

Bölüm 34

PANKREAS NEOPLAZİLERİ

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GİRİŞ

Pankreas ilk iki lomber vertebra hizasında yerleşmiş retroperitoneal bir organdır. Anatomi olarak; baş, boyun, gövde ve kuyruk olmak üzere dört kısma ayrılır. Pankreasın primer maligniteleri, köken aldığı hücrel orijine göre endokrin ve ekzokrin olarak iki başlıkta incelenir, ek olarak nadir görülmekle beraber pankreasa metastaz da izlenebilir (1). Pankreasın endokrin neoplazileri, oldukça heterojen histopatoloji ve prognoza sahiptir. Pankreasın ekzokrin neoplazileri ise agresif ve ölümcül malignitelerdir ve son 4 dekattır tedavi yöntemlerindeki gelişmelere rağmen prognozunda belirgin düzelme görülmemiştir. Pankreasın ekzokrin ve endokrin neoplazileri ayrı başlıklar altında incelenecektir (2).

PANKREASIN ENDOKRİN NEOPLAZİLERİ

Pankreasın endokrin neoplazileri (PEN), oldukça heterojen biyoloji klinik gidiş ve prognoza sahip nadir görülen malignitelerdir ve tüm pankreas malignitelerinin %3'ünü oluşturmaktadır (3). İnsidansı 0.2/100.000'dir ve tipik görünümü iyi sınırlı hipervasküler lezyonlar şeklindedir (2). Sıklıkla 4. veya 5. dekatta tanı konulur ve ekzokrin neoplazmaların tersine kadınlarda daha sıktır.

Multiple endokrin neoplazi (MEN)-1, von Recklinghausen, von Hippel Lindau ve Tuberoskleroz gibi ailesel hastalıklarla ilişkili olabilir ancak vakaların %90'ı sporadiktir. Hormon salgılayıcı özelliği ve klinik bulgularına göre fonksiyonel (gastrinoma, insülinoma, VIPoma, glukagonoma, somatostatinoma vb.) ve non-fonksiyonel olmak üzere ikiye ayrılmaktadır (3). WHO 2017 sınıflandırılmasında ise histopatolojisi, ki-67 indeksi, mitotik indeksi, ve biyolojik özelliklerine göre 'iyi diferansiye endokrin tümör' veya 'kötü diferansiye endokrin karsinom' olmak üzere iki ana başlığa ayrılmıştır. İyi diferansiye tümörler ise grad 1, 2 ve 3 olmak üzere üç gruptur. WHO 2017'i temel alan güncel sınıflandırma Tablo 1'de özetlenmiştir (4).

Fonksiyone tümörlerde klinik bulgular, salgılanan hormona göre değişiklik gösterir, non-fonksiyone tümörlerde ise semptomlar kitle-bası bulguları ile ilişkilidir. Vakaların yaklaşık yarısını fonksiyone tümörler oluşturur ve bunların da yaklaşık %50'si insülinoma ve gastrinomalardır. İnsülinomaların %90'ı benign olmasına rağmen fonksiyonel tümörlerin bir kısmında veya non-fonksiyone tümörlerde malign transformasyon izlenebilir. Ancak ileri evre malign PEN'lerde dahil olmak üzere PEN'lerde prognoz, ekzokrin pankreas malignitelerinden daha iyidir, metastatik hastalıkta bile 5 yıllık Genel Sağkalım (GS) %50 civarındadır (2,3,4,5).

Endokrin tümörlerde salgılanan hormona göre endokrin tedaviler ve/veya cerrahi ter-

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vardır (82,84).

PANKREASIN KİSTİK LEZYONLARI VE SINIFLANDIRMASI

Pankreasın kistik neoplazileri (PKN) genel popülasyonda %2-45 oranında görülmektedir. Biyolojik davranış açısından heterojendir (85). En sık karşılaşılan kistik neoplazmlar; seröz kistadenom, müsinöz kistik neoplazi, intraduktal papiller müsinöz neoplazi, solid psödopapiller neoplazi ve kistik pankreatik endokrin neoplazilerdir (86). Güncel sınıflandırma tablo 3'de verilmiştir. BT ve MR ile yeterince bilgi sağlanamazsa E-USG ile değerlendirme yapılabilir. Ayrıca FNA ile sitolojik değerlendirme imkanı olmaktadır. Uygun tedavi şeması multidisipliner yaklaşımla hasta özelinde belirlenmelidir (85,86).

