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Editorial

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Traumatic Brain Injury: An Update

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Traumatic brain injury (TBI) remains one of the leading causes of trauma-related mortality and morbidity in the United States.[1] An estimated 2.5 million TBI occur annually resulting in 282,000 hospitalization and 50,000 deaths with an estimated economic burden of $141 billion.[2] While TBI accounts for 30% of all injury related deaths, survivors face physical and cognitive disabilities together with an increasing risk for neurodegenerative diseases and lasting effects on the individual, the family and the community. The association between TBI and depression, aggressive behavior, attention and memory deficits, cognitive deficit, suicide, premature death, progressive dementia, seizures and even neurodegenerative diseases is well founded.[3-6]

Primary TBI sets a series of compensatory adjustments including stress and inflammatory responses largely driven by hypoxia and ischemia to cause secondary brain injury. This injury occurs hours to days after the primary insult and manifests as systemic hypertension, intracranial hypertension, cerebral edema, and hypo-perfusion. With the pre-existing primary injury, the secondary brain injury contributes to the mortality and morbidity of TBI.[7] Therefore, the quality of the clinical recovery after TBI depends on the severity of the primary insult, the presence or absence of a TBI-associated coagulopathy and the prevalence, sustainability and progression of the secondary brain injury.[8-11] The direct mechanical brain injury is generally expressed as concussion, contusion, intracranial hemorrhage, or diffuse axonal injury. This primary brain injury cannot be influenced therapeutically, and therefore, the main goal of TBI management is to minimize and halt the progression of the secondary brain injury. Although, guidelines have been established for the management of TBI, the optimal therapeutic management of secondary brain injury in TBI patients remains unclear.[12] Also, since the publication of the Brain Trauma Foundation (BTF) guidelines a decade ago, today's TBI management has not changed significantly and still comprise of tiered management of intracranial pressure (ICP) using sedation, hyperosmolar therapy, and/or craniotomy.

Surgical management of TBI is often a life-saving intervention particularly for mass lesion evacuation; neurosurgical decompression to control an ICP that is refractory to medical treatment or an intractable cerebral hypertension; and in some cases, a depressed skull fracture that is compounded by gross contamination or infection, or by disruption of the dura mater that results in pneumocephalus or an underlying hematoma. Although, there is no consensus as to the optimal timing to intervene surgically, and which surgical technique to use, the neurosurgical techniques that are commonly used in TBI are craniotomy, burr holes operation and craniectomy.[13,14]

Secondary brain injury results from delayed biochemical, metabolic, immunologic, and cellular changes that are triggered by the primary TBI. As this injury is amenable to therapeutic intervention, preclinical research has focused in the development and discovery of potentially effective neuroprotective agents. Specifically, this effort has focused on the mitigation of the role of various pathways involved in the pathogenesis of the secondary brain injury. Among others, the potential neuroprotective roles of calcium-channel antagonists[13]; steroids[14]; N-methyl-D-aspartate (NMDA) antagonists[15,16]; glutamate agonists[17]; oxygen free-radical scavengers[18]; immune-modulators[19,20]; statins[21]; progesterone[22,23]; and hypothermia[24] were evaluated. Although, most of these developmental neuroprotective agents have shown promising results in the preclinical evaluation phase, their translations for clinical use have been disappointing.[13,25,26]

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This is likely to be explained by the complexity of the pathophysiology of TBI and the inability of these developmental agents to modulate the single critical element in the pathogenesis of secondary brain injury, which is cerebral blood flow. The brain has the lowest tolerance to ischemic-hypoxia, making it vulnerable to injury and loss of function even at a relative ischemia due to fluctuations in cerebral blood flow. TBI invariably decreases cerebral blood flow by altering one or more of the mechanisms that regulate and optimize a steady cerebral blood flow to meet neuronal functions and metabolic demands.[27] Preclinical as well as clinical data confirm that TBI-induced neurovascular uncoupling, cerebral blood flow-metabolism uncoupling, and impaired cerebral blood flow autoregulation are determinants of the clinical outcome after TBI.[27-31] Based on this premise, interventions that selectively restore a steady cerebral blood flow are more likely to be effective neuroprotective agents against the secondary brain injury. Procedures that can directly influence cerebral blood flow after TBI are: 1) remote ischemic conditioning (RIC); and 2) β-adrenoceptors blockade.

Remote ischemic conditioning (RIC) is a procedure in which non-injured tissues are subjected to short cycles of non-lethal ischemia and reperfusion in order to exert protection against ischemia reperfusion injury in remote tissues/organs. RIC is easy to apply, safe, non-invasive and cost effective intervention, which can be applied in pre-hospital settings or during transport. RIC activates the body's natural protective pathways against the tissue damage caused by low oxygen levels (ischemia) and reperfusion.[32] The molecular mechanisms underlying the protective effect of RIC are not fully understood, but thought to involve complex interactions of intrinsic protective pathways and mediators, protein transporters and ion channels.[33-39] Brief cycles of non-lethal ischemia and reperfusion in the non-injured organ generate endogenous factors that can protect the target (remote) organs from injury. The transmission of this protective signal is multifactorial, comprising of blood-borne factors, neuronal mechanisms and systemic responses. These then activates a cascade of events in the target organ or tissue, which confers the protective effect. Although, the protective effects of RIC were first demonstrated in acute myocardial infarction, its beneficial effects are also observed in other organs like the lung, the liver, the kidney.[40-42] Recent advances in neurosciences have explored the use of RIC in non-traumatic brain disorders like aneurysmal subarachnoid hemorrhage and ischemic stroke and have shown promising results.[43-46] Joseph and colleagues conducted the first-in-humans randomized trial on RIC in patients with severe TBI.[47] The study demonstrated that specific neuronal markers of TBI such as S100B and NSE were significantly reduced in patients who underwent brief periods of RIC upon arrival in the ED.

TBI sets in motion a host-adaptive neuroendocrine, immune, metabolic and inflammatory response that is integrated by increased sympathetic drive and exaggerated catecholamine surge. An unopposed host stress response exaggerates inflammation, impairs host immunity, and accelerates metabolism and tissue injury, which constitute a secondary brain injury. The concept of opposing this host stress response through neutralization of the catecholamine actions early after TBI is a viable option for neuroprotection against the secondary brain injury. Numerous preclinical studies, retrospective reviews, and meta-analysis data have confirmed the beneficial effects of β-adrenoceptors blockade in the management of TBI.[48-57] In particular, studies have shown that β-Blockers improve in-hospital survival of TBI patients.

Management of TBI is changing towards a personalized approach of early diagnosis, early assessment of associated risk factors that contribute to morbidity and mortality, and early interventions to protect neurons against further damage. Preclinical studies are required to elaborate on the pathophysiology of TBI, and in particular, the pathogenesis of the secondary brain injury that is associated with TBI. Prospective evidence on the short- and long-term benefits of RIC and β-Blockers in the management of TBI is warranted.

REFERENCES

1. CDC Report. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006 (Blue Book). 2010. Web site. https://www.cdc.gov/traumaticbraininjury/tbi_ed.html. Accessed September 7, 2017.

2. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. *MMWR Surveill Summ*. 2017 66(9): 1-16. doi: 10.15585/mmwr.ss6609a1

3. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. *Neurology*. 2014; 83(4): 312-319. doi: 10.1212/WNL.0000000000000616

4. Hutson CB, Lazo CR, Mortazavi F, Giza CC, Hovda D, Chesselet MF. Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. *J Neurotrauma.* 2011; 28(9): 1783-1801. doi: 10.1089/neu.2010.1723

5. Molloy C, Conroy RM, Cotter DR, Cannon M. Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies. *Schizophr Bull*. 2011 37(6): 1104-1110. doi: 10.1093/schbul/sbr091

ISSN 2377-8407 http://dx.doi.org/10.17140/SROJ-4-e003

6. Webster KM, Sun M, Crack P, O'Brien TJ, Shultz SR, Semple BD. Inflammation in epileptogenesis after traumatic brain injury. *J Neuroinflammation*. 2017; 14(1): 10. doi: 10.1186/s12974-016-0786-1

7. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth*. 2007; 99(1): 4-9. doi: 10.1093/bja/aem131

8. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. *Acta Neurochir (Wien)*. 2008; 150(2): 165-175. doi: 10.1007/s00701-007-1475-8

9. Uzzell BP, Dolinskas CA, Wiser RF. Relation between intracranial pressure, computed tomographic lesion, and neuropsychological outcome. *Adv Neurol*. 1990; 52: 269-274.

10. Uzzell BP, Dolinskas CA, Wiser RF, Langfitt TW. Influence of lesions detected by computed tomography on outcome and neuropsychological recovery after severe head injury. *Neurosurgery.* 1987; 20(3): 396-402. doi: 10.1227/00006123-198703000-00007

11. Badri S, Chen J, Barber J, et al. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. *Intensive Care Med.* 2012; 38(11): 1800-1809. doi: 10.1007/s00134-012-2655-4

12. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med.* 2012; 367 (26): 2471-2481. doi: 10.1056/NEJMoa1207363

13. McConeghy KW, Hatton J, Hughes L, Cook AM. A review of neuroprotection pharmacology and therapies in patients with acute traumatic brain injury. *CNS Drugs.* 2012; 26(7): 613-636. doi: 10.2165/11634020-000000000-00000

14. Cooper PR, Moody S, Clark WK, et al. Dexamethasone and severe head injury. A prospective double-blind study. *J Neurosurg.* 1979; 51(3): 307-316. doi: 10.3171/jns.1979.51.3.0307

15. Kabadi SV, Faden AI. Neuroprotective strategies for traumatic brain injury: Improving clinical translation. *Int J Mol Sci.* 2014; 15(1): 1216-1236. doi: 10.3390/ijms15011216

16. McIntosh TK, Vink R, Soares H, Hayes R, Simon R. Effects of the N-methyl-D-aspartate receptor blocker MK-801 on neurologic function after experimental brain injury. *J Neurotrauma*. 1989; 6(4): 247-259. doi: 10.1089/neu.1989.6.247

17. Fei Z, Zhang X, Bai HM, Jiang XF, Wang XL. Metabotropic glutamate receptor antagonists and agonists: Potential neuroprotectors in diffuse brain injury. *J Clin Neurosci.* 2006; 13(10): 1023-1027. doi: 10.1016/j.jocn.2005.11.042

18. Marshall LF, Maas AI, Marshall SB, et al. A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg.* 1998; 89(4): 519-525. doi: 10.3171/jns.1998.89.4.0519

19. Cook AM, Whitlow J, Hatton J, Young B. Cyclosporine A for neuroprotection: Establishing dosing guidelines for safe and effective use. *Expert Opin Drug Saf.* 2009; 8(4): 411-419. doi: 10.1517/14740330903066742

20. Hatton J, Rosbolt B, Empey P, Kryscio R, Young B. Dosing and safety of cyclosporine in patients with severe brain injury. *J Neurosurg.* 2008; 109(4): 699-707. doi: 10.3171/JNS/2008/109/10/0699

21. Wible EF, Laskowitz DT. Statins in traumatic brain injury. *Neurotherapeutics.* 2010; 7(1): 62-73. doi: 10.1016/j.nurt.2009.11.003

22. Stein DG. Is progesterone a worthy candidate as a novel therapy for traumatic brain injury? *Dialogues Clin Neurosci.* 2011 13(3): 352-359.

23. Stein DG, Wright DW, Kellermann AL. Does progesterone have neuroprotective properties? *Ann Emerg Med.* 2008; 51(2): 164-172. doi: 10.1016/j.annemergmed.2007.05.001

24. Busto R, Dietrich WD, Globus MY, Ginsberg MD. Postischemic moderate hypothermia inhibits CA1 hippocampal ischemic neuronal injury. *Neurosci Lett*. 1989; 101(3): 299-304. doi: 10.1016/0304-3940(89)90549-1

25. Chakraborty S, Skolnick B, Narayan RK. Neuroprotection trials in traumatic brain injury. *Curr Neurol Neurosci Rep.* 2016; 16

ISSN 2377-8407 http://dx.doi.org/10.17140/SROJ-4-e003

(4): 29. doi: 10.1007/s11910-016-0625-x

26. Schouten JW. Neuroprotection in traumatic brain injury: A complex struggle against the biology of nature. *Curr Opin Crit Care.* 2007; 13(2): 134-142. doi 10.1097/MCC.0b013e3280895d5c

27. Tan CO, Meehan WP, III, Iverson GL, Taylor JA. Cerebrovascular regulation, exercise, and mild traumatic brain injury. *Neurology*. 2014 83(18): 1665-1672. doi: 10.1212/WNL.0000000000000944

28. Harris JL, Yeh HW, Choi IY, et al. Altered neurochemical profile after traumatic brain injury: (1)H-MRS biomarkers of pathological mechanisms. *J Cereb Blood Flow Metab*. 2012; 32(12): 2122-2134. doi: 10.1038/jcbfm.2012.114

29. Harris NG, Mironova YA, Chen SF, Richards HK, Pickard JD. Preventing flow-metabolism uncoupling acutely reduces axonal injury after traumatic brain injury. *J Neurotrauma.* 2012; 29(7): 1469-1482. doi: 10.1089/neu.2011.2161

30. Lam JM, Hsiang JN, Poon WS. Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury. *J Neurosurg*. 1997; 86(3): 438-445. doi: 10.3171/jns.1997.86.3.0438

31. Richards HK, Simac S, Piechnik S, Pickard JD. Uncoupling of cerebral blood flow and metabolism after cerebral contusion in the rat. *J Cereb Blood Flow Metab.* 2001; 21(7): 779-781. doi: 10.1097/00004647-200107000-00002

