VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

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NEN PRECEPTORSHIP: LA PRATICA CLINICA DELLE NEOPLASIE NEUROENDOCRINE

Istituto Europeo di Oncologia 16-17 Maggio 2019

Approccio diagnostico-terapeutico al paziente con NET gastrointestinale: il radioterapista

Dr. Dario Zerini – Divisione di Radioterapia – Istituto Europeo di Oncologia - Milano

Clinical Oncology 30 (2018) 400–408

Contents lists available at ScienceDirect

Clinical Oncology

Reference	Primary	Grade	No. receiving RT alone/no. receiving RT with surgery	Dose/fractionation	Radiation technique (e.g. CRT versus SBRT/SRS)	Radiosensitising chemotherapy	Radiographic response	Local RFS	Overall RFS	Overall survival	Acute toxicity (grade 3+)	Late toxicity
RT to primary (8)							RT to primary (8)					
[11]	Anus or rectum	All grade 3	12/0	Up-front chemoRT group: 58 Gy ($n = 12$)	NA			NA	13.2 months	39.2 months	NA	NA
[4]	Pancreas (4), gall bladder (5)	2 well-differentiated, 5 poorly differentiated, 2 NA	4/5	50.4 Gy/28	3D-CRT (6), IMRT (3)		Definitive patients: 3/5 CR/PR, 2/5 SD	Resected: 1/4 recurred (4 months). Definitive: 2/5 progressed (5 months, 11 months)	Resected: not reached. Definitive: 5 months.	Not reached	Grade 3 neutropenia (2)	Grade 3 duodenitis (1 at 3 months)
[5]	Pancreas	NA	3/3	50.4 Gy/28	3D-CRT or IMRT	ChemoRT (6)–5-FU or cape	Neoadjuvant patients: 3/3 proceeded to resection. Definitive patients: 3/3 SD	Neoadjuvant: 2/3 recurred at 12 months, 27 months. Definitive: 0/3 progressed	Neoadjuvant: 2/3 had metastases at 12 months, 27 months. Definitive: 1/3 had metastases at 13 months	Not reached	Grade 3 diarrhoea (1).	NR
[6]	Pancreas	10 grade 2, 1 grade 3	11/0	50.4 Gy.	NA	ChemoRT (7) – cape	3 CR, 2 PR, 6 SD	3/11 patients recurred	15 months	32 months	Grade 3 toxicity (1)	Grade 3 toxicity (1)
[7]	Pancreas	6 grade 1–2, 11 grade 3	0/17	50.4 Gy/28	3D-CRT	7 NA, 10 A – 14 with chemoRT (5-FU or cape)	NA	2 year RFS 85%; 3/17 patients recurred	2 year RFS 46%	56 months	NA	NA
[8]	Pancreas	6 grade 1, 1 grade 2, 2 grade 3, 7 not specified	0/16	50.4 Gy/28	2D-CRT (6), 3D-CRT (6), IMRT (4)	ChemoRT (8) - 5-FU (4) or cape (4); RT (8)	NA	1/16 patients recurred	12 months	5 year OS 28%	Grade 3 enteritis (3)	NR
[9]*	Pancreas	NA	14/0	58.4 Gy	NA		Of 26 sites (10 primary, 16 metastases) – 13% CR, 26% PR, 56% SD, 4% PD	2.1 years		2 year	Grade 3 gastric perforation (1), grade 3 large bowel inflammation/sepsis (1).	Grade 3 duodenal stricture (1), grade 3 gastrointestinal bleed (1), grade 5 duodenal perforation (1)
[10]	Pancreas	Well-differentiated	6/0	50.4 Gy/28 for 2 patients; unknown for other 4	3D-CRT	5-FU or capecitabine	4/5 PR	0/6 patients progressed	0/6 patients progressed	NA	Grade 3 fatigue (1)	NR
RT to metastases (4)							RT to metastases (4)					
[12]	Metastatic GEPNET to bone (34) or soft tissue (11)	NA	45/0	NA	NA			4 months		NA	NA	NA
[13]‖	Metastatic GEPNET to brain	NA	NA	NA	WBRT or gamma knife SRS			21 months		19 months	NA	NA
[14]‖	Metastatic GEPNET to brain	NA	NA	NA	WBRT ($n = 24$), partial brain RT ($n = 7$), SRS ($n = 6$)			6.5 months	14.3 months	14.8 months	NA	NA
[9]	Metastatic PNET (liver and bone)	NA	21/0	24.6 Gy	NA		Of 26 sites (10 primary, 16 metastases) – 13% CR, 26% PR, 56% SD, 4% PD	1.5 years		NA	Nil	Nil