Sonuç

Gelişen cerrahi, RT ve sistemik tedavilere rağmen PK'nin sağkalımında beklenen artış sağlanamamıştır. Yeni yaklaşımlar gerekliliği açıktır. Bu amaçla, tanısal tetkikler ve klinisyen dikkati ile erken evrede tanı şansını artırmak önemlidir. Diğer yandan hedefe yönelik ajanlar ve immüno- lojik tedaviler ile optimal tedavi yaklaşımında yakın tarihte önemli değişiklikler beklenmektedir.

KAYNAKLAR

1. Palta, M., Willet, CG., Czito, BG. (2018). Pancreatic Cancer. In E.C. Halperin, D.E. Wazer, C.E. Perez & L.W. Brady (Eds.), Principles and Practice of Radiation Oncology (7nd ed., pp 4509-4541). Philadelphia: Wolter Kluwer.
2. Winter, JM., Brody, JR., Abrams, RA., et al. (2015). Cancer of the Pancreas. In V.T. DeVita, T.S. Lawrence & S.A. Rosenberg (Eds.), Cancer, Principles and Practice of Oncology (10nd ed., pp 657-685). Philadelphia: Wolter Kluwer.
3. Philips S, Shah SN, Vikram R, Verma S, et al. Pancreatic endocrine neoplasms: a current update on genetics and imaging. Br J Radiol. 2012; 85:682-696.
4. Juilmette JM, Nosé V. Neoplasms of the Neuroendocrine Pancreas: An Update in the Classification, Definition, and Molecular Genetic Advances. Adv Anat Pathol. 2019; 26:13-30.
5. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
6. Goldstein, JB., Shroff, RT., Wolff, T. et al. (2016). Pancreatic Cancer. In H.M. Kantarjian & R.A. Wolf (Eds.), The MD Anderson Manual of Medical Oncology (3rd ed., pp 439-461).
7. Benzel J, Fendrich V. Chemoprevention and Treatment of Pancreatic Cancer: Update and Review of the Literature. Digestion. 2018;97:275-287.
8. https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Turkiye_Kanser_Istatistikleri_2015.pdf
9. Hasan S, Jacob R, Manne U, et al. Advances in pancreatic cancer biomarkers. Oncol Rev. 2019;13:410.
10. Mohammed S, Van Buren G 2nd, Fisher WE. Pancreatic cancer: advances in treatment. World J Gastroenterol. 2014;20:9354-9360.
11. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388:73-85.
12. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74: 2913-2921.
13. Keane MG, Horsfall L, Rait G, et al. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. BMJ Open .2014; 4: 5720.
14. Li J, Li Y, Cao G, et al. Early manifestations of pancreatic cancer: the effect of cancer-nerve interaction. Med Hypotheses 2013; 81: 180-182.
15. Kamisawa T, Isawa T, Koike M, et al. Hematogenous metastases of pancreatic ductal carcinoma. Pancreas. 1995; 11: 345-349.
16. O'Brien DP, Sandanayake NS, Jenkinson C, et al. Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. Clin Cancer Res 2015; 21: 622-31.
17. Jahan R, Ganguly K, Smith LM, et al. Trefoil factor(s) and CA19.9: A promising panel for early detection of pancreatic cancer. EBioMedicine. 2019; 42:375-385.
18. Kaur S, Smith LM, Patel A, et al. A Combination of MUC5AC and CA19-9 Improves the Diagnosis of Pancreatic Cancer: A Multicenter Study. Am J Gastroenterol. 2017; 112:172-183
19. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014; 20:7864-7877.
20. Fan Z, Li Y, Yan K, et al. Application of contrast-enhanced ultrasound in the diagnosis of solid pancreatic lesions-acomparison of conventional ultrasound and contrast-enhanced CT. Eur J Radiol. 2013; 82:1385-1390.
21. Işcanlı E, Türkvatan A, Bostancı EB, et al. Assessment of surgical resectability of pancreatic adenocarcinomas with multidetector computed tomography: what are the possibilities and problems? Turk J Gastroenterol. 2014; 25:416-423
22. Pietryga JA, Morgan DE. Imaging preoperatively for pancreatic adenocarcinoma. J Gastrointest Oncol. 2015; 6:343-357