32. Heusch G. Molecular basis of cardioprotection: Signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res* 116(4): 674-699, 2015. doi: 10.1161/CIRCRESAHA.116.305348

33. Hausenloy DJ, Yellon DM. Preconditioning and postconditioning: Underlying mechanisms and clinical application. *Atherosclerosis.* 2009; 204(2): 334-341. doi: 10.1016/j.atherosclerosis.2008.10.029

34. Kanoria S, Jalan R, Seifalian AM, Williams R, Davidson BR. Protocols and mechanisms for remote ischemic preconditioning: A novel method for reducing ischemia reperfusion injury. *Transplantation.* 2007; 84(4): 445-458. doi: 10.1097/01.tp.0000228235.55419

35. Sharma R, Randhawa PK, Singh N, Jaggi AS. Bradykinin in ischemic conditioning-induced tissue protection: Evidences and possible mechanisms. *Eur J Pharmacol.* 2015; 768: 58-70. doi: 10.1016/j.ejphar.2015.10.029

36. Tapuria N, Kumar Y, Habib MM, Abu AM, Seifalian AM, Davidson BR. Remote ischemic preconditioning: A novel protective method from ischemia reperfusion injury--a review. *J Surg Res.* 2008; 150(2): 304-330. doi: 10.1016/j.jss.2007.12.747

37. Turrell HE, Thaitirarot C, Crumbie H, Rodrigo G. Remote ischemic preconditioning of cardiomyocytes inhibits the mitochondrial permeability transition pore independently of reduced calcium-loading or sarcKATP channel activation. *Physiol Rep*. 2014; 2(11): e12231. doi: 10.14814/phy2.12231

38. Jose Alburquerque-Bejar J, Barba I, Valls-Lacalle L, et al. Remote ischemic conditioning provides humoural cross-species cardioprotection through glycine receptor activation. *Cardiovasc Res.* 113(1): 52-60. doi: 10.1093/cvr/cvw242

39. Cuomo O, Vinciguerra A, Cerullo P, et al. Ionic homeostasis in brain conditioning. 2015; *Front Neurosci.* 9: 277. doi: 10.3389/fnins.2015.00277

40. Kanoria S, Jalan R, Davies NA, Seifalian AM, Williams R, Davidson BR. Remote ischaemic preconditioning of the hind limb reduces experimental liver warm ischaemia-reperfusion injury. *Br J Surg.* 2006; 93(6): 762-768. doi: 10.1002/bjs.5331

41. Kierulf-Lassen C, Kristensen ML, Birn H, Jespersen B, Norregaard R. No effect of remote ischemic conditioning strategies on recovery from renal ischemia-reperfusion injury and protective molecular mediators. *PLoS One.* 2015; 10(12): e0146109. doi: 10.1371/journal.pone.0146109

42. Kono Y, Fukuda S, Hanatani A, et al. Remote ischemic conditioning improves coronary microcirculation in healthy subjects and patients with heart failure. *Drug Des Devel Ther.* 2014; 8: 1175-1181. doi: 10.2147/DDDT.S68715

43. England TJ, Hedstrom A, O'Sullivan S, et al. RECAST (Remote Ischemic Conditioning After Stroke Trial): A pilot randomized

ISSN 2377-8407 http://dx.doi.org/10.17140/SROJ-4-e003

placebo controlled phase II trial in acute ischemic stroke. *Stroke.* 2017; 48(5): 1412-1415. doi: 10.1161/STROKEAHA.116.016429

44. Gonzalez NR, Connolly M, Dusick JR, Bhakta H, Vespa P. Phase I clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2014; 75(5): 590-598. doi: 10.1227/NEU.0000000000000514

45. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: A phase Ib study of safety and feasibility. *Stroke*. 2011; 42(5): 1387-1391. doi: 10.1161/STROKEAHA.110.605840

46. Tulu S, Mulino M, Pinggera D, et al. Remote ischemic preconditioning in the prevention of ischemic brain damage during intracranial aneurysm treatment (RIPAT): Study protocol for a randomized controlled trial. *Trials.* 2015; 16: 594. doi: 10.1186/s13063-015-1102-6

47. Joseph B, Pandit V, Zangbar B, et al. Secondary brain injury in trauma patients: The effects of remote ischemic conditioning. *J Trauma Acute Care Surg*. 2015; 78(4): 698-703. doi: 10.1097/TA.0000000000000584

48. Alali AS, Mukherjee K, McCredie VA, et al. Beta-blockers and traumatic brain injury: A systematic review, meta-analysis, and Eastern Association for the surgery of trauma guideline. *Ann Surg*. 2017; doi: 10.1097/SLA.0000000000002286

49. Chen Z, Tang L, Xu X, Wei X, Wen L, Xie Q. Therapeutic effect of beta-blocker in patients with traumatic brain injury: A systematic review and meta-analysis. *J Crit Care.* 2017; 41: 240-246. doi: 10.1016/j.jcrc.2017.05.035

50. Kota DJ, Prabhakara KS, van Brummen AJ, et al. Propranolol and mesenchymal stromal cells combine to treat traumatic brain injury. *Stem Cells Transl Med.* 2016; 5(1): 33-44. doi: 10.5966/sctm.2015-0065

51. Ley EJ, Scehnet J, Park R, et al. The in vivo effect of propranolol on cerebral perfusion and hypoxia after traumatic brain injury. *J Trauma.* 2009; 66(1): 154-159. doi: 10.1097/TA.0b013e31819388be

52. Ley EJ, Clond MA, Bukur M, et al. Beta-adrenergic receptor inhibition affects cerebral glucose metabolism, motor performance, and inflammatory response after traumatic brain injury. *J Trauma Acute Care Surg.* 2012; 73(1): 33-40. doi: 10.1097/TA.0b013e31825a769b

53. Liu MY. Protective effects of propranolol on experimentally head-injured mouse brains. *J Formos Med Assoc.* 1995; 94(7): 386-390.

54. Loftus TJ, Efron PA, Moldawer LL, Mohr AM. Beta-blockade use for traumatic injuries and immunomodulation: A review of proposed mechanisms and clinical evidence. *Shock.* 2016; 46(4): 341-351. doi: 10.1097/SHK.0000000000000636

55. Mohseni S, Talving P, Thelin EP, Wallin G, Ljungqvist O, Riddez L. The Effect of beta-blockade on survival after isolated severe traumatic brain injury. *World J Surg*. 2015; 39(8): 2076-2083. doi: 10.1007/s00268-015-3039-z

56. Murry JS, Hoang DM, Barmparas G, et al. Prospective evaluation of early propranolol after traumatic brain injury. *J Surg Res.* 2016; 200(1): 221-226. doi: 10.1016/j.jss.2015.06.045

57. Schroeppel TJ, Fischer PE, Zarzaur BL, et al. Beta-adrenergic blockade and traumatic brain injury: Protective? *J Trauma.* 2010; 69(4): 776-782. doi: 10.1097/TA.0b013e3181e981b8

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Case Report

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The Trans-Diaphragmatic Hydatid Cyst: An Unconventional Surgical Strategy

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ABSTRACT

Introduction: The hydatid disease is a zoonotic infection due to the tapeworm echinococcus granulosus (TEG). In 50-70% of the cases, the hydatid cyst is observed with a hepatic localization. The trans-diaphragmatic extension of a liver hydatid cyst is rarely reported in the literature. Here, we report the singularity of our observation which focuses on-an abdominal approach rather than a thoracotomy and the way we handle the diaphragmatic defect.
Observation: A 34-year-old male patient presented with a right hypochondriac pain evolving since 2 years. The abdominal examination found a bulging just below the right costal margin. The ultrasound and computed tomography (CT) scan images show an enormous liver hydatid cyst covering the entire posterior right section and extending beyond the diaphragm to the right hemi-thorax. Our therapeutic strategy consisted of a resection of the protruding dome with aspiration and evacuation of all the hydatid material. We did not close the diaphragmatic defect because there was no communication with the thorax contents. Our management had no negative impact on the patient in 2 years of follow-up.
Conclusion: Being rarely reported in the literature, the trans-diaphragmatic hydatid cyst is an uncommon situation. The surgical intervention is the main stay treatment. Our management of the diaphragmatic defect was unconventional. The singularity of our approach is to not close the diaphragmatic defect since we considered the remaining fibrous capsule as a closure, avoiding a laborious dissection and a complex diaphragmatic reconstruction.

KEY WORDS: Surgery; Trans-diaphragmatic; Hydatid cyst; Zoonotic infection; Tapeworm; Echinococcus granulosus.

ABBREVIATIONS: TEG: Tapeworm Echinococcus Granulosus; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; E: Echinococcus; WBC: White Blood Cell; ELISA: Enzyme-linked immunosorbent assay.

INTRODUCTION

The hydatid disease or the echinococcosis is a parasitic infection due to the Echinococcus (E) tapeworm infestation. It is an endemic disease in many regions worldwide. Mainly, it is a zoonotic infection caused by the adult E-worm beared by the definitive host. Humans are infected accidentally by ingesting the worm's eggs. Many organs can be observed to be the sites of localized hydatid cyst especially during the primary echinococcosis. In adults, the liver is the main site in 50-70% of the cases followed by the lungs in 10-30%.[1,2] The trans-diaphragmatic extension of a hepatic hydatid cyst is an uncommon situation, rarely reported in the literature. Herein, we present the case of a voluminous hydatid cyst of the hepatic right posterior section extended to the inferior pulmonary right lobe and our surgical management for the same.

CASE REPORT

A 34-years-old male, with no previous medical history, consulted our department for a right

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upper quadrant pain evolving since 2 years without radiation associated to asthenia and weight loss. The patient had no history of fever, neither digestive nor respiratory symptoms. During the abdominal examination, we found a bulging just below the right costal margin with no tenderness during palpation. The respiratory system examination showed dullness instead of resonance at the percussion of the inferior part of the right hemi-thorax. Biologic investigations revealed hemoglobin 11 g/ml, white blood cell (WBC) 8400/mm^3 and eosinophils were not elevated. An abdominal ultrasound confirmed the diagnosis of a voluminous hepatic hydatid cyst partially calcified which extended through the diaphragmatic dome. An additional thoraco-abdominal CT scan showed a large hydatid cyst covering almost the totality of the right posterior section of the liver and extending beyond the diaphragm in the right hemi-thorax. This cyst was calcified in its inferior part and contained multiple daughter vesicles (Figure 1). The indirect immunofluorescence and the enzyme-linked immunosorbent assay (ELISA) test for the *E. granulosus* were significantly positive. A pre-operative Albendazol therapy (400 mg per day) for 3 months was indicated. The surgery was done through a midline laparotomy; no hepatectomy was done instead of that a protruding dome resection was performed just above the calcified part with aspiration and evacuation of its contents (liquid, membranes and the daughter cysts), taking the pre-caution to confine the operation site with H_2O_2 soaked compresses to avoid any spillage. There was no biliary fistula identified. The rent in the diaphragm was about 7 cm, made essentially from the fibrous hull or capsule of the superior part of the hydatid cyst without any bronchial fistula. We also found that the superior part of the fibrous capsule of the cyst was continuous with the diaphragm, preventing any communication between the thoracic and the abdominal contents. Our decision was to end the surgery just by a drainage of the remnant cavity (inter hepato-diaphragmatic space) without closing the diaphragmatic rent. We show you our surgical strategy by 4 diagrams (Sketches).

The post-operative course was uneventful. The patient remained asymptomatic after 24 months of follow-up; the recent CT scan showed no recurrences, also there was no negative impact of our decision to consider the fibrous capsule as a diaphragmatic closure (Figure 2).

DISCUSSION

The hydatid disease is a parasitic infection cause by the Echinococcus tapeworm. It has worldwide prevalence, especially in countries like Morocco where sheep rearing is carried out on a large scale. Although, the liver and the lungs are the most frequently affected viscera by the hydatid cyst, other organs such as the spleen, the kidneys, and the brain could also be affected.

