Rola medycyny nuklearnej w raku rdzeniastym tarczycy

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Na podstawie wykładów wygłoszonych w trakcie EANM 2022, Barcelona

- MARCUS LUSTER „State of the Art Nuclear Medicine Imaging o MTC”
- CHRISTOF ROTTENBURGER „Radioligand Therapy in MTC”

MTC

- Wywodzi się z komórek parafollikularnych (komórek C)
- Stanowi około 2% wszystkich raków tarczycy
- 25% przypadków to postaci dziedziczne
- Markery nowotworowe: kalcytonina, CEA
- Terapia jodem radioaktywnym (RAI) nie znajduje zastosowania w jego leczeniu
- Gorsze rokowanie w porównaniu do raka zróżnicowanego
- Leczenie operacyjne jest jedynym postępowaniem terapeutycznym dającym możliwość całkowitej remisji; rekomendowana rozległość zabiegu operacyjnego zależy od wyników obrazowania (USG) i stężenia kalcytoniny
- Rokowanie zależy od stopnia zaawansowania w momencie rozpoznania (zaawansowania miejscowego i obecności przerzutów odległych)

Ogólne zasady postępowania

- Jeżeli jest to możliwe należy dążyć do radykalnego leczenia operacyjnego
- Stężenie kalcytoniny pooperacyjnie powinno być niewykrywalne
- Jeżeli stężenie kalcytoniny w okresie pooperacyjnym > 600 pg/ml istnieje wysokie prawdopodobieństwo przerzutów odległych
- F-DOTA-PET jest skuteczną metodą wykrywania choroby przetrwałej/meta, jeżeli stężenie kalcytoniny > 150 pg/ml
- Jeżeli w preparacie stwierdza się > 10 przerzutowych węzłów chłonnych lub obecne są przerzuty odległe: prawdopodobieństwo uzyskania remisji jest nikłe (chirurgiczne zabiegi z intencją paliatywną lub inne metody leczenia lokoregionalnego)
- Chemioterapia cytotoksyczna nie jest skuteczna
- Leczenie palitywne/kontrola choroby: TKI

Czynniki prognostyczne

- Czas podwojenia stężenia kalcytoniny/CEA
- Wychwyt [^{18}F]-FDG w guzie (PET)
- Obecność somatycznej mutacji protoonkogenu RET (M918T)
- Nadekspresja receptorów VEGF, EGF

Rola medycyny nuklearnej w diagnostyce MTC

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Positron Emission Tomography Imaging in Medullary Thyroid Carcinoma: Time for Reappraisal?

Fréderic Castinetti[1] and David Taïeb[2]

TABLE 1. PREOPERATIVE IMAGING STUDIES BEFORE INITIAL SURGERY ACCORDING TO DIFFERENT CLINICAL SCENARIOS

Presentation	*Surgery*	*Preoperative imaging studies*[a]
MEN2 diagnosed by genetic screening and no clinical evidence of disease	Prophylactic total thyroidectomy (if no disease on preoperative US)	Neck US
MTC (MEN2 or sporadic) <10 mm without evidence of metastatic nodes on neck US and serum calcitonin <200 pg/mL	Total thyroidectomy and prophylactic central LN dissection	Neck US
MTC (MEN2 or sporadic) ≥10 mm without evidence of LN metastasis on neck US	Total thyroidectomy and central LN dissection, prophylactic ipsilateral (sporadic) or bilateral (MEN2) lateral LN dissection	Neck US, neck and chest CT?, ^{18}F-FDOPA PET/CT scan?
MTC (MEN2 or sporadic) with abnormal nodes on neck US	Total thyroidectomy and therapeutic central and lateral LN dissection (bilateral in MEN2)	Neck US, neck and chest CT, ^{18}F-FDOPA PET/CT scan?
MTC (MEN2 or sporadic) with suspicion of distant metastases (calcitonin >500 pg/mL)	In the absence of distant metastases, total thyroidectomy and therapeutic cervico-mediastinal and bilateral lateral LN dissection In the presence of distant metastases, surgery can be performed for preventing locoregional complications	Neck US, neck, chest, and abdomen/pelvis CT (or hepatic MRI), bone scintigraphy and bone marrow MRI, ^{18}F-FDOPA PET/CT scan?, ^{18}F-FDG PET/CT scan?