Conclusions: There are limited, retrospective data on the overall activity and safety of EBRT in GEPNETS. EBRT generally seems to be well tolerated in selected PNET patients with encouraging activity. Well-designed prospective studies in clearly defined populations are required to clarify the role of EBRT in neuroendocrine tumours.

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J Gastrointest Surg (2012) 16:1981–1992
DOI 10.1007/s11605-012-1951-1

REVIEW ARTICLE

Treatment of Liver Metastases in Patients with Digestive Neuroendocrine Tumors

Roberta Elisa Rossi · Sara Massironi · Matilde Pia Spampatti · Dario Conte · Clorinda Ciafardini · Federica Cavalcoli · Maddalena Peracchi

Received: 13 March 2012 / Accepted: 24 June 2012 / Published online: 25 July 2012
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Table 1 Grades of recommendation for alternative treatment options in neuroendocrine liver metastases[18]

1. Surgical resection of hepatic metastases should be the first-line treatment option for patients within resection criteria. Grade of recommendation C
2. In case of unresectable disease, loco-regional treatments may be an alternative treatment option. Grade of recommendation C
3. Standard medical therapies prescribed for distant or recurrent neuroendocrine tumors include long-acting somatostatin analogues (octreotide and lanreotide) for both palliation of hormonal symptoms and for the control of tumor growth. Grade of recommendation A
4. In case of failure of both surgical and medical therapies, liver transplantation (OLT) with total tumor hepatectomy may be an alternative option for selected patients with neuroendocrine liver metastases. Grade of recommendation D
5. The use of radiolabeled somatostatin analogues is a promising treatment modality for inoperable or metastatic gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs). Grade of recommendation C
6. Chemotherapy is recommended in neuroendocrine carcinoma (NEC) G3. Grade of recommendation B
7. Everolimus and sunitinib are promising therapies for advanced pancreatic NETs, though a definite grade of recommendation requires further studies

There is considerable controversy regarding the optimal management of patients with neuroendocrine hepatic metastases. At present, a variety of therapeutic options exist for metastatic neuroendocrine disease (Fig. 3). These options include surgery, loco-regional therapies, such as transcatheter arterial embolization (TAE) or chemoembolization (TACE) or loco-regional radiotherapy or radioembolization,

