

## Supplementary material

**Supplementary Table 1** Results of trans-arterial embolization (TAE) and chemo-embolization (TACE) studies in patients with liver metastases from neuroendocrine neoplasms (NENs)

Author; Year [Supplementary Ref]	Number of patients (n)	Treatment	Primary location	Symptom relief (%)	Response rate (%) (ORR/SD)	Median PFS (months)	Median OS (months)
Bloomston 2017 [1]	122	TACE (doxorubicin, mitomycin, cisplatin)	SI-NEN	92	82/12	19	33
Carrasco 1986 [2]	25	TAE (sponge)	SI-NEN and other	87	94/-	11	16
Chen 2017 [3]	91	TAE or TACE (doxorubicin, mitomycin, cisplatin)	GEP-NEN and other	-	-	15-8.1	-
De Baere 2008 [4]	20	TACE (drug-eluting bead)	SI-NEN	-	80/15	15	-
Dhir 2017 [5]	91	TACE (streptozotocin)	GEP-NEN and other	54	23/47	18	44
Diamondidou 1998 [6]	20	TACE (cisplatin)	GEP-NEN	67	78/22	-	-
Dong 2011 [7]	123	TACE (doxorubicin, streptozotocin)	GEP-NEN and other	-	62/24	-	65
Egger 2020 [8]	197	TACE (doxorubicin, mitomycin, cisplatin)	GEP-NEN and other	-	42/92	19.9	50.1
Gaur 2011 [9]	18	TACE (drug-eluting bead, doxorubicin)	SI-NEN	-	58/42	14	-
Granberg 2007 [10]	15	TAE (embospheres)	SI-NEN and other	42	35/56	6	-
Ho 2007 [11]	46	TAE (polyvinyl alcohol or sponge) or TACE (doxorubicin, mitomycin, cisplatin)	GEP-NEN	78-75	45-45/32-45	23-16	42-44
Hur 2013 [12]	42	TACE (doxorubicin)	SI-NEN	-	58/-	16	39
Kamat 2008 [13]	38	TAE (polyvinyl alcohol or sponge) or TACE (not available)	GEP-NEN and other	65	44/-	9	19
Kim 1999 [14]	30	TACE (cisplatin, doxorubicin, 5FU, streptozotocin)	GEP-NEN	-	25 to 50/-	24	15
Kress 2003 [15]	26	TACE (doxorubicin)	GEP-NEN and other	-	8/53	-	-
Liu 2019 [16]	17	TAE (plus octreotide LAR)	GEP-NEN	-	76/24	-	-
Loewe 2003 [17]	23	TAE (cyanoacrylate)	SI-NEN	56	73/23	-	69
Marrache 2007 [18]	67	TACE (doxorubicin, streptozotocin)	GEP-NEN	91	73/36	15	-
Pitt 2008 [19]	100	TAE (sponge, embospheres, polyvinyl alcohol) or TACE (cisplatin, adriamycin)	GEP-NEN	76	-	-	26
Strosberg 2006 [20]	84	TAE (polyvinyl alcohol, embospheres)	GEP-NEN and other	80	48/52	-	36
Therasse 1993 [21]	23	TACE (doxorubicin)	SI-NEN	100	35/24	29	24
Varker 2007 [22]	27	TACE (doxorubicin, mitomycin, cisplatin)	GEP-NEN and other	77	61/-	5	28
Yao 2001 [23]	20	TACE doxorubicin, mitomycin, cisplatin)	GEP-NEN	50	25/10	32	40

5FU, 5-fluorouracil; GEP-NEN, gastronenteropancreatic neuroendocrine neoplasm; ORR, objective response rate (complete and partial response); PFS, progression-free survival; LAR, long-acting repeatable small intestinal neuroendocrine neoplasm; TACE, transarterial chemoembolization; TACE, transarterial chemoembolization; OS, overall survival; SI-NEN,