[a]Before thyroidectomy, all patients are required to undergo evaluation for pheochromocytoma with biochemical testing. If metanephrines are elevated, an abdominal computed tomography and/or magnetic resonance imaging is indicated.
?, optional; ^{18}F-FDG, 18F-flurodeoxy glucose; ^{18}F-FDOPA, 6-18F-fluoro-L-3,4-dihydroxyphenylalanine; LN, lymph node; MEN2, multiple endocrine neoplasia type 2; MRI, magnetic resonance imaging; MTC, medullary thyroid carcinoma; PET/CT scan, positron emission tomography/computed tomography scan; US, ultrasound.

[^{18}F]-FDOPA vs. [^{18}F]-FDG

- Czas podwojenia kalcytoniny > 2 lat: [^{18}F]-FDOPA > [^{18}F]-FDG
- Czas podwojenia kalcytoniny < 2 lat: [^{18}F]-FDOPA = [^{18}F]-FDG
- Czas podwojenia CEA < 2 lat: [^{18}F]-FDOPA < [^{18}F]-FDG

Complementary Roles of ^{18}F-DOPA PET/CT and ^{18}F-FDG PET/CT in Medullary Thyroid Cancer

Saila Kauhanen[*1,2], Camilla Schalin-Jäntti[*3], Marko Seppänen[1,4], Sami Kajander[1], Sami Virtanen[5], Jukka Schildt[6], Irina Lisinen[1], Aapo Ahonen[6], Ilkka Heiskanen[7], Mika Väisänen[7], Johanna Arola[8,9], Pirkko Korsoff[10], Tapani Ebeling[11], Timo Sane[3], Heikki Minn[1,12], Matti J. Välimäki[3], and Pirjo Nuutila[1,13]