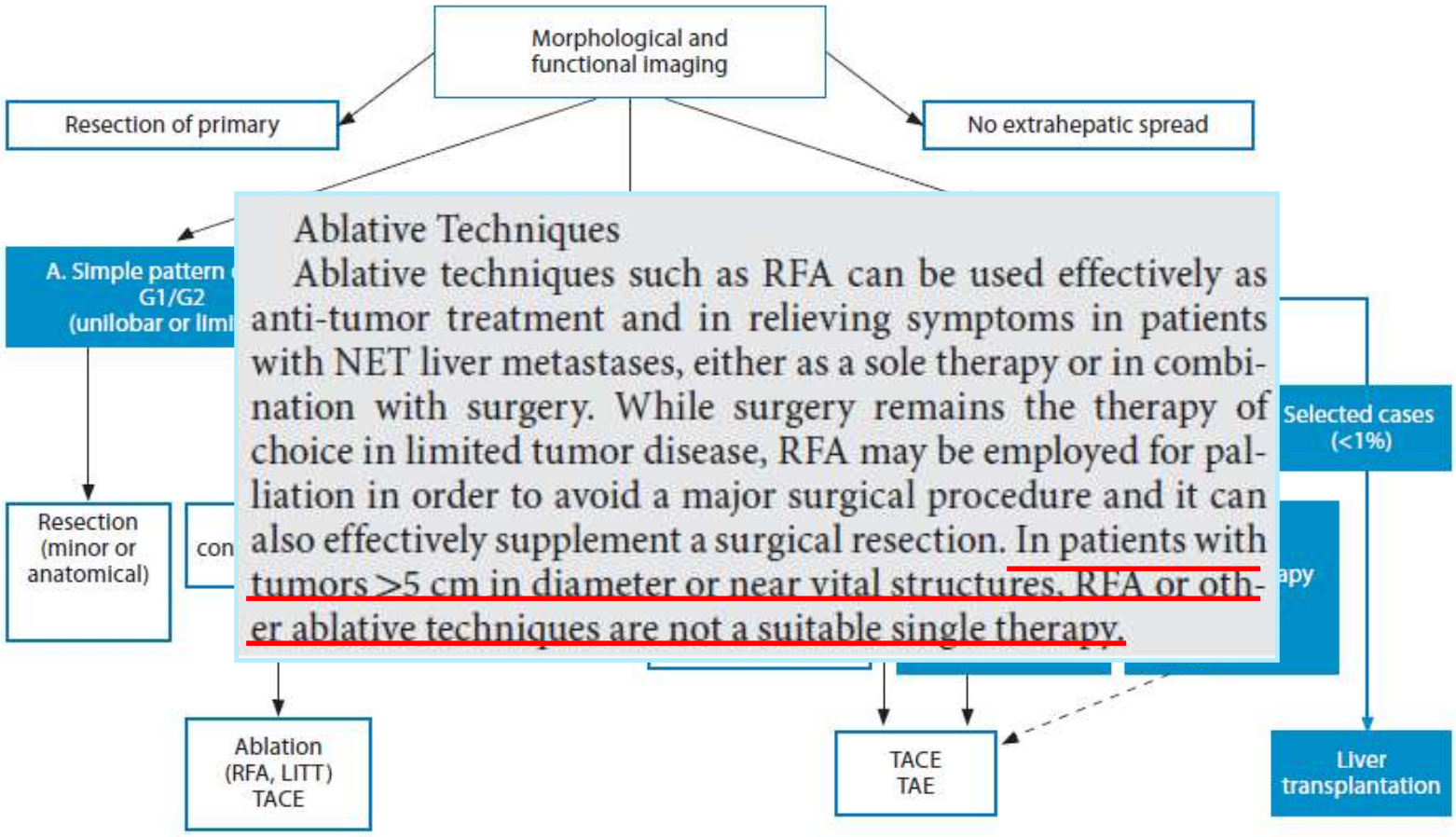
NET Liver Metastasis: thinking an alternative locoregional approach

Only 25% of the patients with oligometastasis to the liver can undergo resection due to the lesion size, lesion localiziation or comorbidities

Relapse rate after RFA were high when tumors were >3 cm or close to large vascular structures

RFA local control 73- 93% similar to SBRT
RFA Severe complications rate in 6-9%
SBRT severe complications rate < 1%

Liver metastasis ENETS guidelines



Ablative Techniques

Ablative techniques such as RFA can be used effectively as anti-tumor treatment and in relieving symptoms in patients with NET liver metastases, either as a sole therapy or in combination with surgery. While surgery remains the therapy of choice in limited tumor disease, RFA may be employed for palliation in order to avoid a major surgical procedure and it can also effectively supplement a surgical resection. In patients with tumors >5 cm in diameter or near vital structures, RFA or other ablative techniques are not a suitable single therapy.

Original article

Strahlenther Onkol 2014 · 190:872–881
DOI 10.1007/s00066-014-0714-1
Received: 13 May 2014
Accepted: 28 June 2014
Published online: 5 August 2014
© Springer-Verlag Berlin Heidelberg 2014

Florian Sterzing[1,2] · Thomas B. Brunner[3] · Iris Ernst[4] · Wolfgang W. Baus[5] · Burkhard Greve[4] · Klaus Herfarth[2] · Matthias Guckenberger[6]

[1] Klinische Kooperationseinheit Strahlentherapie, Deutsches Krebsforschungszentrum (dkfz), Heidelberg, Germany
[2] Abteilung für Radioonkologie und Strahlentherapie, Radiologische Universitätsklinik, Heidelberg, Germany
[3] Klinik für Strahlenheilkunde, Radiologische Klinik, Universitätsklinikum Freiburg, Freiburg, Germany
[4] Klinik für Strahlentherapie – Radioonkologie, Universitätsklinikum Münster, Münster, Germany
[5] Klinik und Poliklinik für Strahlentherapie, Universitätsklinikum Köln, Köln, Germany
[6] Klinik für Radio-Onkologie, UniversitätsSpital Zürich, Zürich, Switzerland