The trans-diaphragmatic presentation where the he-

Figure 1: CT Scan Images Showing the Trans-Diaphragmatic Hydatid Cyst.
A) 1: Intrathoracic Extension of the Hydatid Cyst. B) 2: The Liver Hydatid Cyst Covering the Right Posterior Section of the Liver. 3: The Daughter Vesicle. 4: The Fibrous Capsule of the Cyst. C) Coranal Cut. 5: The Liver Hydatid Cyst. 6: The Calcified Part of the Cyst. 7: The Intrathoracic Extension through the Diaphragm. D) 8: The Sandglass Shape Accorging to Gomez et al.[4]

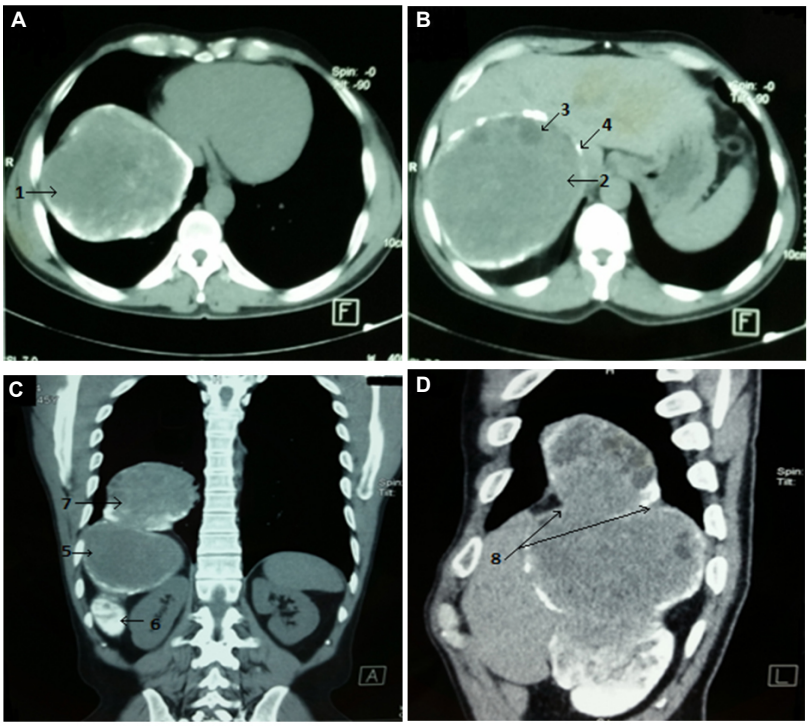

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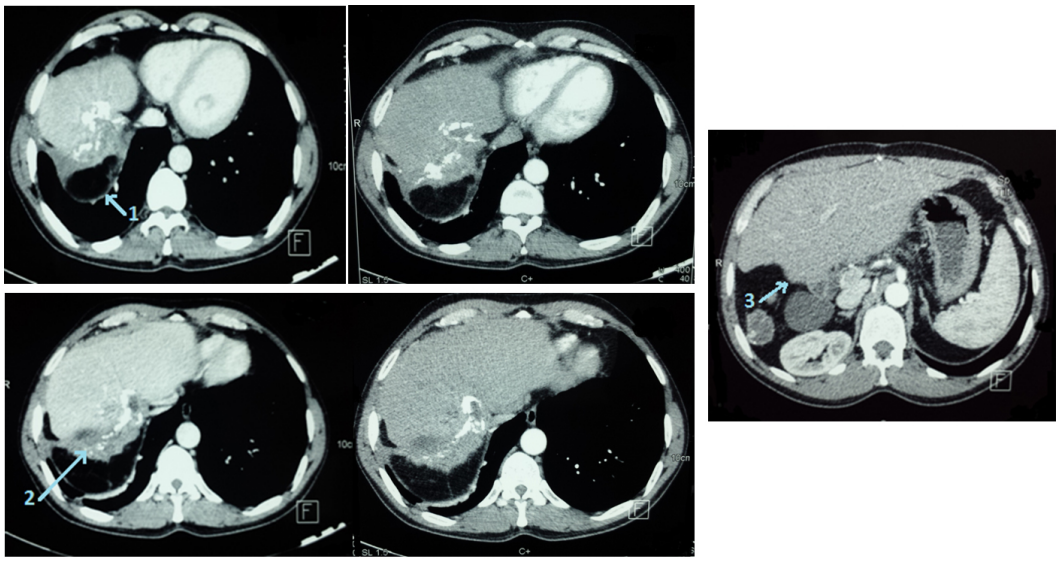
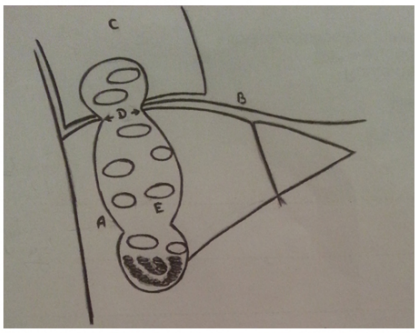
Figure 2: Post-operative CT Scan Images Showing No Recurrences and No Negative Impact of our Decision of not Closing the Diaphragmatic Rent.

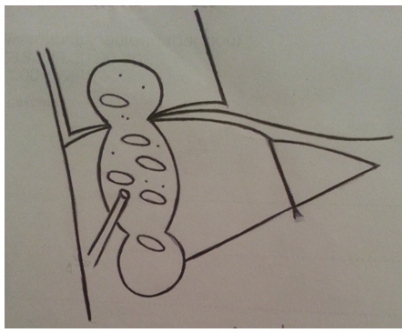


1. The fibrous capsule is continuous with the diaphragm.
2. Absence of any recurrences of the the hydatid cyst.
3. A liver compensatory hyperthrophy.

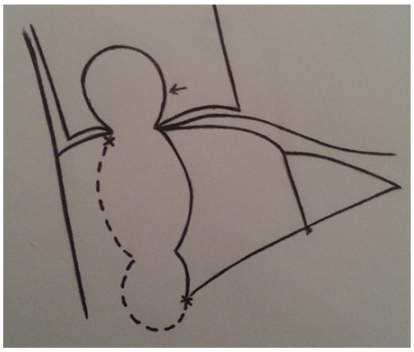
Sketch 1: A) The Trans Diaphragmatic Hydatid Cyst. B) The Diaphragm. C) The Right Lung. D) The Diaphragm Rent. E) Daughter Vesicles.



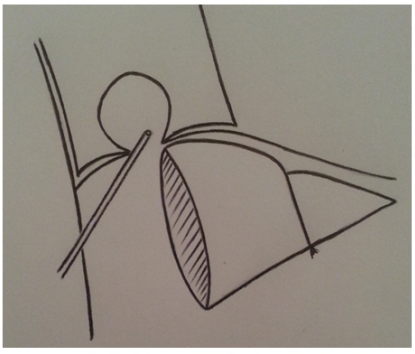
Sketch 2: Aspiration and Evacuation of the Hydatid Cyst Content.



Sketch 3: Resection of the Protruding Dome without Performing any Hepatectomy.



Sketch 4: Drainage of the Remnant Cavity without Closing the Diaphragmatic Rent Defect.



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patic hydatidcyst invades the lung is rarely reported; it represents only 2% in a study with more than 1150 patients with liver hydatid cyst.[3] According to the classification that evaluates the diaphragmatic and trans-diaphragmatic extension of a hepatic hydatid cyst by Gomez et al[4] our patient had a Grade 3 trans-diaphragmatic involvement: a "sandglass" cyst perforating the diaphragm and growing inside the thoracic cavity without any connection with the bronchi.

The diagnosis is easily confirmed by ultrasound, CT scan or even magnetic resonance imaging (MRI),[2,5] offering a number of information such as the cyst measurement, its localization and impact on the adjacent anatomical structures (vascular and biliary structures), the WHO classification, and the presence of a diaphragmatic rent, its dimensions or a communication with the bronchial tubes.

The treatment of hydatid cysts is well established by the WHO: an anthelmintic treatment (Albendazol), pre- and post-operatively combined with surgery, which remains the mainstay treatment although it has to be as conservative as possible for the healthy parenchyma.[6] Recently, a percutaneous treatment has been developed based on echo-guided puncture, aspiration of the hydatid material, injection of protoscolicidal agents and finally re-aspiration (PAIR).[2] The percutaneous treatment isn't indicated in communicating hydatid cysts.

The hydatid cyst may evolve in many organs separately.[7] The synchronous trans-diaphragmatic extension of a hepatic hydatid cyst to the right lung is uncommon.[8] In the literature, the one stage trans-diaphragmatic approach for the liver cyst through a right thoracotomy (7^{th}-8^{th} intercostal space) is highly recommended, because it can cure the lung and the hepatic cysts, simultaneously eliminating the requirement of a second surgical intervention.[8,9] On the contrary, the trans-diaphragmatic approach for a right lung cyst through a laparotomy is only reported in 1 patient from the 50 patients evaluated by Aydin et al[10] series. In fact put 4 conditions to adopt this specific approach:

- An absolute indication for laparotomy;
- The pulmonary cyst isn't voluminous or complicated;
- Absence of pleural adhesions;
- The pulmonary cyst is reachable by a trans-diaphragmatic approach through laparotomy (the right lower lung lobe).

Whatever the approach is (thoracotomy or laparotomy), the surgical procedure must contain the following steps: protection by soaked compresses with proto-scolicidal agents, aspiration of the cyst liquid through a needle, opening the cyst to evacuate the remnant material, fistulae obliteration (bronchial or biliary), opening the diaphragm to reach the other cyst and re-do the same steps and finally drainage and closure of the diaphragmatic defect.

The particularity of our observation is the second case reported to treat a trans-diaphragmatic extension of a liver hydatid cyst through a laparotomy. This approach was adopted for multiple reasons:

- The patient had no respiratory symptoms which means there was no communication between the cyst and the bronchi; a condition that will be difficult technically to cure through a laparotomy;
- The cyst was Grade 3 of Gomez classification and invading the inferior pulmonary lobe making it reachable *via* a laparotomy;
- The liver hydatid cyst was large and covering the entire right posterior section. The probability of biliary fistulae is very high. We thought that the laparotomy approach would give us the global view for an optimal management of these biliary fistulae.

Our patient had a 24 month follow-up. There were no recurrences or complications directly related to our decision of not resecting thefibrous capsule or approaching the diaphragm's margins (Figure 2).

CONCLUSION

Trans-diaphragmatic hydatid cyst is rarely reported in the literature. The surgical treatment is generally performed through a thoracotomy. The laparotomic approach may be used only if the hydatid cyst is reachable and affecting the inferior part of the right lung. Our strategy of not closing the diaphragmatic rent and considering the fibrous hull as a cure to the defect did help us evade a large diaphragmatic dissection and a complex reconstruction with no negative impact on our patient.

AUTHORS' CONTRIBUTIONS

HH drafted the manuscript. AM, MA, MR, FS, AH critically revised the manuscript. All authors read and approved the final manuscript.

CONSENT

The patients gave a signed statement, which authorizes the use of her personal and/or medical information in the publication of this study.

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None. Compliance with ethical guidelines.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests. First and corresponding author Dr. Hajar Hachim. 5^{th} year resident in General surgery.

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REFERENCES

1. Jourdan JL, Morris DL. Hydatid liver disease. In: Holzheimer RG, Mannick JA, eds. *Surgical Treatment: Evidence-Based and Problme-Oriented*. Munich, Germany: Zuckschwerdt; 2001.

2. Von Sinner W. Advanced medical imaging and treatment of human cystic echinococcosis. *Semin Roentgenol*. 1997; 32(4): 276-290. doi: 10.1016/S0037-198X(97)80022-3

3. Borrie J, Shaw JHF. Hepatobronchial fistula caused by hydatid disease. *Thorax*. 1981; 36: 25-28. Web site. http://thorax.bmj.com/content/thoraxjnl/36/1/25.full.pdf. Accessed March 18, 2017.

4. Gomez R, Moreno E, Leinaz C, et al. Diaphragmatic or transdiaphragmatic thoracic involvement in hepatic hydatid disease: Surgical trends and classification. *World J Surg*. 1995; 19(5): 714-719. doi: 10.1007/BF00295911

5. Gharbi HA, Hareine W, Baruner MW, et al. Ultrasound examination of the hydatid liver. *Radiology*. 1981; 139(2): 459-463. doi: 10.1148/radiology.139.2.7220891

6. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echniococcosis in humans. *Bull World Health Org*. 1996; 74(3): 231-242. Web site. https://www.questia.com/library/journal/1G1-18652645/guidelines-for-treatment-of-cystic-and-alveolar-echinococcosis. Accessed March 18, 2017.

7. Amendolara M, Bucca D, Barbarino C, et al. Surgical management of symptomatic simple hepaticcysts. *G Chir*. 2012; 33(1-2): 17-20.

8. Sahin E, Enön S, Cangir AK, et al. Single-stage transthoracic approach for right lung and liver hydatid disease. *J Thoracic Cardiovasc Surg*. 2003; 126(3): 769-773. doi: 10.1016/S0022-5223(03)00366-0

9. Kir A, Baran E. Simulateous operation for hydatidcyst of right lung and liver. *Thoracic Cardiovasc Surg*. 1995; 43(1): 62-64. doi: 10.1055/s-2007-1013772

10. Aydin Y, Celik M, Ulas AB, Eroglu A. Transdiaphragmatic approach to liver and lunghydatidcysts. *Turk J Med Sci*. 2012; 42(Suppl 2): 1388-1393. Web site. http://journals.tubitak.gov.tr/medical/abstract.htm?id=12223. Accessed March 18, 2017.

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Ileal Interposition with Gastric Bipartition and a Weight-Adjusted Sleeve Gastrectomy: A New Model of Metabolic Surgery

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ABSTRACT

Background: Metabolic surgery for the treatment of type 2 diabetes patients, with body mass index (BMI) less than 35 kg/m^2 has been found to be increasing every year. Duodenoileal interposition with sleeve gastrectomy and transit bipartition (TB) has strong effects on control of type 2 diabetes mellitus. However, both procedures may have long-term problems. Due to duodenal exclusion, endoscopic evaluation of the duodenum and biliary tract becomes impossible after duodenoileal interposition. The TB may have the risk of severe malabsorption due to enlargement of the gastroileostomy. We performed ileal interposition and TB in patients with class 1 obesity having type 2 diabetes, with ethical approval. The new modification included in this paper, was performed in 3 patients, one of whom had a BMI of 30 kg/m^2. The aim of this innovation is to treat obese (BMI >30 kg/m^2), type 2 diabetes patients with an effective, but less malabsorptive procedure.
Objectives: The modification that we propose, aims to preserve normal duodenal anatomy and prevent possible duodenal transection related surgical problems and secure the absorptive component of proximal intestines without the need of an adjustment in gastroileostomy anastomosis.
Materials and Methods: All patients underwent total laparoscopic ileal interposition with gastric bipartition and a weight-adjusted sleeve gastrectomy.
Results: All tree patients stopped insulin use after surgery. No complications occurred.
Conclusions: Ileal interposition with gastric bipartition and a weight-adjusted sleeve gastrectomy is a safe and effective procedure for treatment of type 2 diabetes patients with or without obesity.