Rola scyntygrafii/PET receptorów somatostatynowych w MTC

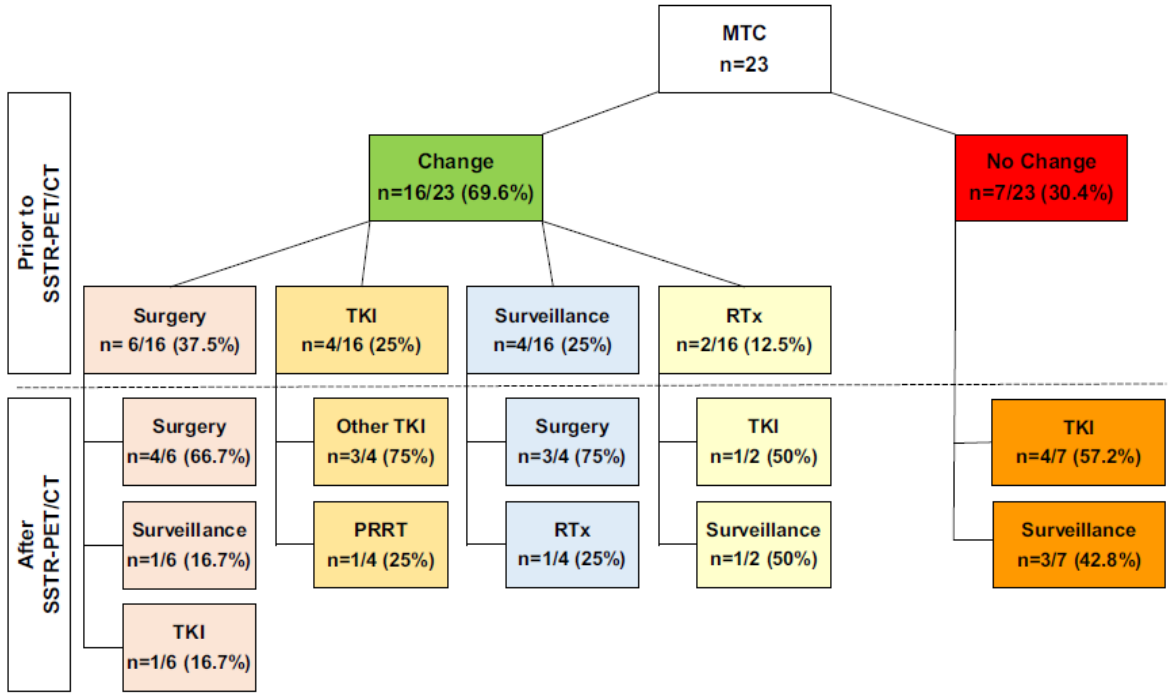

Fig. 1 Overview of patients affected with medullary thyroid carcinoma (MTC), which underwent somatostatin receptor (SSTR)-directed positron emission tomography/computed tomography (PET/CT). Therapy prior to and after SSTR-PET/CT is displayed. In more than 69% of the patients, SSTR-PET/CT resulted in treatment initiation, with most patients switched to surgery or tyrosine kinase inhibitors (TKI). PRRT Peptide Receptor Radionuclide Therapy, RTx external beam radiation.

Somatostatin receptor-directed molecular imaging for therapeutic decision-making in patients with medullary thyroid carcinoma

Sebastian E. Serfling[1] · Yingjun Zhi[2] · Felix Megerle[3] · Martin Fassnacht[3] · Andreas K. Buck[1] · Constantin Lapa[4] · Rudolf A. Werner[1,5]

Rola badań z zakresu medycyny nuklearnej w obrazowaniu MTC wg wytycznych

TABLE 2. INDICATION FOR POSITRON EMISSION TOMOGRAPHY IMAGING ACCORDING TO GUIDELINES

	^{18}F-FDOPA	^{18}F-FDG	^{68}Ga-SSA
ATA 2015 (3)	Not recommended	Not recommended	Not recommended
ESMO 2019 (4)	At initial diagnosis when serum CT >500 pg/mL or suspicion of distant metastasis In persistent/recurrent MTC with serum CT >150 pg/mL	In cases with short serum CT and CEA levels, doubling times (<1 year) or MTC with an aggressive behavior (e.g., CEA levels disproportionately high compared with CT levels)	To assess the feasibility of PRRT
EANM 2020 (7)	In persistent/recurrent MTC with serum CT >150 pg/mL	In cases with short serum CT and CEA levels, doubling times (<1 year) or MTC with an aggressive behavior	In selected cases with inconclusive morphological and functional imaging and to assess the feasibility of PRRT

ATA, American Thyroid Association; CEA, carcinoembryonic antigen; CT, calcitonin; EANM, European Association of Nuclear Medicine; ESMO, European Society of Medical Oncology; PRRT, peptide receptor radionuclide therapy.

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SPECIAL ARTICLES

Positron Emission Tomography Imaging in Medullary Thyroid Carcinoma: Time for Reappraisal?

Fréderic Castinetti[1] and David Taïeb[2]

Terapia radioizotopowa ukierunkowana na receptory somatostatyny w MTC - podstawy

- 60% MTC wykazuje ekspresję SSTR2 (w 35% jest to ekspresja słaba; umiarkowana w 15% i silna w 10% przypadków)
- Ekspresja SSTR2 występuje częściej u osób z dziedzicznymi postaciami raka (MEN2A/B)

Terapia radioizotopowa ukierunkowana na receptory somatostatyny w MTC – dotychczasowe wyniki (1)

Table 1. PRRT targeting SSRs with 90Y and 177Lu-SSA in MTC.