**Supplementary Table 2** Results of peptide receptor radionuclide therapy (PRRT) studies in patients with liver metastases from neuroendocrine neoplasms (NENs)

Author; year [Supplementary Ref]	Number of Patients (n)	Treatment type and dose (GBq)	Study design	Primary tumor location	Response rate (%) (ORR/SD)	Median PFS (months)	Median OS (months)
Bodei 2011 [24]	51	$^{177}\text{Lu}$ -DOTATATE (3.7–7.4)	Phase 1-2	GEP-NEN and other	32.6/-	36	Not reached
Bodei 2016 [25]	78	$^{177}\text{Lu}$ -octreotide or $^{90}\text{Y}$ -octreotide (3.7–6.5)	Retrospective	GEP-NEN and other	18.5/54	Not reached	Not reached
Bushnell 2010 [26]	90	$^{90}\text{Y}$ -edotreotide (4.4)	Phase 2	SI-NEN	4.4/70	16.3	26.9
Cwikla 2010 [27]	60	DOTATOC Y-90	Phase 2	GEP-NEN	23/77	17	22
Del Prete 2017 [28]	36	$^{177}\text{Lu}$ -octreotide (5.9–15.9)	Retrospective	GEP-NEN and other	12/88	17.4	18.9
Del Prete 2019 [29]	39	$^{177}\text{Lu}$ -octreotide (7.4)	Phase 2	GEP-NEN and other	23/70	15.9	Not reached
Delpassand 2014 [30]	37	$^{177}\text{Lu}$ -DOTATATE (7.4)	Phase 2	GEP-NEN	28/44	Not reached	-
Hamiditarbar 2017 [31]	132	$^{177}\text{Lu}$ -Octreotide (7.4)	Retrospective	GEP-NEN and other	9/50	30	Not reached
Kwelkboom 2008 [32]	310	[ $^{177}\text{Lu}$ -DOTA(0)-Tyr(3)]-octreotate (3.7–7.4)	Retrospective	GEP-NEN	46/-	40	46
Paganelli 2014 [33]	43	$^{177}\text{Lu}$ -Dotatate (3.7–5.5)	Phase 2	GI-NEN	7/77	36	Not reached
Pfeifer 2011 [34]	69	$^{90}\text{Y}$ -DOTATOC or $^{177}\text{Lu}$ -DOTATOC	Retrospective	GEP-NEN	23.6/61.8	29	Not reached
Sabet 2015 [35]	61	$^{177}\text{Lu}$ -octreotide (7.9)	Retrospective	SI-NEN	44/47.5	33	61
Sansovini 2013 [36]	52	$^{177}\text{Lu}$ -DOTATATE (3.7–5.5)	Prospective	Pancreatic NEN	39/46	29	Not reached
Soydal 2016 [37]	29	$^{177}\text{Lu}$ -DOTATATE (7.4)	Retrospective	GEP-NEN and other	28/62	-	-
Sward 2010 [38]	29	$^{177}\text{Lu}$ -DOTA(0)-Tyr(3)]-octreotide (8)	Retrospective	GEP-NEN	38/50	-	-
Valkema 2006 [39]	58	$^{90}\text{Y}$ -DOTA <sup>0</sup> , Tyr <sup>3</sup> ] Octreotide	Phase 1	GEP-NEN	22/45	14.3	36.7

GI-NEN, gastrointestinal neuroendocrine neoplasm; GEP-NEN, gastrinreleasing pancreatic neuroendocrine neoplasm; ORR, objective response rate (complete and partial response); PFS, progression-free survival; OS, overall survival; SI-NEN, small intestinal neuroendocrine neoplasm.