KEY WORDS: Gastric bipartition; Weight-adjusted sleeve gastrectomy; Duodenoileal interposition; Transit bipartion; Type 2 diabetes; Metabolic surgery; Obesity; Gastroileostomy anastomosis.

ABBREVIATIONS: BMI: Body Mass Index; TB-SG: Transit bipartition with sleeve gastrectomy; OAD: Oral Anti Diabetic; ICV: Ileocecal valve; II-DSG: Interposition with diverted sleeve gastrectomy;

INTRODUCTION

Metabolic surgery for type 2 diabetes patients with BMI <35 kg/m^2 is increasing every year with promising outcomes. However, the difficult learning curve is the prominent factor leading to very slow widespread acceptance.[1] Ileal interposition with diverted sleeve gastrectomy (II-DSG) has powerful metabolic effects, giving good control of type 2 diabetes and associated problems (Figure 1).[2-22] Transit bipartition with sleeve gastrectomy (TB-SG) has been getting increased acceptance due to its greater feasibility compared to II-DSG and the advan-

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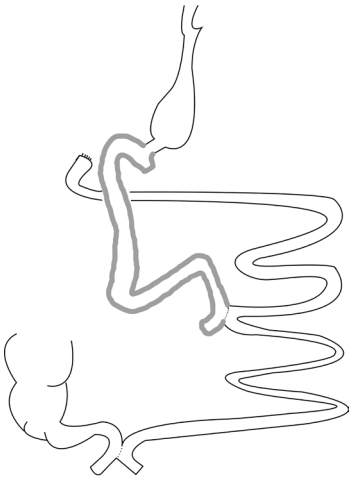
tage of preservation of the normal physiology and anatomy of duodenum; although, both procedures have some pros and cons. II-DSG patients have a bypassed duodenum which is important in eliminating the foregut's negative incretin effects on insulin; however, this prevents any biliary access, if required later. TB-SG overcomes this problem by preserving the normal duodenal access, which makes the procedure more physiologic and easier to perform. With time, the gastroileal anastomosis has a tendency to enlarge resulting in "functional bypass" of duodenum, enhancing the anti-diabetic effect of the procedure. However, as the food is directed more into the ileum, greater malabsorption may occur which will be a severe risk for low BMI patients (Figure 2).

The modification that we propose is aimed at overcoming these factors by eliminating the risk of malabsorption and the inability to reach the duodenum endoscopically. As time goes by, there is an increasing amount of food that is directed through the gastro-ileal anastomosis, causing functional bypass of the duodenum to diminish the foregut suppression on insulin without causing severe malabsorption due to redirection of food to proximal jejunum to be digested, mimicking normal anatomy. We present this report of the first 3 cases of this procedure in obese type 2 diabetic patients.

MATERIALS AND METHODS

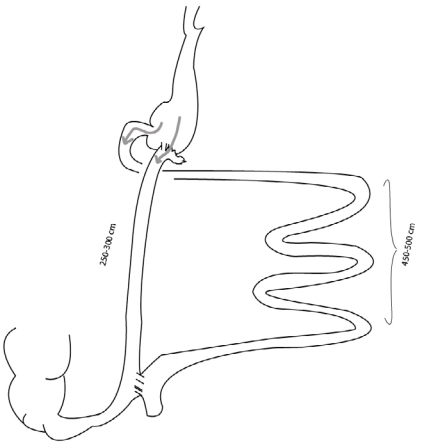
All three patients were males, with ages 43, 45 and 56 years. They had been undergoing diabetes treatment for longer than 3 years with poor control of diabetes, having HbA1c >7.5 % with medical treatment and lifestyle modification. The first patient was using only oral anti-diabetic (OAD) treatment, while the other two were using insulin for more than a year besides OADs. The data of the patients are detailed in the Tables 1 and 2.

Figure 1: Duodenoileal Interposition.



Duodenoileal Interposition

Figure 2: Transit Bipartition.



Transit Bipartition

Table 1: Pre-Operative Data.

Patient	Age	BMI (kg/m²)	Diabetes Duration (Years)	Fasting Glucose (mg/dL)	PP Glucose (mg/dL)	Fasting C-Peptide (ng/ml)	PP C-Peptide (ng/ml)	HbA1c (%)	OAD	Insulin
1	45	40	8	189	284	3,79	5,90	9.6	Yes	No
2	56	37	6	190	273	4.15	5.52	9.7	Yes	1 y
3	43	30	9	296	349	2.86	3.19	10.2	Yes	2 y

BMI: Body Mass Index; PP: Post Prandial; OAD: Oral Anti-Diabetic Drugs.

Table 2: Operative Data.

Patient	Age	Gender	BMI (kg/m²)	Previous Surgery	Surgery time (min)	Discharge day	Complication
1	45	Male	40	No	198	4	No
2	56	Male	37	No	201	5	No
3	43	Male	30	No	178	4	No

BMI: Body Mass Index

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The ileal interposition and transit bipartition (TB) was performed internationally. The procedure we propose is not a completely new procedure but a modification to the existing procedures (Figure 3). Thus, only a detailed informed consent was deemed necessary at our hospital. All of the patients were given detailed comparative information about the surgery, with the alternatives *via* videos, animations and pictures of the procedures. All three patients gave detailed informed consents prior to surgery.

Surgery was carried out after completing all the preoperative preparations. The patients were placed in a supine position with legs spread and a reverse Trendelenburg at 30 degrees. Central venous catheter and arterial lines were then placed. We used a left paraumblical port as usual for camera. A 15 mm trocar in the right upper quadrant and a 12 mm trocar in the left upper quadrant were placed for dissection and transections. A 5 mm trocar at the xyphoid for gastric mobilization and liver retraction and another 5 mm at the left lower quadrant for measurement of the bowels were placed. The dissection is started as usual for stomach mobilization on greater curvature. A 36 F bougie is used for calibration and to start transection. After the sleeve was performed, the staple line was oversewn with running 3/0 polydioxanone (PDS) suture. Then the table was set to neutral position for bowel preparation. The omentum was transected up to the transverse colon, enabling the ileal graft to be taken up in an antecolic fashion, with least tension. The complete small bowel was measured from the ligament of Treitz to the ileoceacal valve (ICV) with a measuring grasper having marking at 10 cm. The jejunum was marked at 100 cm from the Treitz with double legged suture distally and thermal mark with harmonic scalpel proximally. The terminal ileum was transected at 40 and 200 cm from ICV. The distal end of the ileal segment was marked with a double legged suture and proximal end with a single legged one. The distal ileum and the proximal bilio-pancreatic limb were staple anastomosed side-to-side and the mesenteric defect was closed with separate prolene sutures. The proximal end of the ileal segment was brought next to the antrum in an antecolic fashion. The ileum was fixed to the posterior wall of the antrum for 4-5 cm with interrupted sutures. The gastro-ileostomy is fashioned side-to-side with stapler and the staple orifice is closed with PDS 3/0 running suture. Leak tests were done with methylene blue dye to check the integrity of the gastro-ileal anastomosis.

After the leak test, the Peterson's defect was closed with interrupted 3/0 prolene sutures. The last anastomosis was side-side between the distal end of the ileal segment and proximal 100 cm of jejunum from the Trietz. The mesenteric defect was again closed with interrupted 3/0 prolene sutures. A single drain was placed under the gastroileostomy. The patients were discharged on the 4^{th}-5^{th} post-operative days without any clinical problem.

RESULTS

Patients were followed-up for early complications during the first 30 days after surgery and for the glycemic control at 1 and 3 months. No complications were observed in any of the patients. Data from patients were collected during the 30 and 90 days follow-ups. All patients achieved remission of diabetes with HbA1c <6.5 %, 90 days after surgery. The data of the 30 days and 90 days follow-ups are detailed in Tables 3 and 4.

DISCUSSION

Type 2 diabetes is a condition prevalent ubiquitously, mostly linked with mild to severe obesity. Bariatric surgery has proven superiority over conservative treatments and lifestyle changes for patients with BMI >35 kg/m^2. The promising results of

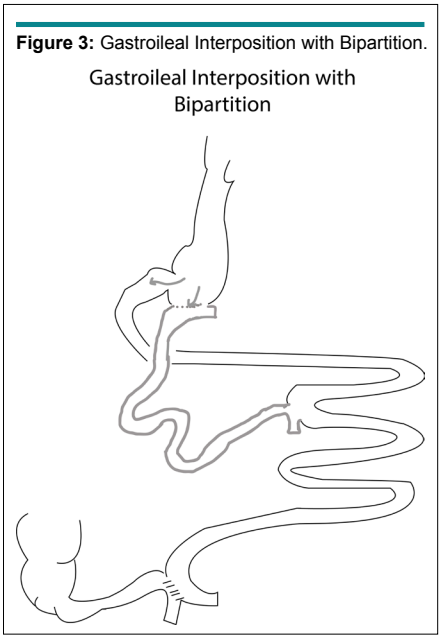

Figure 3: Gastroileal Interposition with Bipartition.

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Table 3: Post-Operative 30 Days Data.

Patient	Duration (Days)	BMI (kg/m²)	% Excess BMI Loss (%EBMIL)	% Total Body Weight Loss (% TBWL)	Fasting Glucose (mg/dL)	PP Glucose (mg/dL)	HbA1c (%)	OAD	Insulin
1	30	33.8	15 %	15%	110	140	6.9	No	No
2	30	32.6	11 %	12 %	116	107	6.7	No	No
3	30	27.4	11 %	10 %	139	142	8.9	No	No

BMI: Body Mass Index; %EBMIL: Percentage Excess Body Mass Index Loss; % TBWL: PercentageTotal Body Weight Loss; PP: Post Prandial; OAD: Oral Anti-Diabetic Drugs.

Table 4: Post-Operative 3 Months Data.

Patient	Duration	BMI (kg/m²)	% Excess BMI Loss (%EBMIL)	% Total Body Weight Loss (% TBWL)	Fasting Glucose (mg/dL)	PP Glucose (mg/dL)	HbA1c (%)	OAD	Insulin
1	3 months	27.4	31 %	30%	110	90	6.4	No	No
2	3 months	28.2	21 %	21 %	85	103	5.9	No	No
3	3 months	26	16 %	17 %	90	98	5.8	No	No

BMI: Body Mass Index; %EBMIL: Percentage Excess Body Mass Index Loss; % TBWL:PercentageTotal Body Weight Loss; PP: Post Prandial; OAD: Oral Anti-Diabetic Drugs.

bariatric surgery, in obesity related diabetes amongst morbidly obese and class ll obese patients (BMI >35 kg/m²), had triggered the search for treatment of diabetes associated with severe insulin resistance and/or insulinopenia in patients with BMI <35 kg/m². Although, the classical bariatric procedures might have good results to some extent, the purely restrictive techniques lack sufficient glycemic control, while malabsorptive techniques carry the risk of severe malnutrition. ll-DSG surgery, proposed by De Paula et al had opened a new era for effective "non-malabsorptive" metabolic surgical option for low BMI diabetic patients.

De Paula et al[2] briefly explained and showed the "neuroendocrine ileal brake" mechanism which strongly supports the hind-gut hypothesis with promising results in type 2 diabetes. The technique is challenging and has a long learning curve to be safely practiced and therefore, has not gained widespread acceptance. TB proposed by Santoro et al[21] has a simpler technique compared to II-DSG with almost the same promising results on the control of type 2 diabetes, though in higher BMI patients. The advantages of this technique are preserving the anatomical continuity of the pylorus and duodenum, and maintaining endoscopic access to the biliary tree; it is also simpler to perform as it avoids duodenal dissection, transection and anastomosis and there is no fear of duodenal stump leaks. No intestinal segment is anatomically bypassed. However, the diameter of the gastro-ileostomy tends to enlarge to direct the food mainly to distal ileal segment to create a functional biliopancreatic diversion of proximal intestines and malabsorption. Santoro et al[21] had to revise the diameter of the gastroileostomy after primary surgery. This is an unwanted problem for the true definition of "metabolic surgery" and there must not be any anastomotic and/or volume restrictions to preserve the metabolic outcomes for a surgical technique to be considered as metabolic, in our opinion. The II-DSG is a good example of true metabolic surgery having good outcomes (including our humble experience), whereas the TB has the risk of unpredictable progress depending on the size of the gastro-ileal anastomosis. If the anastomosis gets narrowed by a stricture, then all of the metabolic benefits may diminish, whereas if it enlarges, the surgery might become severely malabsorptive in time.

Two of our patients who had II-DSG had developed biliary stones that needed surgery because it is impossible to perform endoscopic retrograde cholangiopancreatography (ERCP) when the duodenum is anatomically excluded. As our experience with TB increased and we observed good and satisfactory control of diabetes in a similar patient population as with II-DSG, we started to think of how we could modify and combine the advantages of these two techniques. The solution was very simple: to transect the alimentary limb of the TB, proximal to the distal ileostomy and connect to proximal jejunum in order to divert the bowel contents back to the beginning of the small intestines.

This is a simple modification of the II-DSG and TB. This easily and intentionally, directs undigested food to the interposed distal ileal segment and avoids any concerns regarding size of the gastro-ileostomy. We eliminated the risk of severe malabsorption by connecting the distal end of the interposed ileal segment to the very proximal part of the jejunum so that food has sufficient small bowel length, to maintain almost normal absorption of micronutrients. Our modification preserves the anatomical continuity of pylorus and duodenum as in TB. As we do a liberal anastomosis, and if we assume it to dilate with time, then we suppose that most of the gastric contents will functionally bypass the duodenum and go through the gastro-ileostomy.