References			Demographics				Disease Data		Treatment Schedule and Follow-Up				
Authors	Year	Type of Study	Subjects *n*	Age-Years Mean (Median) (Range)	F/M *n*	Mutation Status *n*	Disease Status at Baseline	Subjects with Metastases %	Radioisotope	Dose/Cycle GBq	Cycles *n*	Cumulative Dose-GBq Mean (Median) (Range)	Follow-Up Months Mean (Median) (Range)
Otte et al. [21]	1999	NS	2	64.5 (64.5) (62–67)	2/0	NS	NS	2 (100%)	90Y	1.6–2.9	4	9.4 (9.4) (9.2–9.6)	2 (2) (2–2)
Waldherr et al. [22]	2001	NS	12	55.8 (60.0) (24–72)	5/7	1 MEN2 11 NS	Progressive	NS	90Y	NS	1–4	8.1 (9.1) (1.7–14.0)	NS
Paganelli et al. [23]	2001	NS	3	51.0 (55.0) (34–64)	2/1	NS	NS	2 (67%)	90Y	1.8	3	5.5 (5.5) (5.5–5.5)	11 (12) (10–12)
Bodei et al. [24]	2003	NS	8	45.4 (46.5) (31–67)	1/7	NS	Progressive in 3/8 patients	8 (100%)	90Y	2.9–4.8	2	7.9 (8.5) (5.9–9.6)	19 (21) (4–26)
Bodei et al. [25]	2004	Retrospective	21	51.4 (53.0) (31–78)	8/13	NS	Progressive	21 (100%)	90Y	2.2–5.1 (max)	2–8	10.7 (10.4) (7.6–19.2)	(3–40)
Gao et al. [26]	2004	NS	1	57.0	0/1	NS	Progressive	1 (100%)	90Y	3.3	4	13.2	NS
Iten et al. [27]	2007	Prospective	31	(56.7) (24–77)	10/21	2 MEN2 (1 additional MEN1), 28 NS	Progressive	31 (100%)	90Y	3.7 (GBq/m^2)	1–5	(12.6) (1.7–29.6)	(12) (1–107)
Budiawan et al. [28]	2013	NS	8	59.1 (61.0) (40–76)	4/4	NS	Progressive	8 (100%)	90Y and/or 177Lu	NS	1–3	NS	NS
Vaisman et al. [29]	2015	Prospective	7	NS	NS	NS	Progressive	NS	177Lu	7.4	4	29.6 (29.6) (29.6–29.6)	(8–12)
Lapa et al. [30]	2015	Retrospective	4	49.0 (44.0) (33–75)	2/2	2 MEN2 2NS	NS	4 (100%)	177Lu	NS	2–5	31.4 (31.4) (23.7–39.0) 2 patients NS	NS
Salavati et al. [31]	2016	NS	28	47.9 (26–72)	14/14	NS	NS	28 (100%)	90Y and/or 177Lu	NS	≤ 5	NS	NS
Beukhof et al. [32]	2019	Retrospective	10	(63.0) (19–75)	6/4	6 sporadic 4 NS	Progressive in 8/10 patients	10 (100%)	177Lu	NS	4 (mean)	(27.8–29.6)	NS
Parghane et al. [33]	2020	Retrospective	43	(48.0) (25–80)	8/35	NS	Progressive	43 (100%)	177Lu	5.5 (mean)	1–6	18.5 (5.55–33.3)	(20) (8–78)
Satapathy et al. [34]	2020	Retrospective	8	46.0 (47.5) (22–70)	5/3	8 sporadic	Progressive or advanced or inoperable	8 (100%)	177Lu *	6.0–7.4	1–4	19.1 (20.9) (6.4–27.8)	40 (34) (14–69) 1 patient NS
-	1999–2020	-	186	-	67/112	-	Progressive or Advanced or Inoperable 142/149 (95.3%)	166/167 (99.4%)	-	-	-	-	-

References	Radiographic Response						Biochemical Response		Treatment Outcome			Treatment Toxicity		
Authors, Year	Subjects Suitable for Evaluative *n*	Response Criteria	PD *n* (%)	SD *n* (%)	PR *n* (%)	CR *n* (%)	Subjects Suitable for Evaluative *n*	Response Criteria (Calcitonin, CT)	Response	PFS Months	OS Months	Discontinuation *n* (%)	Grade III/IV Nephrotoxicity *n* (%)	Grade III/IV Haemotoxicity *n* (%)
Otte et al., 1999 [21]	2	NS	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0	-	-	NS	NS	0 (0%)	0 (0%)	0 (0%)
Waldherr et al., 2001 [22]	12	WHO	7 (58%)	5 (42%)	0 (0%)	0 (0%)	0	-	-	NS (TTP: mean 8, median 10, range 3–14)	NS	0 (0%)	0 (0%)	NS

