaSellar Lesions

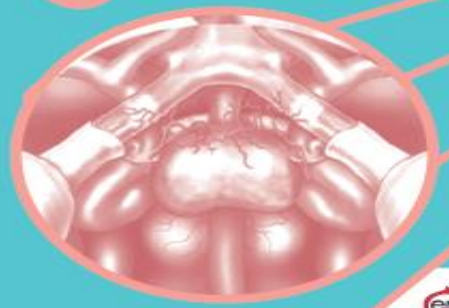
organized by

European NeuroEndocrine Association

5-7 December 2019

Megaron International Conference Centre
Athens, Greece

www.6eneaworkshop.com



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17, Asklipiou Str., 10680 Athens-Greece, Tel.: +30 210 3634944, Fax: +30 210 3631690, E-mail: info@era.gr, Web site: www.era.gr


Grazie per l'attenzione