This will give the operation a further benefit of "functional duodenal exclusion", which is expected in TB and anatomically present in II-DSG; also a better and stronger ileal stim-

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ulation to evoke more potent incretin effect. However, in TB, this "functional exclusion of proximal intestines" might provoke a risk of "functional malabsorption", due to massive food transit directly to the very distal intestines. In gastro-ileal interposition, as we divert the ileal contents back to the proximal jejeunum, the normal absorption will continue after the metabolic stimulation is done.

The proposed technique is of moderate complexity, in between two well-known metabolic surgeries. The additional anastomosis gives greater security with respect to malabsorption when TB is considered. The gastro-ileostomy is simpler than duodeno-ileostomy, avoiding duodenal preparation and transection, and any possible complications due to this dissection.

This first and early report of our technique lacked the long-term follow-up with respect to glycemic control and weight stabilization with a very limited patient number. These are the limitations of this report. Further long-term follow-up with a greater number of patients will give a better understanding of the efficacy of this new metabolic surgery.

CONCLUSION

Ileal interposition and gastric bipartition with BMI-adjusted sleeve gastrectomy is a feasible technique which preserves the hind gut stimulation and normal duodenal anatomy for future endoscopy, while eliminating the risk of malabsorption due to enlargement of the gastro-ileal anastomosis. Further studies will give us a better understanding of our primitive assumptions.

CONFLICTS OF INTEREST

None of the authors have anything to disclose.

REFERENCES

1. Rubino F, Nathan DM, Eckel RH, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: A joint statement by international diabetes organizations. *Obes Surg*. In press.

2. De Paula AL, Macedo ALV, Prudente AS, et al. Laparoscopic sleeve gastrectomy with ileal interposition ("neuroendocrine break")-pilot study of a new operation. *Surg Obes Relat Dis*. 2006; 2(4): 464-467. doi: 10.1007/s00464-007-9472-9

3. De Paula AL, Macedo ALV, Rassi N, et al. Laparoscopic treatment of metabolic syndrome in patients with type 2 diabetes mellitus. *Surg Endosc*. 2008; 22(12): 2670-2678. doi: 10.1007/s00464-008-9808-0

4. De Paula AL, Macedo ALV, Rassi N, et al. Laparoscopic treatment of type 2 diabetes mellitus for patients with a body mass index less tahn 35. *Surg Endosc*. 2008; 22: 706-716. doi: 10.1007/s00464-008-9808-0

5. De Paula AL, Macedo ALV, Schraibman V, Mota BR, Vencio S. Hormonal evaluation following laparoscopic treatment of type 2 diabetes mellitus patients with BMI 20-34. *Surg Endosc*. 2009; 23(8): 1724-1732. doi: 10.1007/s00464-008-0168-6

6. De Paula AL, Macedo ALV, Mota RB, Schraibman V. Laparoscopic ileal interposition associated to a diverted sleeve gastrectomy is an effective operation for the treatment of type 2 diabetes mellitus patients with BMI 21-29. *Surg Endosc*. 2009; 23(6): 1313-1320. doi: 10.1007/s00464-008-0156-x

7. De Paula AL, Stival A, Halpern A, Vencio S. Thirty-day morbidity and mortality of the laparoscopic ileal interposition associated with sleeve gastrectomy for the treatment of type 2 diabetic patients with BMI<35: An analysis of 454 consecutive patients. *Worl J Surg*. 2011; 35(1): 102-108. doi: 10.1007/s00268-010-0799-3

8. De Paula AL, Stival AR, Macedo ALV et al. Prospective randomized controlled trial comparing 2 versions of laparoscopic ileal interposition associated with sleeve gastrectomy for patients with type 2 diabetes with BMI 21-34 kg/m^2. *Surg Obes Relat Dis*. 2101; 6(3): 296-305. doi: 10.1016/j.soard.2009.10.005

9. De Paula AL, Stival AR, De Paula CCL, Halpern A, Vêncio S. Impact on dyslipidemia of the laparoscopic ileal interposition associated to sleeve gastrectomy in type 2 diabetic patients. *J Gastrintest Surg*. 2010; 14(8): 1319-1325. doi: 10.1007/s11605-010-1252-5

10. Venchio S, Stival AR, Alfredo H, Depaula CC, DePaula AL. Early mechanisms of glucose improvement following laparoscopic ileal interposition associated with a sleeve gastrectomy evaluated by the euglycemic hyperinsulinemic clamp in type 2 diabetic patients with BMI below by the euglycemic hyperinsulinemic clamp in type 2 diabetic patients with BMI below 35. *Dig Surg*. 2011; 28: 293-298. doi: 10.1159/000330272

11. De Paula AL, Stival A, Halpern A, et al. Improvement in insülin sensitivity and b-cell function following ileal interposition with sleeve gastrectomy in type 2 diabetic patients: Potential mechanisms. *J Gastrintest Surg*. 2011; 15: 1344-1355. doi: 10.1007/s11605-011-1550-6

12. De Paula AL, Stival AR, DePaula CC, Halpern A, Vencio S. Surgical treatment of type 2 diabetes in patients with BMI below 35: Mid-term outcomes of the laparoscopic ileal interposition associated with a sleeve gastrectomy in 202 consecutive cases. *J Gastrintest Surg*. 2012; 16(5): 967-976. doi: 10.1007/s11605-011-1807-0

13. Tinocco A, El-Kadre L, Aquiar L, Tinoco R, Savassi-Rocha P. Short-term and mid-term control of type 2 diabetes mellitus by laparoscopic sleeve gastrectomy with ileal interposition. *World J Surg*. 2011; 35(10): 2238-2244. doi: 10.1007/s00268-011-1188-2

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14. Kumar KV, Ugale S, Gupta N, et al. Ileal interposition with sleeve gastrectomy for control of type 2 diabetes. *Diabetes Technol Ther*. 2009; 11(12): 785-789. doi: 10.1089/dia.2009.0070

15. Kota SK, Ugale S, Gupta N, et al. Ileal Interposition with Diverted sleeve gastrectomy for treatment of Type 2 diabetes. *Indian J Endocrinol Metab*. 2012; 16(Suppl 2): S458-S459. doi: 10.1089/dia.2009.0070

16. Kota SK, Ugale S, Gupta N, Modi KD. Laparoscopic ileal interposition with diverted sleeve gastrectomy for treatment of type 2 diabetes. *Diabetes Metab Syndr*. 2012; 6(3): 125-131. doi: 10.1016/j.dsx.2012.09.014

17. Kota SK, Ugale S, Gupta N, et al. Ileal interposition with sleeve gastrectomy for treatment of type 2 diabetes mellitus. *Indian J Endocrinol Metab*. 2012; 16(4): 589-598. doi: 10.4103/2230-8210.98017

18. Ugale S, Gupta N, Modi KD, et al. Prediction of remission after metabolic surgery using a novel scoring system in type 2 diabetes - a retrospective cohort study. *J Diabetes Metab Disord*. 2014; 13(1): 89. doi: 10.1186/s40200-014-0089-y

19. Celik A, Ugale S, Ofluoglu H, et al. Metabolic outcomes of laparoscopic diverted sleeve gastrectomy with ileal Transposition (DSIT) in obese type 2 diabetic patients. *Obes Surg*. 2015; 25(11): 2018-2022. doi: 10.1007/s11695-015-1671-1

20. Ramakrishnapillai P, Pai M, Shams F, et al. Effectiveness of minimally invasive hybrid surgery for ileal interposition (MIHSII) for the resolution of type 2 diabetes. *Surg Innov*. 2015 pii: 1553350615589523. doi: 10.1177/1553350615589523

21. Santoro S, Castro LC, Velhote MC, et al. Sleeve gastrectomy with transit bipartition: A potent intervention for metabolic syndrome and obesity. *Ann Surg*. 2012; 256(1): 104-110. doi: 10.1097/SLA.0b013e31825370c0

22. Mui WL, Lee DW, Lam KK. Laparoscopic sleeve gastrectomy with loop bipartition: A novel metabolic operation in treating obese type II diabetes mellitus. *Int J Surg Case Rep*. 2014; 5(2): 56-58. doi: 10.1016/j.ijscr.2013.12.002

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Review

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Surgery in the Era of Molecular Medicine: Review of Gastroenteropanreatic Neuroendocrine Tumours

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ABSTRACT

The management of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) has evolved rapidly in the last two decades. Therefore, it is important that surgeons practicing in molecular medicine era have a clear understanding of the ever-changing landscape in GEP-NETs treatment and specifically how it influences the thinking and concepts of surgical treatment and research, in the context of transdisciplinary management.

KEY WORDS: Neuroendocrine tumour; Neuroendocrine neoplasm; Carcinoids; NETs; GEP-NETs; Molecular medicine era.

ABBREVIATIONS: NETs: Neuroendocrine tumurs; PNETs: Pancreatic Neuroendocrine Tumours; DES: Diffuse Endocrine System; GEP: Gastroenteropancreatic; PD: Poorly Differentiated; ZES: Zollinger-Ellison Syndrome; VIP: Vaso-active intestinal peptide; PYY: Peptide YY; PP: Pancreatic Polypeptide; EUS: Endoscopic ultrasonography; TAE: Trans Arterial Embolization; TACE: Trans Arterial Chemo-Embolization; VEGF: Vascular Endothelium Growth Factor; PPPD: Pylorus Preserving Pancreaticoduodenectomy; mTOR: mammalian target of rapamycin; FDG: Fluorodeoxyglucose; PET: Positron Emission Tomography.

INTRODUCTION

Neuroendocrine tumours (NETs), are historically known as carcinoid. Siegfried Oberndorfer called it "Karzinoide Tumoren" when he first described seven cases of tumourlets in 1907.[1] Phenotypically, NETs cells exhibit features of both endocrine and neural cells. NETs have a wide spectrum of biologic behavior and natural history, ranging from indolent to aggressive and benign to malignant. Majority of NETs are found within the gastroenteropancreatic (GEP) axis, mirroring pattern of distribution on endocrine cells of the diffuse endocrine system (DES) within the digestive tract. Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) is a huge family of diverse functional and non-functional tumours, including all variety of pancreatic neuroendocrine tumours (PNETs), gastric NET (GNETs), peri-ampullary NETs, biliary tract NETs (BNET), duodenal NET (DNETs), jejunal-ileum NETs (JiNETs), appendiceal NET (ANETs), colonic and rectal NETs. By and large, JiNETs and PNETs constitute the largest subgroup within the GEP system. Only in recent decades, clinicians and scientists are beginning to understand NETs better, not withstanding more research and clinical trials are needed. This article covers an overview on the general principles in GEP-NETs management which may guide future research and trial questions in the molecular medicine era.

CLASSIFICATION

Due to the limited clinical utility and poor correlation with clinical behavior and prognosis,

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the obsolete classification of NETs according to the embryologic origin into foregut, midgut and hindgut has fallen in clinical disuse. With better understanding on the natural history, NETs classification has evolved. The latest version of World Health Organization (WHO) 2017 classification has gained widespread acceptance in guiding diagnosis and strategizing clinical therapy (Table1).[2]

In the WHO 2000 and 2017 classification, the main change was the switch from cell differentiation to tumour cells grading. Tumour grading schemes in GEP-NETs classification are based on three parameters, i.e., differentiation, mitotic count and Ki-67 index for cellular proliferation (Table 2).[2] Further observation on the discordance between cell differentiation and tumour grading, based on mitosis and proliferation index, prompted revision to the new WHO 2017 classification, where a separate category of poorly differentiated (PD) neuroendocrine carcinoma NEC Grade 3(G3) was appended.

With the new WHO 2017 classification, clinical data on the biological behaviors, clinical management and survival outcomes on the different classes of tumours are needed. Along with the advances in molecular sciences, incorporating molecular onco-taxonomy will refine the future version of NET classification and staging.[2]

GEP-NETs Family and Clinical Presentation

GEP-NETs are a group of heterogeneous tumours, encompassing GNETs, DNETs, peri-ampullary NETs, BNETs, PNETs, JiNETs, ANETs, colonic and rectal NETs.

Pathophysiologically, these tumours are either functional or non-functional tumours. Functional NETs secrete one or more bioactive compounds which produce paraneoplastic syndromes. Non-functional tumours are either non-secretory tumours or secrete bioinactive compounds. The biologic compounds can be hormones or peptide such as glucagon, insulin, somatostatin, serotonin, histamine, gastrin, cholecystokinin, gastric inhibitory peptide, glucagon-like peptide, secretin, ghrelin, motilin, vaso-active intestinal peptide (VIP), neurotensin, peptide YY (PYY) and pancreatic polypeptide (PP).

Gastric NETs

GNETs are a heterogeneous group of neoplasms and its classification has evolved along with the recent WHO 2017 version. Currently, GNETs are classified into GNET G1 and G2, gastric neuroendocrine carcinoma (NEC G3). A NEC can be either large cell or small cell.

Table 1: WHO Classifications of Neuroendocrine Tumours.

WHO 1980	WHO 2000	WHO 2010	WHO 2017
Carcinoid	Well differentiated (WD) endocrine tumour	NET* G1 (carcinoid)	NET G1
	WD endocrine carcinoma	NET* G2	NET G2 NET G3 WD NEN@
	Poorly differentiated endocrine/small cell carcinoma	NEC# (large cell or small cell type)	NEC G3 Poorly differentiated NEN, large or small cell type
Mucocarcinoid	Mixed exocrine-endocrine carcinoma	Mixed adenoneuroendocrine carcinoma MANEC	Mixed neuroendocrine-nonenuroendocrine neoplasm, MiNEN
Mixed forms carcinoid-adenocarcinoma			
Pseudo tumour lesions	Tumour-like lesions	Hyperplastic and preneoplastic lesions	

NEC#: neuroendocrine carcinoma; NET*: neuroendocrine tumour; NEN@: Neuroendocrine Neoplasia.