Review

Advances in the Management of Medullary Thyroid Carcinoma: Focus on Peptide Receptor Radionuclide Therapy

Erika Grossrubatscher [1,*,†], Giuseppe Fanciulli [2,*,†], Luca Pes [3], Franz Sesti [4], Carlotta Dolci [5], Federica de Cicco [6], Annamaria Colao [6], Antongiulio Faggiano [4] and NIKE Group [‡]

Terapia radioizotopowa ukierunkowana na receptory somatostatyny w MTC – dotychczasowe wyniki (2)

References	Radiographic Response						Biochemical Response			Treatment Outcome		Treatment Toxicity		
Authors, Year	Subjects Suitable for Evaluative *n*	Response Criteria	PD *n* (%)	SD *n* (%)	PR *n* (%)	CR *n* (%)	Subjects Suitable for Evaluative *n*	Response Criteria (Calcitonin, CT)	Response	PFS Months	OS Months	Discontinuation *n* (%)	Grade III/IV Nephrotoxicity *n* (%)	Grade III/IV Haemotoxicity *n* (%)
Paganelli et al., 2001 [23]	3	WHO	0 (0%)	3 (100%)	0 (0%)	0 (0%)	0	-	-	NS	NS	0 (0%)	0 (0%)	NS
Bodei et al., 2003 [24]	7	WHO	2 (29%)	3 (43%)	1 (14%)	1 (14%)	0	-	-	NS	NS	0 (0%)	0 (0%)	7 (88%)
Bodei et al., 2004 [25]	21	SWOG	7 (33%)	12 (57%)	0 (0%)	2 (10%)	21	PD (increase ≥ 25% in basal value) SD (none of the others) PR (decrease ≥ 50% in basal value) CR (<15 pg/mL)	12 (57%) 3 (14%) 5 (24%) 1 (5%)	NS	NS	0 (0%)	NS	1 (5%)
Gao et al., 2004 [26]	1	WHO	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1	Pre-therapy and Post-therapy values	10,461 pg/mL; 3414 pg/mL	NS (TTP: 6)	NS	0 (0%)	0 (0%)	0 (0%)
Iten et al., 2007 [27]	0	-	-	-	-	-	31	Post-PRRT Prolongation of CT Doubling Time (≥100%)	Response = 18/31 (58%)	NS	16 (median) 1-107 (range)	2 (6%): kidney toxicity	1 (3%)	1 (3%)
Budiawan et al., 2013 [28]	0	-	-	-	-	-	0	-	-	NS	NS	0 (0%)	0 (0%)	0 (0%)
Vaisman et al., 2015 [29]	7	RECIST 1.1	1 (14%)	3 (43%)	3 (43%)	0 (0%)	0	-	-	NS	NS	0 (0%)	0 (0%)	0 (0%)
Lapa et al., 2015 [30]	4	RECIST 1.1 "in most cases"	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0	-	-	NS	NS	NS	NS	NS
Salavati et al., 2016 [31]	0	-	-	-	-	-	0	-	-	NS	24 in PD (median) 36 in SD (median) 72 in PR (median)	NS	NS	NS
Beukhof et al., 2019 [32]	10	RECIST 1.1	6 (60%)	4 (40%)	0 (0%)	0 (0%)	0	-	-	8 (median) 4–144 (range)	14 (median) 5–144 (range)	0 (0%)	0 (0%)	0 (0%)
Parghane et al., 2020 [33]	43	RECIST 1.1	16 (37%)	25 (58%)	2 (5%)	0 (0%)	43	PD (increase ≥ 30% in basal value) SD (none of the others) PR (decrease ≥ 50% in basal value) CR (<15 pg/mL)	21 (49%) 4 (9%) 13 (30%) 5 (12%)	24 (median)	26 (median)	0 (0%)	0 (0%)	0 (0%)
Satapathy et al., 2020 [34]	7	RECIST 1.1	1 (14%)	6 (86%)	0 (0%)	0 (0%)	5	Increase ≥ 25% in basal value None of the others Decrease ≥ 50% in basal value CT < 15 pg/mL	2 (40%) 2 (40%) (20%) 0 (0%)	NS	NS	0 (0%)	0 (0%)	0 (0%)
-	117	-	44 (37.6%)	64 (54.7%)	6 (5.1%)	3 (2.6%)	101	-	-	-	-	2/154 (1.3%)	1/133 (0.8%)	9/139 (6.5%)