Stereotactic body radiotherapy for liver tumors

Principles and practical guidelines of the DEGRO Working Group on Stereotactic Radiotherapy

Table 2 Favorable patient characteristics for trials testing stereotactic radiotherapy for liver metastases

Variable
Colorectal or breast cancer primaries
No extrahepatic disease
≤ 3 liver lesions
≤ 6 cm largest diameter
> 1.5 cm from luminal gastrointestinal organs
No or minimal prior systemic therapy
Locally controlled or potentially treatable primary tumor
Good performance status and life expectancy ≥ 6 months

limitations and potential bias. In summary, SBRT and RFA achieve local control in 67–92 % and 79–93 % of cases, with overall survival being 30–62 % (2 years) and 42–77 % (2 years), respectively. The rate of severe complications in SBRT versus RFA is < 1 % versus 6–9 %. Thus, SBRT is at least as effective and tolerated as RFA.

static disease is known. Usually a number of three to eight metastases in one to three organs is discussed with more strict definitions in more aggressive tumors such as gastric cancer and with more relaxed constraints in slowly progressing diseases such as neuroendocrine tumors. The

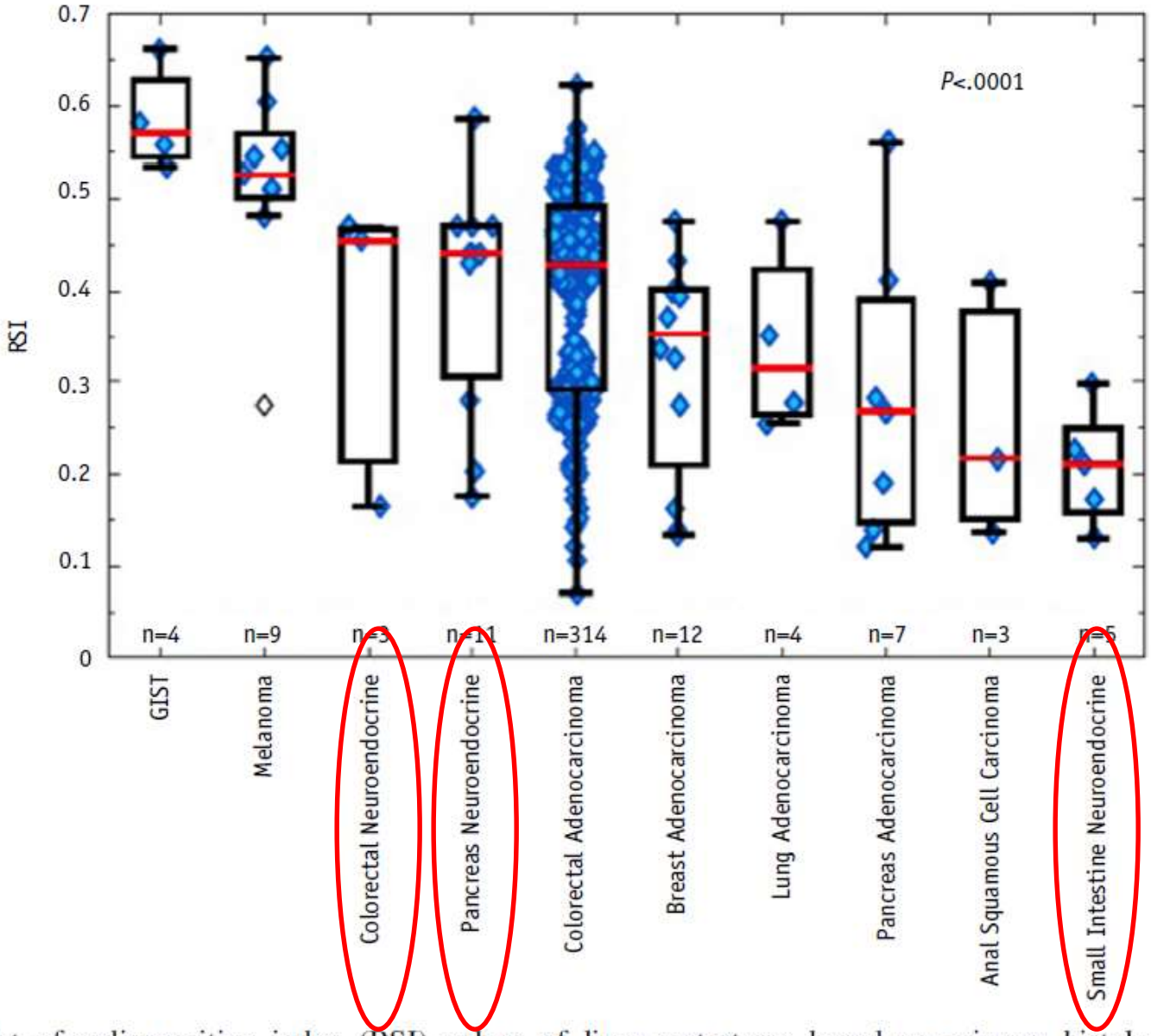


Fig. 1. Box plot of radiosensitive index (RSI) values of liver metastases based on primary histology. *Abbreviation:* GIST = gastrointestinal stromal tumor. Unfilled diamonds represent outliers using the standard 1.5 interquartile range rule.

Stereotactic RT: hit the target

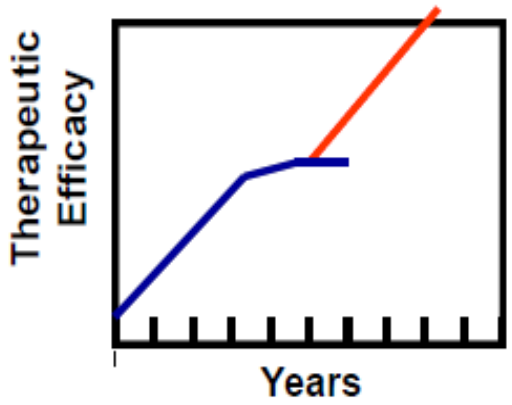
SBRT:

- **high precision**
- **High dose in a few fractions (1 – 5)**
- **Delivered to small target**
- **High selectivity**

- Not invasive: doesn't require anesthesia
- Lasts 20 min
- reduced toxicity: severe complications < 1%

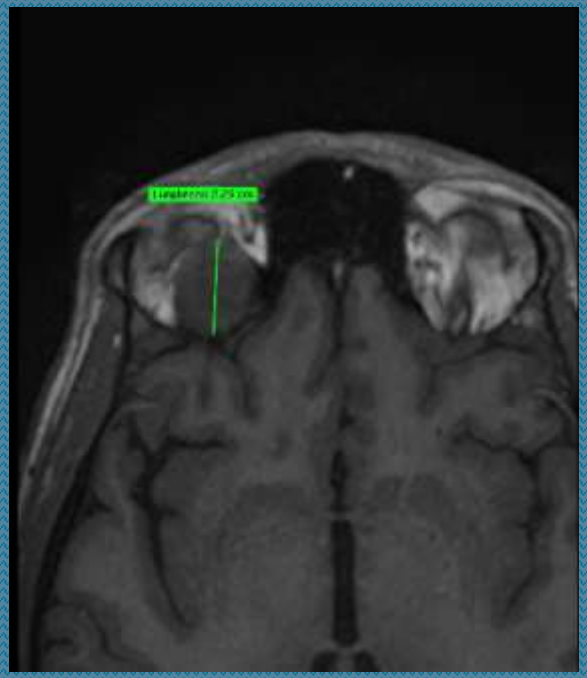
Stereotactic radiotherapy: a new radiobiologist's prospective