Table 2: Tumour Grading for GEP-NETs (WHO 2010 Classification).[2]

GEP-NETs Grade	Mitotic Index	Ki-67 Index
Grade I (G1)	Mitotic Count <2 per 10 High Power Fields (HPF)	≤2%
Grade 2 (G2)	Mitotic Count 2-20 per 10 High Power Fields (HPF)	3-20%
Grade 3 (G3)	Mitotic Count >20 per 10 High Power Fields (HPF)	>20%

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The sub-classification of GNETs are enterochromaffin-like (ECL) NETs cells, Type I GNETs [associated with immune chronic atrophic gastritis], Type II GNETs [associated with Zollinger-Ellison Syndrome (ZES) and multiple endocrine neoplasia (MEN) Type 1] and Type III sporadic GNETs.

Type I GNETs are usually limited to the gastric mucosa and submucosa in contradistinction to Type III GNETs, which frequently invade beyond the submucosa and extend into the regional lymph nodes. Gastrinoma tends to occur in multiple sites within the gastrinoma triangle as defined by three points, superiorly by the confluence of the cystic and common bile ducts, inferiorly by the junction of the second and third parts of duodenum and medially by the junction of the neck and body of pancreas. GNETs may co-exist with adenocarcinoma as part of the same tumour or independently. Recent research reviewed its association with the over-expression of p53 protein and PDX-1 transcription factor.[3,4]

Biliary Tract NETs

Among the GEP-NETs, BNETs are the rarest and mostly located at the common hepatic duct (CHD) and proximal common bile duct.[5] Generally, they are non-functioning tumours, although they may express gastrin, serotonin and PP. The high grade BNETs and mixed adenoneuroendocrine carcinomas are more common than the well differentiated (WD) NETs.[6]

Duodenal NETs

The commonest DNETs are gastrin producing G-cell tumour and somatostatin-producing D-cell tumours. The gastrin producing DNET variety is known as gastrinoma. It presents as Zollinger-Ellison Syndrome (ZES), characterized by abdominal pain, recurrent gastric and duodenal ulceration, gastroesophageal reflux symptoms and diarrhea. Majority are associated with multiple endocrine neoplasia (MEN) syndrome Type 1. On the other hand, the somatostatin-producing NETs are associated with neurofibromatosis Type I.[7]

D-cell DNETs usually arise in the periampullary region and patients may present with obstructive jaundice when the tumour occludes the ampulla of Vater.[8]

Pancreatic NETs

PNETs are a diverse group of cancer and account for less than 3% of all pancreatic tumours.[9] Most PNETs are diagnosed incidentally. These cancers arise from pancreatic endocrine cells when some PNETs secrete active hormones which cause symptoms related to the hormones. They are called functional PNETs. Most PNETs are non-functional tumours, i.e., either inactive hormones and do not have hormone related symptoms. Non-functional PNETS are generally asymptomatic in the early stage and for that reason they are often diagnosed in the advanced stage of the disease. Hormones secreted are diverse including insulin, glucagon, VIP, gastrin and somatostatin.

PNETS are classified by the nature of hormones they secrete such as insulinoma, glucagonoma, gastrinoma, PPoma, VIPoma and somatostatinoma as illustrated in Table 3. The presenting symptoms correspond to the nature of hormone secreted. Some of the well-known clinical syndromes are associated with PNETs, e.g., hyperinsulinemic-hypoglycemic syndrome or Whipple's triad in insulinoma, ZES in gastrinoma, Vernal Morrison Syndrome or watery diarrhea, hypokalemia, hypochlorhydria and acidosis (WDHHA) in VIPoma patients (Table 3). Some PNETs are associated with hereditary tumour syndromes such as MEN syndrome and Von Hippel-Lindau (VHL) syndrome. In MEN syndrome, the clinical clue is often gleaned from a positive family history of pancreatic, parathyroid and pituitary tumour in young family members. Menin gene mutation is the underlying genetic pathology.

While most of PNETs are WD tumours, a small group is PD NECs. They are sub-classified into small cell carcinomas

Table 3: Pancreatic NETs and Symptomatology.

PNETs Type	Hormones	Symptoms
Insulinoma	Insulin	Neuroglycopaenia symptoms e.g., lethargy, giddiness, blurring of vision (Whipple's Triad)
Gastrinoma	Gastrin	Gastric ulcer May be associated with MEN Syndrome
Glucagonoma	Glucagon	May present with skin rash (necrolytic migratory erythema)
VIPoma	VIP	Watery diarrhea, hypokalemia and achlorhydria (Vernal Morrison Syndrome)
Somatostatinoma	Somatostain	Steatorrhoea
Pancreatic Polypeptodomas (PPoma)	Pancreatic polypeptide	Change in satiety
Non-functioning Tumour	Inactive hormones or none	Mass effects of tumour

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and large cell carcinomas. The later is more common.[10]

Jejuno-ileal NETs

Most of JiNETs are diagnosed during investigation for the primary tumour in an asymptomatic metastatic liver tumour or incidentally during a health screening. The commonest symptom in JiNETs is abdominal pain which could be due to one or many of these reasons: bowel dysmotility, subacute bowel obstruction and mesenteric angina secondary to mesentery fibrosis. Other presenting symptoms may be secondary to mass effect and hormones hypersecretion. Serotonin hypersecretion causes secretory diarrhea, flushing and intermittent bronchial wheezing and Hedinger's syndrome, collectively, known as carcinoid syndrome. More than 95% of these cases are associated with liver metastasis where serotonin and peptide hormones are released from the metastases. Carcinoid crisis characterized by hypo- or hypertension, severe bronchospasm and cardiac arrhythmias may be precipitated by anaesthesia and surgery in some patients.

Majority of JiNETs are G1 NETs. Rarely are they highly proliferative with poor histological differentiation variety. About 30% of patients with JiNETs present with carcinoid syndrome.

Appendiceal NETs

ANETs are often diagnosed incidentally after an appendix operation. A large majority of these patients are asymptomatic. Carcinoid syndrome is not common unless patients present with extensive local disease or metastatic tumour. More than one third of ANETs are located at the tip of the appendix.

In addition to the classic serotonin-secreting ANETs, there are L-cell type NETs, tubular and goblet cell ANETs. Histologically, the Goblet cell type is a mixed adenoendocrine carcinoma and is biologically more aggressive.[11] Till date, genetic association has not been reported.

Colonic and Rectal NETs

The natural history of NETs arising from colon and rectum is distinctly different. Majority of the colorectal NETs occur in the rectum and rarely in the caecum.[12] Most of the colonic NETs patients are asymptomatic in the early stage. Some patients may present with occult or overt bleeding per rectum, pain and constipation. Often, at the time of presentation, the colonic NETs already metastasize to the liver, lymph nodes and peritoneum.

Rectal NETs may be small or polypoid at the time of initial detection. Majority of rectal NETs are non-functional; however, they may secrete PP, somatostatin and PYY. Unlike metastatic colonic NETs, carcinoid syndrome is not typical of metastatic rectal NETs.[13]

The current unresolved issue centers on the classification and biologic behavior of L-cell type NETs which are detected in 50% to 80% of rectal NETs using a combination of L-cell markers, GLP1, GLP2, PYY and PPY, immune-typing.[14,15]

DIAGNOSTIC APPROACH

The diagnostic approach runs systematically starting from the assessment of clinical presentation and syndrome, followed by diagnosis and tumour stage confirmation. The diagnosis could be suspected from symptomatology or clinical syndromes, supported by an initial biochemistry and biomarkers. Serum chromogranin A is a useful general biomarker for the diagnosis of neuroendocrine tumour.[16] In PD G3 GEP-NETs, Chromogranin A (CgA) may be normal and in such situations neuron-specific enolase (NSE) is an alternative tumour marker. Specific biomarkers such as serum serotonin, insulin, glucagon, PP and gastrin may be helpful, e.g., for JiNETs, the recommended biochemistry tests are CgA and 24 Hours urine 5-HIAA or serum serotonin, if available.

To confirm GEP-NETs, immunohistochemistry (IHC) remains the gold standard (Figure 1). CgA and synaptophysin immunohistochemistry are the key diagnostic markers. From WHO 2010 classification, Ki-67(MIB-1) is imperative to grade GEP-NETs. For the biopsy of tumour tissues, endoscopy is helpful in visualizing gastrointestinal NETs while endoscopic ultrasonography (EUS) guides PNETs biopsy. CT scan guided percutaneous approach is an excellent approach to target liver metastasis.

Multiphasic CT scan of the abdomen, pelvis and thorax is helpful in localizing and assessing the primary loco-regional and metastatic extent of GEP-NETs. Other imaging modalities such as magnetic resonance imaging (MRI), trans-abdominal ultrasonography, EUS and positron emission tomography (PET) scan may be considered where appropriate. PET CT or MRI scans using Fluoro-Deoxy-Glucose (FDG) and Ga-Doctatate tracers are ordered to assess the metabolic activity of the tumours and the presence of somatostatin receptors respectively (Figure 2). Accurate staging greatly helps in clinical management stratification.

The clinical investigation algorithms are individualized to specific type of GEP-NETs. A combination of biochemistry, tumour biomarkers, imaging, endoscopy and biopsy are necessary to gather enough clinical information for therapeutic planning. The European Neuroendocrine Tumor Society (ENETS) has published the consensus statements on the clinical diagnostic approach of GEP-NETs in 2004, 2009, 2012 and 2016.[17-20]

PRINCIPLES OF MANAGEMENT

Complex GEP-NETs patients are best evaluated and managed by a multidisciplinary team in a network of interdisciplinary and transdisciplinary setting. Curative treatments should be offered to all potential patients as far as the current available therapies

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Figure 1: Pancreas NETs.

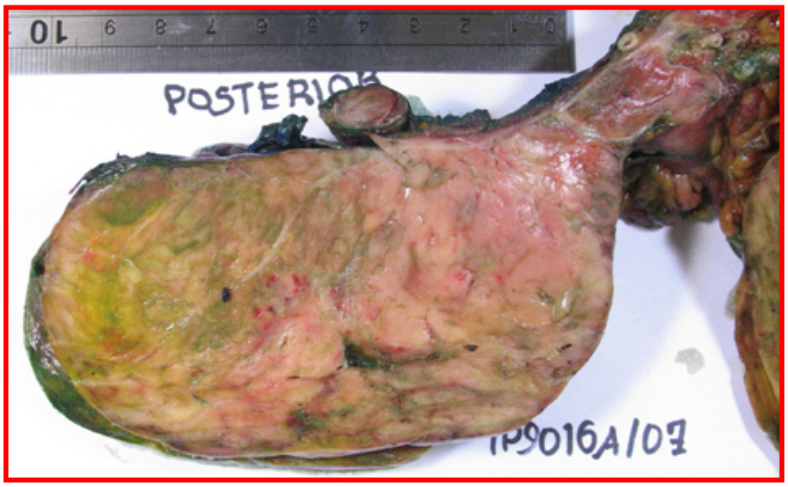
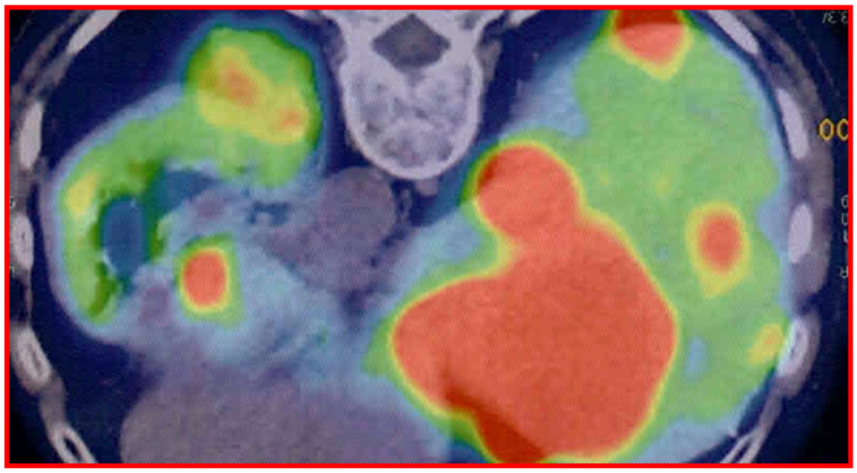


Figure 2: F-18 FDG PET.



are concerned.

The principles and goals of managing GEP-NETs are to control hormone and tumour related symptoms, if present, and to improve survivorship by curative surgery or tumour ablation. Tumour sites, grade and stage, hormone functionality and performance status of patients, guide the choice of therapeutic options available for symptoms and tumour control. Current therapeutic repertoire in the management of GEP-NETs include surgery, organ transplantation, liver directed chemotherapy and ablative therapy, selective internal radiotherapy, hormonal therapy, immunotherapy, systemic chemotherapy and targeted molecular therapy.

The salient points on the therapeutic options are summarized and highlighted in the management of GEP-NETs.

Surgery

A rule of thumb in the management of early stage GEP-NETs is that, all patients with local disease should be considered for R0 curative surgery to completely remove the primary tumour unless patients are not fit for surgery. The other roles of surgery are debulking or cytoreductive surgery and palliative surgery.