## Supplementary References

1. Bloomston M, Al-Saif O, Klemanski D, et al. Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. *J Gastrointest Surg* 2007;11:264-271.
2. Carrasco CH, Charnsangavej C, Ajani J, Samaan NA, Richli W, Wallace S. The carcinoid syndrome: palliation by hepatic artery embolization. *AJR Am J Roentgenol* 1986;147:149-154.
3. Chen JX, Rose S, White SB, et al. Embolotherapy for Neuroendocrine Tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. *Cardiovasc Interv Radiol* 2017;40:69-80.
4. de Baere T, Deschamps F, Territheau C, et al. Transarterial chemoembolization of liver metastases from well differentiated gastroenteropancreatic endocrine tumors with doxorubicin-eluting beads: preliminary results. *J Vasc Interv Radiol* 2008;19:855-861.
5. Dhir M, Shrestha R, Steel JL, et al. Initial treatment of unresectable neuroendocrine tumor liver metastases with transarterial chemoembolization using streptozotocin: a 20-year experience. *Ann Surg Oncol* 2017;24:450-459.
6. Diamandidou E, Ajani JA, Yang DJ, et al. Two-phase study of hepatic artery vascular occlusion with microencapsulated cisplatin in patients with liver metastases from neuroendocrine tumors. *AJR Am J Roentgenol* 1998;170:339-344.
7. Dong XD, Carr BI. Hepatic artery chemoembolization for the treatment of liver metastases from neuroendocrine tumors: a long-term follow-up in 123 patients. *Med Oncol* 2011;28(Suppl 1):S286-S290.
8. Egger ME, Armstrong E, Martin RC, et al. Transarterial chemoembolization vs radioembolization for neuroendocrine liver metastases: a multi-institutional analysis. *J Am Coll Surg* 2020;230:363-370.
9. Gaur SK, Friese JL, Sadow CA, et al. Hepatic arterial chemoembolization using drug-eluting beads in gastrointestinal neuroendocrine tumor metastatic to the liver. *Cardiovasc Interv Radiol* 2011;34:566-572.
10. Granberg D, Eriksson LG, Welin S, et al. Liver embolization with trisacryl gelatin microspheres (embosphere) in patients with neuroendocrine tumors. *Acta Radiol* 2007;48:180-185.
11. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. *AJR Am J Roentgenol* 2007;188:1201-1207.
12. Hur S, Chung JW, Kim HC, et al. Survival outcomes and prognostic factors of transcatheter arterial chemoembolization for hepatic neuroendocrine metastases. *J Vasc Interv Radiol* 2013;24:947-956; quiz 57.
13. Kamat PP, Gupta S, Ensor JE, et al. Hepatic arterial embolization and chemoembolization in the management of patients with large-volume liver metastases. *Cardiovasc Interv Radiol* 2008;31:299-307.
14. Kim YH, Ajani JA, Carrasco CH, et al. Selective hepatic arterial chemoembolization for liver metastases in patients with carcinoid tumor or islet cell carcinoma. *Cancer Invest* 1999;17:474-478.
15. Kress O, Wagner HJ, Wied M, Klose KJ, Arnold R, Alfke H. Transarterial chemoembolization of advanced liver metastases of neuroendocrine tumors--a retrospective single-center analysis. *Digestion* 2003;68:94-101.
16. Liu YM, Lian F, Zhou XF, et al. Safety and efficacy of transarterial embolization combined with octreotide LAR on reducing tumor burden for neuroendocrine tumor liver metastasis. *Zhonghua Yi Xue Za Zhi* 2019;99:1142-1146.
17. Loewe C, Schindl M, Cejna M, Niederle B, Lammer J, Thurnher S. Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and lipiodol: assessment of mid- and long-term results. *AJR Am J Roentgenol* 2003;180:1379-1384.
18. Marrache F, Vullierme MP, Roy C, et al. Arterial phase enhancement and body mass index are predictors of response to chemoembolisation for liver metastases of endocrine tumours. *Br J Cancer* 2007;96:49-55.
19. Pitt SC, Knuth J, Keily JM, et al. Hepatic neuroendocrine metastases: chemo- or bland embolization? *J Gastrointest Surg* 2008;12:1951-1960.