PRRT: peptide receptor radionuclide therapy; SSR: somatostatin receptor; 90Y: 90 yttrium; 177Lu: lutetium; SSA: somatostatin analogue; MTC: medullary thyroid carcinoma; F: female; M: male; GBq: GigaBecquerel; NS: not specified; MEN: multiple endocrine neoplasia; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response; PFS: progression-free survival; OS: overall survival; WHO: World Health Organization; TTP: time-to-progression; SWOG: Southwest Oncology Group; RECIST: Response Evaluation Criteria In Solid Tumours. * Concomitant low-dose oral capecitabine therapy (1.250 mg/m^2/day from day 0 to day 14 of each PRRT therapy).

Review

Advances in the Management of Medullary Thyroid Carcinoma: Focus on Peptide Receptor Radionuclide Therapy

Erika Grossrubatscher [1,*,†], Giuseppe Fanciulli [2,*,†], Luca Pes [3], Franz Sesti [4], Carlotta Dolci [5], Federica de Cicco [6], Annamaria Colao [6], Antongiulio Faggiano [4] and NIKE Group [‡]

Inne opcje/perspektywy

- Radioimmunoterapia z bispecyficznymi przeciwciałami monoklonalnymi p/CEA i biwalentnym haptenem znakowanym ^{131}I
- Znakowani antagoniści SSTR2
- Receptor cholecystokininy (CCK2-R)

Table 4. Summary of recent clinical studies with radiolabeled CCK2R targeting peptide analogs.

Study Acronym	Sponsor	Intervention/Treatment	Identifier	Recruitment Status
GRAN-T-MTC	Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy	[^{111}In]In-CP04, Gelofusine	ClinicalTrials.gov (accessed on 22 September 2021): NCT03246659	Completed
Ga-68-CCK2R PET/CT in NET	Medical University of Innsbruck, Austria	[^{68}Ga]Ga-DOTA-MGS5	EudraCT: 2020-003932-26	Recruiting
Lumed phase 0/A and phase I	University Hospital Basel, Switzerland	[^{177}Lu]Lu-PP-F11N, Gelofusine (phase 0/A)	ClinicalTrials.gov (accessed on 22 September 2021): NCT02088645	Completed (phase 0/A) Recruiting (phase I)
Lumed phase 0/B	University Hospital Basel, Switzerland	[^{177}Lu]Lu-PP-F11N, Sacuitril	ClinicalTrials.gov (accessed on 22 September 2021): NCT03647657	Recruiting

Review

Update on Preclinical Development and Clinical Translation of Cholecystokinin-2 Receptor Targeting Radiopharmaceuticals

Elisabeth von Guggenberg [1,*], Petra Kolenc [2,3], Christof Rottenburger [4], Renata Mikolajczak [5] and Alicja Hubalewska-Dydejczyk [6]

Terapia radioizotopowa w MTC wg wytycznych

- ATA 2015: „treatment with radiolabeled molecules or pretargeted radioimmunotherapy may be considered in selected patients, ideally in the setting of well-designed clinical trial”
  - PRRT ukierunkowana na receptory somatostatyny
  - Radioimmunoterapia z bispecyficznymi przeciwciałami monoklonalnymi i biwalentnym haptenem znakowanym ^{131}I
- ESMO 2019: „radionuclide therapy is an option in selected cases”
  - PRRT ukierunkowana na receptory somatostatyny