Curative oncologic surgery aims at R0 surgical resection of the primary tumour and locoregional lymph nodes. For GNETs, depending on the site, size and depth of invasion of the tumour, the surgical options are endoscopic mucosal resection, subtotal gastrectomy with lymphadenectomy and total gastrectomy with lymphadenectomy. For JiNETs, segmental enterectomy with clearance of mesenterial and retroperitoneal lymph nodes is indicated. ANETs with low risk factors, i.e., tumour

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size <1 cm, invasion up to submucosa and clear surgical margin, simple appendicectomy is an adequate treatment.[18] Patients with high risk factors in ANETs, right hemicolectomy with lymphadenectomy is necessary if R0 resection is the goal. Likewise, for colonic NETs, right or left hemicolectomy with resection of the accompanied lymph nodes is recommended depending on the location and extent of primary tumour. Anterior resection and abdominoperineal resection are options for rectal NETs. Less invasive surgery such as transanal minimally invasive surgery and transanal endoscopic microsurgical resection may be indicated for early small rectal NETs.[19]

Curative pancreatic surgery may involve enucleation of tumour, segmental pancreatectomy, Whipple's operation, pylorus preserving pancreaticoduodenectomy (PPPD) and subtotal distal pancreatectomy. In advanced surgical centers with minimal invasive expertise, some of these operations can be performed laparoscopically or with robotic surgery. The choice on the nature of operation is determined by the location and extent of tumours, e.g. early small periampullary NETs is amenable with curative PPPD. High cure rate can be expected when R0 surgical resection is performed. For instance, a cure rate of more than 90% of the patients has been reported for sporadic insulinoma.[20]

Debulking, cytoreductive surgery or complete liver metastatectomy in selected patients with liver-only diseases in metastatic GEP-NETs, confer both improved symptoms control and long-term survivorship.[21] It also has an added benefit of rendering medical therapy more effectively in controlling the residual tumour.

Palliative surgery may be necessary to relieve the intestinal obstruction caused by mesenteric fibrosis or tumour mass effects in patients with advanced GEP-NETs.

Organ Transplantation

Due to organ scarcity, orthotopic liver transplantation remains an option for only highly selected patients. The current selection criteria take into account patients showing an absence of extrahepatic metastasis with the involvement of less than 50% of the hepatic volume, undergoing pre-transplantation R0 resection of the primary tumour and those who are unresponsive or have exhausted all medical therapies. Aggressive GEP-NETs is an exclusion criterion.[22] When a strict inclusion for liver transplantation is adopted, the 5-year overall survival rate of 52% can be expected.[23]

Liver Directed Loco-regional Therapy

For metastatic GEP-NETs patients who have liver-only disease and are not surgical candidates, the choice of loco-regional therapies include radiofrequency ablation (RFA), transarterial embolization (TAE) or chemoembolization (TACE) and radioactive isotope Yttrium-90 microsphere radioembolization therapy (RET).[24] These modalities of treatment can be used in combination with systemic chemotherapy or molecular therapy. RFA is recommended for the treatment of tumours less than 5 cm. Trans-arterial embolization (TAE) and trans-arterial chemoembolization (TACE) are indicated as a diagnostic approach for treating G1 and G2 NETs in patients showing reasonable liver function and those who are free from portal vein thrombosis. Although, a good objective response has been reported for Yttrium-90 microspheres RET, comparative randomized trial between Yttrium-90 microspheres RET and TACE is not available.[25]

Hormonal Therapy

Somatostatin analogues (SSA) have been proven to have significant impacts in terms of controlling both, the symptoms and anti-tumour proliferation.[26,27] SSA acts by reducing and blocking hormone secretion by the tumour, inhibiting neuroendocrine tumour growth, reducing gastrointestinal secretion and inhibiting peristalsis. These effects are achieved by binding with five subtypes of somatostatin receptors (sst1-5). Clinical response in terms of anti-proliferative effects is significant in JiNETs patients and, in term of hormone related symptoms, it can be observed prominently in PNETs.[28] In patients with VIPoma, SSA rapidly reverses the watery diarrhea, hypokalemia, hypochlorhydria, acidosis (WDHHA) syndrome and glucagonoma symptoms,[29] and is used to treat necrolytic migratory erythema rash.[30] In the carcinoid syndrome, SSA promptly palliates flushing and blushing symptoms.[31]

Octreotide, lanreotide and pasireotide are somatostatin analogues which are currently available for clinical use (Tables 4 and 5). They have different somatostatin receptor affinities. Octreotide and lanreotide bind avidly to sst2 receptor and have

Table 4: Molecular Directed Therapy for PNETs.

Study Phase (References)	Therapy	Response Rate	Survival (Months)
Phase II[41]	Sorafenib	10%	PFS=11.9
Phase III[37]	Sunitinib	9.3%	PFS=11.4
Phase II[42]	Pazopanib/Octreotide	17%	PFS=11.7
Phase III[38]	Everolimus	73%	PFS=11
Phase II[40]	Temsirolimus	6.7%	TTP=6

PFS: Progression free survival; TTP: Time-To-Progression.

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Table 5: Molecular Directed Therapy for Advanced NETs.

Study Phase (References)	Therapy	Stable Disease	Survival
Phase III[29]	Octreotide	66.7%	PFS=14.3 months
Phase II[43]	Bevacizumab/Octreotide	77%	PFS at 18 months 95%
Phase III[44]	Everolimus/Octreotide	84%	PFS=16.4 months
Phase II[45]	Imatinib	63%	PFS=24 weeks
Phase II[40]	Temsirolimus	58.3%	TTP=6 months

PFS: Progression free survival; TTP: Time-To-Progression.

moderate binding affinity to the sst3 and 5 receptors while pasireotide binds with greater affinity to the somatostatin receptors (sst1, 2, 3 and 5). Pasireotide has a higher affinity for sst5 receptor than octreotide.[32] Somatostatin analogues are generally effective as a therapeutic approach for mitotically inactive tumours with avid somatostatin receptor expression. It is recommended as a first-line medical therapy for patients with WD G1 PNETs.[33] Generally, SSA is contraindicated in PD G3 GEP-NETs because majority of the G3 NETs lack somatostatin receptors and the likelihood of its resistance to SSA therapy is higher. In metastatic G1 and G2 non-functional pancreatic NETs, lanreotide has been shown to prolong progression-free survival.[34] Somatostatin analogues are generally well tolerated having good safety and adverse effect profiles.

However, trials to define its use as adjuvant therapy following R0 surgical resection of GEP-NETs are currently ongoing.

Systemic Cytotoxic Chemotherapy

The chemosensitivity of GEP-NETs is predicted from its tumour grade, tumour differentiation and primary tumour site. PD high grade NETs are generally very responsive to chemotherapy while the WD G1 NETs are resistant to cytotoxic chemotherapy. Therefore, systemic chemotherapy is recommended for patients who are diagnosed with metastatic G2 NETs, G3 NEC and those with inoperable progressive liver metastases in G1 or G2 NETs. In patients with G1 NETs, the response rate to systemic chemotherapy remains poor. The commonly considered cytotoxic drugs include cisplatinum, etoposide, streptozotocin and 5-fluorouracil (5-FU) or doxorubicin.[35] Temozolomide based chemotherapy, alone or in combination with capecitabine, has been shown to have anti-tumour effects generating a good tumour response.[36]

Biologic Targeted Therapy

Most GEP-NETs are characterized by hypervascularity with a frequent expression of VEGF ligand and receptors. Anti-VEGF agent that inhibits vascular endothelium growth factor (VEGF) pathway ultimately disrupts the drivers of angiogenesis. Anti-VEGF can be targeted at either the tyrosine kinase VEGF receptors on the tumour cell membranes or the circulating VEGF. Tyrosine kinase VEGF receptor inhibitors, sunitinib and pazopanib have been shown to be effective in controlling the progression of advanced PNETs.[37] Bevacizumab is a monoclonal antibody that targets the circulating VEGF-A.

The mammalian target of rapamycin (mTOR) inhibitor targets the mTOR enzyme in the phosphatidylinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway that is responsible for cell growth, proliferation and metabolism. Everolimus, an mTOR inhibitor, has been tested in advanced PNETs which indicated anti-tumour effect with significant improvement in progression-free survival.[38] Everolimus has an additional advantage in decreasing the insulin release from the pancreatic beta cells in metastatic insulinoma patients.[39] Patients with metastatic insulinoma requiring a high dosage of diazoxide to control the overproduction of insulin hormones and hypoglycemia may show a favorable response to the treatment. Temsirolimus is the other mTOR inhibitor which has been tested clinically for advanced neuroendocrine carcinomas.[40]

The clinical outcomes, measured by response rate, stable disease rate, progression free survival (PFS) and time-to-progression (TTP), of some of these molecular directed therapies for PNETs and advanced NETs are summarized in Tables 4 and 5 respectively.[41-45]

Immunotherapy

Alpha-Interferon (IFN) therapy is one of the possible treatment options for GEP-NETs. Both, JiNETs and functioning PNETs are sensitive to the anti-secretory and anti-proliferative effects of alpha-IFN.[46] It controls symptoms and tumour growth effectively through immune stimulation, inhibition of angiogenesis and induction of cell cycle arrest.[47] However, its use is limited by the adverse effects of flu-like symptoms, depression and myelosuppression.[48] Therefore, it is usually implemented as a second line therapy. Fever, fatigue, anorexia and weight loss are common symptoms associated with this method of treatment. Interferon combined with somatostatin analogues has a synergistic effect in the symptoms and tumour control, an example being, patients with carcinoid syndrome who are refractory to octreotide treatment.

The impact of anti-PD1 and anti-PD-L1 on the treatment of neuroendocrine carcinoma has yet to be extensively explored. While clinical success has been witnessed in other types of cancers, clinical trials and research lack sufficient evidences

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in GEP-NETs currently.

Peptide Receptor Targeted Radiotherapy (PRRT)

Emerging data on PRRT in the treatment of metastatic GEP-NETs using ^{90}Yttrium and ^{177}Lutetium labelled Doctatate PRRT has been promising. Patients who have either functioning or non-functioning GEP-NETs with dense somatostatin receptors on tumours as demonstrated by positive Ga-Doctatate PET/CT scan are considered as a suitable recipient of PRRT.[49] Objective response rates in the range of 20% to 40% have been clinically reported.[50] The main adverse effects of this treatment modality are bone marrow and renal toxicities. Further studies and clinical trials are currently underway to clarify its roles and indications in the management of GEP-NETs.[51]

The first preliminary PRRT phase III trial NETTER-1 result was published in 2016.[52] In comparison to the octreotide LAR 60 mg, PRRT using ^{177}Lutetium significantly improved the treatment response rate and progression-free survival of patients with advanced metastatic midgut NETs.[53] A few other Phase III clinical trials for PRRT are currently underway and clinicians are eagerly awaiting the final outcome of the study.

Potentially, PRRT may have a role in the neoadjuvant setting to downstage an unresectable to resectable tumour, or render the safety of cytoreductive surgery. Surgeons must keep an eye on this emerging modality that could potentially have a tremendous impact on the surgical management of GEP-NETs.

Longitudinal Evaluation

Depending on the biology and grade of GEP-NETs, a regular medical review of clinical, biochemical parameters and imaging at an interval between 3 to 6 months is recommended. A clinical review at a closer interval is recommended for aggressive G3 GEP-NETs. Serum CgA and NSE remain useful general non-specific biomarker for follow-up in the affected patients. Other relevant tumour-specific markers and imaging are helpful in the assessment of treatment response, tumour recurrence, tumour progression, tumour dedifferentiation and prognostication. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan or dual-tracer PET/CT scans using FDG and Ga-Doctatate may be recommended (Figure 3). The dual-tracer PET scan has the advantage with respect to the assessment of 'flip-flop' phenomenon which results in a poor prognosis in NETs patients. It happens when tumours lose the expression of somatostatin receptors and exhibit an increased FDG hypermetabolism during the process of tumour dedifferentiation. When GEP-NETs progress rapidly or fail to respond to therapy or whenever imaging is unhelpful, a re-biopsy of liver metastases to reassess proliferative activity of the tumour is recommended.

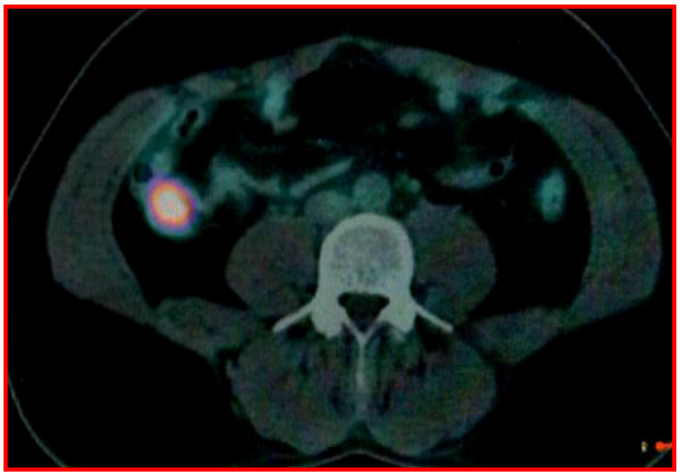
Prognosis and Survivorship

In general, G1 and G2 NETs show an indolent clinical tumour progression marked by several years of survivorship and good performance status, while the G3 NETs have a more aggressive clinical course with shorter survivorship.

The main prognostic factors for GEP-NETs include the site of origin of NETs, grade and classification of malignant tumours (TNM staging of the tumour.[54] Clinical prognosis can be adversely affected by the presence of high urinary 5-HIAA and CgA, carcinoid heart syndrome and carcinoid syndrome.