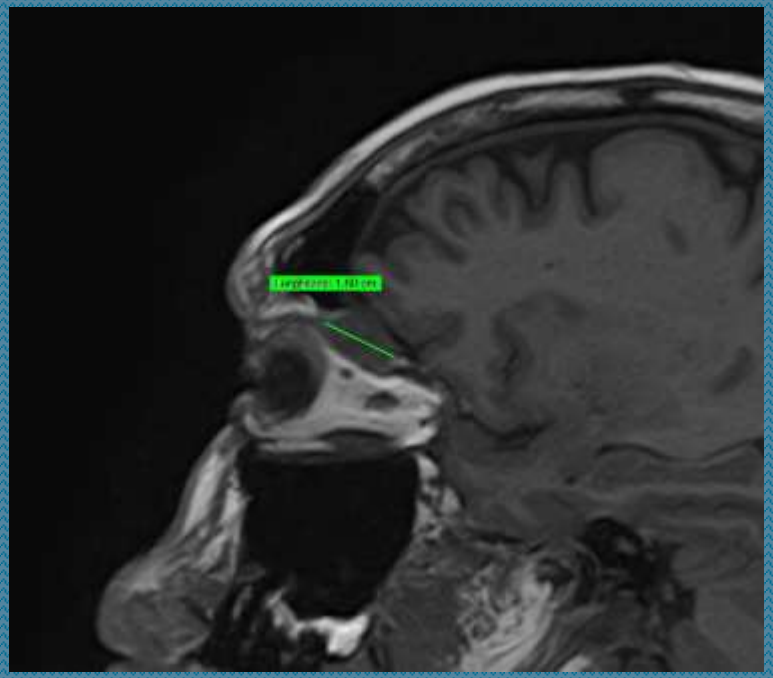
- *So far, progress in Radiotherapy was dominated by technical developments*



- *Further and future progress requires the implementation of achievements in Translational Molecular Radiation Biology !*

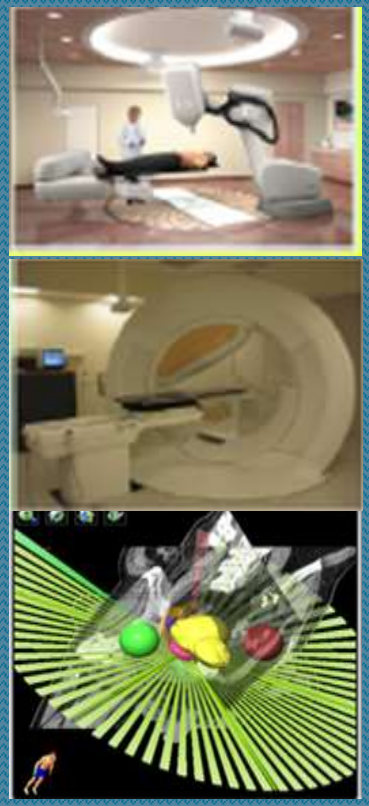
L.L. 51 aa
tumore neuroendocrino ben differenziato del corpo del pancreas, Ki-67 10% (biopsia ossea del Marzo 2017), metastatico allo scheletro e al mediastino, in paziente con MEN-1, ed ora in progressione retrooculare destra





Radioterapia stereotassica: la «moderna»radioterapia

vero
SBRT **UNLEASHED**



Rectal NECs

Medicine®

OBSERVATIONAL STUDY

OPEN

Radiochemotherapy Versus Surgery in Nonmetastatic Anorectal Neuroendocrine Carcinoma

A Multicenter Study by the Association des Gastro-Entérologues Oncologues

Bertrand Brieau, MD, Céline Lepère, MD, Thomas Walter, MD, PhD, Thierry Lecomte, MD, PhD, Rosine Guimbaud, MD, PhD, Sylvain Manfredi, MD, PhD, David Tougeron, MD, PhD, Françoise Desseigne, MD, PhD, Nelson Lourenco, MD, Pauline Afchain, MD, Farid El Hajbi, MD, Benoit Terris, MD, PhD, Philippe Rougier, MD, PhD, and Romain Coriat, MD, PhD

In patients with anorectal localized NEC, chemotherapy with or without radiation obtained a similar outcome as surgery and this conservative approach could be deemed a reasonable option.

NEUROENDOCRINE CARCINOMAS (NECs) GUIDELINES

Table 1

NANETS guidelines for the treatment of poorly differentiated NECs (RT).

Treatment of poorly differentiated NECs		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, list order does not imply order of therapy		
Disease stage	**Intervention**	**Recommendation**
Locoregional disease, resectable clinical stage T1–2, N0	Surgical resection, including removal of tumor with negative margins. Risk of recurrence is high, however.	Recommend
	Postoperative therapy with 4 to 6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low.	Recommend
Clinical stage in excess of T1–2, N0	Chemotherapy with or without concurrent radiotherapy.	Recommend
	Surgery where morbidity is low, particularly where risk of obstruction is high. Risk of recurrence is high, however. Consider postoperative therapy with 4 to 6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low.	Consider
Locoregional disease, unresectable	Platinum-based chemotherapy regimen (cisplatin or carboplatin and etoposide) for 4 to 6 cycles with concurrent or sequential radiation	Recommend

Note: Retrieved from "Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors" by P. Kunz et al. 2013. *Pancreas*, 42, p. 576.