20. Strosberg JR, Choi J, Cantor AB, Kvols LK. Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors. *Cancer Control* 2006;13:72-78.
21. Therasse E, Breitmayer F, Roche A, et al. Transcatheter chemoembolization of progressive carcinoid liver metastasis. *Radiology* 1993;189:541-547.
22. Varker KA, Martin EW, Klemanski D, Palmer B, Shah MH, Bloomston M. Repeat transarterial chemoembolization (TACE) for progressive hepatic carcinoid metastases provides results similar to first TACE. *J Gastrointest Surg* 2007;11:1680-1685.
23. Yao KA, Talamonti MS, Nemcek A, et al. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. *Surgery* 2001;130:677-682; discussion 82-85.
24. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with (1)(7)(7)Lu-DOTATATE: the IEO phase I-II study. *Eur J Nucl Med Mol Imaging* 2011;38:2125-2135.
25. Bodei L, Kidd M, Modlin IM, et al. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. *Eur J Nucl Med Mol Imaging* 2016;43:839-851.
26. Bushnell DL, Jr., O'Dorisio TM, O'Dorisio MS, et al. 90Y-octreotide for metastatic carcinoid refractory to octreotide. *J Clin Oncol* 2010;28:1652-1659.
27. Cwikla JB, Sankowski A, Sankowski A, et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. *Ann Oncol* 2010;21:787-794.
28. Del Prete M, Buteau FA, Beauregard JM. Personalized (177)Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: a simulation study. *Eur J Nucl Med Mol Imaging* 2017;44:1490-1500.
29. Del Prete M, Buteau FA, Arsenault F, et al. Personalized (177)Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. *Eur J Nucl Med Mol Imaging* 2019;46:728-742.
30. Delpassand ES, Samarghandi A, Zamanian S, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for patients with somatostatin receptor-expressing neuroendocrine tumors: the first US phase 2 experience. *Pancreas* 2014;43:518-525.
31. Hamiditarbar M, Ali M, Roys J, et al. Peptide receptor radionuclide therapy with 177Lu-Octreotide in patients with somatostatin receptor expressing neuroendocrine tumors: six years' assessment. *Clin Nucl Med* 2017;42:436-443.
32. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008;26:2124-2130.
33. Paganelli G, Sansovini M, Ambrosetti A, et al. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. *Eur J Nucl Med Mol Imaging* 2014;41:1845-1851.
34. Pfeifer AK, Gregersen T, Gronbaek H, et al. Peptide receptor radionuclide therapy with Y-DOTATOC and (177)Lu-DOTATOC in advanced neuroendocrine tumors: results from a Danish cohort treated in Switzerland. *Neuroendocrinology* 2011;93:189-196.

35. Sabet A, Dautzenberg K, Haslerud T, et al. Specific efficacy of peptide receptor radionuclide therapy with (177)Lu-octreotate in advanced neuroendocrine tumours of the small intestine. *Eur J Nucl Med Mol Imaging* 2015;42:1238-1246.
36. Sansovini M, Severi S, Ambrosetti A, et al. Treatment with the radiolabelled somatostatin analog Lu-DOTATATE for advanced pancreatic neuroendocrine tumors. *Neuroendocrinology* 2013;97:347-354.
37. Soydal C, Peker A, Ozkan E, Kucuk ON, Kir MK. The role of baseline Ga-68 DOTATATE positron emission tomography/computed tomography in the prediction of response to fixed-dose peptide receptor radionuclide therapy with Lu-177 DOTATATE. *Turk J Med Sci* 2016;46:409-413.
38. Sward C, Bernhardt P, Ahlman H, et al. [177Lu-DOTA 0-Tyr 3]-octreotide treatment in patients with disseminated gastroenteropancreatic neuroendocrine tumors: the value of measuring absorbed dose to the kidney. *World J Surg* 2010;34:1368-1372.
39. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3] octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med* 2006;36:147-156.