The 5-year overall survival rates for patients with non-functioning PNETs are estimated to be 26% to 58%.[55] Localized PNETs following R0 surgical resection show excellent prognosis and a 5-year survival is estimated in the range of 60% to 100%.[56,57] In patients with liver metastasis, the overall 5-year survival rate ranges from 20% to 38%.[58]

Figure 3: Ga-Doctatate PET Scan-Ileal NETs.



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CONCLUSION

GEP-NETs is a heterogeneous group of tumours originating from the digestive diffuse endocrine system. They have a wide spectrum of biologic and oncologic diversity. With a better understanding of GEP-NETs, clinical diagnosis could be made more prompt and precise, such that therapeutic intervention could be more tumour type specific and prognostication could be more accurate.

Multimodal management provided by a multi- and trans-disciplinary team remains the key element for ensuring the clinical success and good outcome. More basic science research and clinical trials on classification, oncobiology, diagnostic and prognostic biomarkers, imaging technology and innovative therapeutics are needed to push the frontier in GEP-NETs management.[59]

REFERENCES

1. Oberndorfer S. Karzinoide tumoren des dunndarms [In German]. *Frankfurt Z Pathol* . 1907: 426-432.

2. WHO. Neuroendocrine Tumour Grading System. 2017. Web site. http://www.agps.org.au/resources/AGPS_AGM_programs/2016_AGM_presentations/Gill_WHO%202017%20Neuroendocrine%20October%2027.pdf. Accessed June 25, 2017.

3. Nishikura K, Watanabe H, Iwafuchi M, Fujiwara T, Kojima K, Ajioka Y. Carcinogenesis of gastric endocrine cell carcinoma: Analysis of histopathology and p53 gene alteration. *Gastric Cancer*. 2003; 6(4): 203-209. doi: 10.1007/s10120-003-0249-0

4. Buettner M, Dimmler A, Magener A, et al. Gastric PDX-1 expression in pancreatic metaplasia and endocrine cell hyperplasia in atropic corpus gastritis. *Mod Pathol*. 2004; 17(1): 56-61. doi: 10.1038/sj.modpathol.3800015

5. Michalopoulos N, Papavramidis TS, Karayannopoulou G, et al. Neuroendocrine tumours of extrahepatic biliary tract. *Pathol Oncol Res*. 2014: 20(4): 765-775. doi: 10.1007/s12253-014-9808-4

6. Noronha YS, Raza AS. Well differentiated neuroendocrine carcinoid_ tumours of the extrahepatic biliary ducts. *Arch Pathol Lab Med.* 2010; 134(7): 1075-1079. doi: 10.1043/2008-0764-RS.1

7. Garbrecht N, Anlauf M, Schmitt A, et al. Somatostatin-producing neuroendocrine tumours of the duodenum and pancreas: Incidence, types, biologic behavior, association with inherited syndromes, and functional activity. *Endocr Relat Cancer*. 2008; 15(1): 229-241. doi: 10.1677/ERC-07-0157

8. Dayal Y, Tallberg KA, Nunnemacher G, DeLellis RA, Wolfe HJ. Duodenal carcinoids in patients with and without neurofibromatosis. A comparative study. *Am J Surg Pathol*. 1986; 10 (5): 348-357.

9. Öberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Pract Res Clin Gastroenterol*. 2005; 19(5): 753-781. doi: 10.1016/j.bpg.2005.06.002

10. Shi C, Klimstra DS. Pancreatic neuroendocrine tumours: Pathologic and molecular characteristics. *Semin Diagn Pathol*. 2014; 31(6): 498-511. doi: 10.1053/j.semdp.2014.08.008

11. Deschamps L, Couvelard A. Endocrine tumours of the appendix: A pathologic review. *Arch Pathol Lab Med*. 2010; 134(6): 871-875. doi: 10.1043/1543-2165-134.6.871

12. Jetmore AB, Ray JE, Gathright JB Jr, McMullen KM, Hicks TC, Timmcke AE. Rectal carcinoids: The most frequent carcinoid tumor. *Dis Colon Rectum*. 1992; 35 (8): 717-725. doi: 10.1007/BF02050318

13. Levy AD, Sobin LH. From the archives of the AFIP. Gastrointestinal carcinoids: Imaging features with clinicopathologic comparison. *Radiographics*. 2007; 27(1): 237-257. doi: 10.1148/rg.271065169

14. Kim JY, Kim KS, Kim KJ, et al. Non-L cell immunophenotype and large tumour size in rectal neuroendocrine tumours are associated with aggressive clinical bahaviour and worse prognosis. *Am J Surg Pathol*. 2015; 39(5): 632-643. doi: 10.1097/PAS.0000000000000400

15. Sohn JH, Cho MY, Park Y, et al. Prognostic significance of defining L-cell type on the biologic behavior of rectal neuroendocrine tumours in relation with pathological parameters. *Cancer Res Treat.* 2015; 47(4): 813-822. doi: 10.4143/crt.2014.238

16. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: Is it a useful marker of neuroendocrine tumors? *J Clin Oncol*. 2007; 25: 1967-1973. doi: 10.1200/JCO.2006.10.1535

17. Plöckinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004; 80(6): 394-424. doi: 10.1159/000085237

18. Prommegger R, Obrist P, Ensinger C, et al. Retrospective evaluation of carcinoid tumours of the appendix in children. *World J Surg*. 2002; 26: 1489-1492. doi: 10.1007/s00268-002-6440-3

19. Yamaguchi N, Isomoto H, Nishiyama H, et al. Endosscopic submucosal dissection for rectal carcinoid tumours. *Surg Endosc.* 2010; 24(3): 504-508. doi: 10.1007/s00464-009-0606-0

20. Rothmund M, Angelini L, Brunt M. et al. Surgery for benign

ISSN 2377-8407
http://dx.doi.org/10.17140/SROJ-4-121

insulinoma: An international review. *World J Surg*. 1990; 14(3): 393-399. doi: 10.1007/BF01658536

21. Que FG, Nagorney DM, Batts KP, Linz LJ, Kvols LK. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg*. 1995; 169(1): 36-43. doi: 10.1016/S0002-9610(99)80107-X

22. Le Treut P, Delpero JR, Dousset B, et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors: A 31-case French multicentric report. *Ann Surg*. 1997; 225(4): 355-364.

23. Le Treut YP, Gregoire E, Klempnauer J, et al. Liver transplantation for neuroendocrine tumours in Europe – results and trends in patient selection: A 213 case Europe Liver Transplant Registry study. *Ann Surg*. 2013; 257: 807-815. doi: 10.1097/SLA.0b013e31828ee17c

24. Eriksson BK, Larsson EG, Skogseid BM, Lofberg AM, Lorellius LE, Oberg KE. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer*. 1998; 83: 2293-2301. doi: 10.1002/(SICI)1097-0142(19981201)83:11<2293::AID-CNCR8>3.0.CO;2-E

25. Kennedy AS, Dezam WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: Early results in 148 patients. *Am J Clin Oncol*. 2008; 31: 271-279. doi: 10.1097/COC.0b013e31815e4557

26. Lamberts SWJ, van der Lely AJ, de Herder WW, Hofland LJ. Octreotide. *N Engl J Med*. 1996; 334: 246-254. doi: 10.1056/NEJM199601253340408

27. Caplin ME, Pavel M, Cwikla JB. Lanreotide in metastatic enteropancreatic neuroendocrine tumours. *N Engl J Med*. 2014; 371(3); 224-233. doi: 10.1056/NEJMoa1316158

28. Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours. Report on a double-bind randomized trial. *J Intern Med*. 1995; 237(3): 369-275. doi: 10.1111/j.1365-2796.1995.tb01175.x

29. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double blind, prospective, randomized study on the effectofoctretide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: A report from the PROMID Study Group. *J Clin Oncol*. 2009; 27: 4656-4663. doi: 10.1200/JCO.2009.22.8510

30. O'Dorisio TM, Gaginella TS, Mekhjian HS, Rao B, O'Dorisio MS. Somatostatin and analogues in the treatment of VIPoma. *Ann N Y Acad Sci*. 1988; 527: 528-535. doi: 10.1111/j.1749-6632.1988.tb27006.x

31. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of long-acting somatostatin analogue. *N Engl J Med*. 1986; 315: 663-666. doi: 10.1056/NEJM198609113151102

32. Schmid HA, Schoeffter P. Functional activity of the multiligand analog SOM230 at human recombinant somatostatin receptor subtypes supports its usefulness in neuroendocrine tumors. *Neuroendocrinology*. 2004; 80(Suppl 1): 47-50. doi: 10.1159/000080741

33. Eriksson B, Kloppel G, Krenning E, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors – well-differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology*. 2008; 87(1): 8-19. doi: 10.1159/000111034

34. Caplin M, Ruszniewski P, Pavel M, et al. A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic Neuro Endocrine Tumors (CLARINET). *Eur J Cancer*. 2013; 49.

35. Janson ET, Ronnblom L, Ahlstrom H, et al. Treatment with alpha-interferon versus alpha-interferon in combination with streptozocin and doxorubicin in patients with malignant carcinoid tumors: A randomized trial. *Ann Oncol*. 1992; 3(8): 635-638. doi: 10.1093/oxfordjournals.annonc.a058291

36. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer*. 2011; 117(2): 268-275. doi: 10.1002/cncr.25425

37. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011; 364: 501-513. doi: 10.1056/NEJMoa1003825

38. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrinetumors. *N Engl J Med*. 2011; 364: 514-523. doi: 10.1056/NEJMoa1009290

39. Fuhrer DK, Kobayashi M, Jiang H. Insulin release and suppression by tacrolimus, rapamycin and cyclosporine A are through regulation of the ATP-sensitive potassium channel. *Diabetes Obes Metab*. 2001; 3(6): 393-402. doi: 10.1046/j.1463-1326.2001.00150.x

40. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer*. 2006; 95(9): 1148-1154. doi: 10.1038/sj.bjc.6603419

41. Hobday TJ, Rubin J, Holen K, et al. MC044h, a phase II trial of sorafenib in patients with metastatic neuroendocrine tumours (NET): A Phase II Consortium study. *J Clin Oncol*. 2007 ASCO Annual Meeting Proceedings Part 1, 2007; 25(Suppl 18): 4504. doi: 10.1200/jco.2007.25.18_suppl.4504

ISSN 2377-8407
http://dx.doi.org/10.17140/SROJ-4-121

42. Phan AT, Yao JC, Fogelman DR, et al. A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (santostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC). *J Clin Oncol*. 2010; 28(Suppl 15): 4001.

43. Yao JC, Phan A, Hoff PM et al. Targeting vascular endothelial growth factor in advanced carcinoid tumour: A random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon akpha-2b. *J Clin Oncol*. 2008; 26: 1316-1323. doi: 10.1200/JCO.2007.13.6374

44. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomized, placebo-controlled, phase 3 study. *Lancet*. 2011; 378: 2005-2012. doi: 10.1016/S0140-6736(11)61742-X

45. Yao JC, Zhang JX, Rashid A, et al. Clinical and in vitro studies of imatinib in advanced carcinoid tumour. *Clin Cancer Res*. 2007; 13(1): 234-240. doi: 10.1158/1078-0432.CCR-06-1618

46. Biesma B, Willemse PH, Mulder NH, et al. Recombinant interferon alpha-2b in patients with metastatic apudomas: Effect on tumours and tumour markers. *Br J Cancer.* 1992; 66(5): 850-855.

47. Oberg K. Interferons in the management of neuroendocrine tumours and their possible mechanism of action. *Yale J Biol Med*. 1992; 65: 519-529; discussion 531-536.

48. Oberg K, Eriksson B, Janson ET. Interferon alone or in combination with chemotherapy or other biologicals in the treatment of neuroendocrine gut and pancreatic tumors. *Digestion*. 1994; 3: 64-69. doi: 10.1159/000201204

49. Forrer F, Valkema R, Kwekkeboom DJ, de Jong M, Krenning EP. Neuroendocrine tumors. Peptide receptor radionuclide therapy. *Best Pract Res Clin Endocrinol Metab.* 2007; 21(1): 111-129. doi: 10.1016/j.beem.2007.01.007

50. 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(13): 2124-2130. doi: 10.1200/JCO.2007.15.2553

51. 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; 3 6(2): 147-156. doi: 10.1053/j.semnuclmed.2006.01.001

52. Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: Progression-free surviva, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumours treated with 177-Lu-Dotatate. *J Clin Oncol*. 2016; 34(4): 194-194. doi: 10.1200/jco.2016.34.4_suppl.194

53. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumours. *N Engl J Med*. 2017; 376(2): 125-135. doi: 10.1056/NEJMoa1607427

54. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol*. 2005; 89(3): 151-160. doi: 10.1002/jso.20179

55. Halfdanarson TR, Rubin J, Farnell MB, et al. Pancreatic endocrine neoplasms: Epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer*. 2008; 15(2): 409-427. doi: 10.1677/ERC-07-0221

56. Madeira I, Terris B, Voss M. et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut*. 1998; 43: 422-427. doi: 10.1136/gut.43.3.422

57. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factor and survival in 324 patients with pancreatic endocrine tumour treated at a single institution. *Clin Cancer Res.* 2008; 14: 7798-7803. doi: 10.1158/1078-0432.CCR-08-0734

58. Carty S, Jensen RT, Norton JA, et al. Prospective study of aggressive resection of metastatic pancreatic endocrine tumour. *Surgery*. 1992; 112(6): 1024-1031.

59. Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. *J Clin Oncol*. 2011; 29(7): 934-943. doi: 10.1200/JCO.2010.33.2056