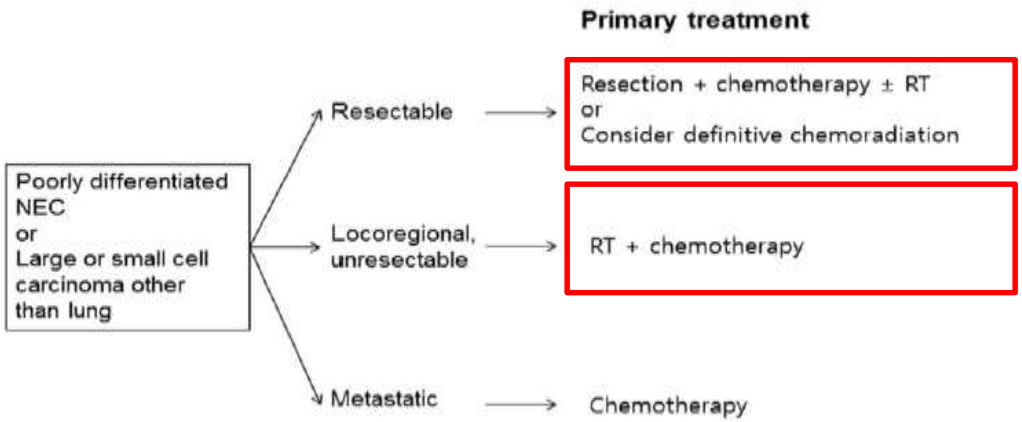


Figure 5. NCCN guidelines for treatment of poorly differentiated NECs, Version 2. 2016 (Retrieved https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#neuroendocrine).

Modrek *et al. Radiation Oncology* (2015) 10:101
DOI 10.1186/s13014-015-0411-y

RADIATION ONCOLOGY

RESEARCH Open Access

Radiation therapy improves survival in rectal small cell cancer - Analysis of Surveillance Epidemiology and End Results (SEER) data

Aram S Modrek[1], Howard C Hsu[2], Cynthia G Leichman[3] and Kevin L Du[2*]

Abstract

Background: Small cell carcinoma of the rectum is a rare neoplasm with scant literature to guide treatment. We used the Surveillance Epidemiology and End Results (SEER) database to investigate the role of radiation therapy in the treatment of this cancer.

Methods: The SEER database (National Cancer Institute) was queried for locoregional cases of small cell rectal cancer. Years of diagnosis were limited to 1988–2010 (most recent available) to reduce variability in staging criteria or longitudinal changes in surgery and radiation techniques. Two month conditional survival was applied to minimize bias by excluding patients who did not survive long enough to receive cancer-directed therapy. Patient demographics between the RT and No_RT groups were compared using Pearson Chi-Square tests. Overall survival was compared between patients who received radiotherapy (RT, n = 43) and those who did not (No_RT, n = 28) using the Kaplan-Meier method. Multivariate Cox proportional hazards model was used to evaluate important covariates.

Results: Median survival was significantly longer for patients who received radiation compared to those who were not treated with radiation; 26 mo vs. 8 mo, respectively (log-rank P = 0.009). We also noted a higher 1-year overall survival rate for those who received radiation (71.1% vs. 37.8%). Unadjusted hazard ratio for death (HR) was 0.495 with the use of radiation (95% CI 0.286-0.858). Among surgery, radiotherapy, sex and age at diagnosis, radiation therapy was the only significant factor for overall survival with a multivariate HR for death of 0.393 (95% CI 0.206-0.750, P = 0.005).

Conclusions: Using SEER data, we have identified a significant survival advantage with the use of radiation therapy in the setting of rectal small cell carcinoma. Limitations of the SEER data apply to this study, particularly the lack of information on chemotherapy usage. Our findings strongly support the use of radiation therapy for patients with locoregional small cell rectal cancer.

Grazie!

Per contatti: dario.zerini@ieo.it

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