23. Tummers WS, Willmann JK, Bonsing BA, et al. Advances in Diagnostic and Intraoperative Molecular Imaging of Pancreatic Cancer. *Pancreas*. 2018; 47:675-689.
24. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. *World J Gastroenterol*. 2018; 24:2047-2060.
25. Zhang Y, Huang J, Chen M, Jiao LR. Preoperative vascular evaluation with computed tomography and magnetic resonance imaging for pancreatic cancer: a meta-analysis. *Pancreatology*. 2012; 12:227-233.
26. Brennan DD, Zamboni GA, Raptopoulos VD, et al. Comprehensive preoperative assessment of pancreatic adenocarcinoma with 64-section volumetric CT. *Radiographics* 2007; 27:1653-1666.
27. Conrad C, Fernández-Del Castillo C. Preoperative evaluation and management of the pancreatic head mass. *J Surg Oncol*. 2013; 107:23-32.
28. Tang S, Huang G, Liu J, et al. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. *Eur J Radiol* 2011; 78: 142-150.
29. Wang Z, Chen JQ, Liu JL, et al. FDG-PET in diagnosis, staging and prognosis of pancreatic carcinoma: a meta-analysis. *World J Gastroenterol*. 2013; 19: 4808-4817
30. Rijkers AP, Valkema R, Duivenvoorden HJ, et al. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. *Eur J Surg Oncol*. 2014; 40: 794-804.
31. Hariharan D, Constantinides VA, Froeling FE, et al. The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers—a meta-analysis. *Eur J Surg Oncol*. 2010; 36:941-948.
32. Lu C, Xu CF, Wan XY, et al. Screening for pancreatic cancer in familial high-risk individuals: A systematic review. *World J Gastroenterol*. 2015 Jul 28;21(28):8678-86.
33. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol*. 2006 Jun;4(6):766-81
34. Canto MI, Hruban RH, Fishman EK, American Cancer of the Pancreas Screening (CAPS) Consortium. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology*. 2012 Apr;142(4):796-804;
35. Canto MI, Harinck F, Hruban RH, et al International Cancer of Pancreas Screening (CAPS) Consortium. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013 Mar;62(3):339-47.
36. <https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas>
37. Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. *Pancreatology*. 2016; 16:28-37.
38. Hammel P, Huguet F, Van Laethem J-L et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *J Clin Oncol* 2013;31(suppl): abstr LBA4003.
39. Sultana A, Smith CT, Cunningham D et al. Systematic review, including metaanalyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer*. 2007; 96: 1183-1190.
40. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988;80(10):751-755.
41. Klaassen DJ, MacIntyre JM, Catton GEi et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373-378.
42. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008;19:1592-1599
43. Loehrer PJ, Feng Y, Cardenas H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 2011; 29:4105-4112.
44. Esnaola NF, Chaudhary UB, O'Brien P, et al. Phase 2 trial of induction gemcitabine, oxaliplatin, and cetuximab followed by selective capecitabine-based chemoradiation in patients with borderline resectable or unresectable locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2014; 88:837-844.
45. Moureau-Zabotto L, Phelip JM, Afchain P, et al. Concomitant administration of weekly oxaliplatin, fluorouracil continuous infusion, and radiotherapy after 2 months of gemcitabine and oxaliplatin induction in patients with locally advanced pancreatic cancer: a Groupe Coordinateur Multidisciplinaire en Oncologie phase II study. *J Clin Oncol*. 2008; 26:1080-1085.
46. Nakachi K, Furuse J, Kinoshita et al. A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2010; 66:527-534.
47. Wagener DJ, Hoogenraad WJ, Rougier P, et al. Results of a phase II trial of epirubicin and cisplatin (EP) before and after irradiation and 5-fluorouracil in locally advanced pancreatic cancer: an EORTC GITCCG study. *Eur J Cancer*. 1996; 32:1310-1313.

48. Kurt E, Kurt M, Kanat O, et al. Phase II study of induction chemotherapy with gemcitabine plus 5-fluorouracil followed by gemcitabine-based concurrent chemoradiotherapy for unresectable locally advanced pancreatic cancer. *Tumori*. 2006; 92:481–486.
49. Faisal F, Tsai HL, Blackford A, et al. Longer course of induction chemotherapy followed by chemoradiation favors better survival outcomes for patients with locally advanced pancreatic cancer. *Am J Clin Oncol*. 2016; 39:18–26.
50. Ke QH, Zhou SQ, Yang JY, et al. S-1 plus gemcitabine chemotherapy followed by concurrent radiotherapy and maintenance therapy with S-1 for unresectable pancreatic cancer. *World J Gastroenterol*. 2014; 20:13987–1392.
51. Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol*. 2007;25(3):326–31.
52. Hammel P, Huguet F, van Laethem JL, LAP07 Trial Group. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA*. 2016; 315:1844–1853.
53. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol*. 2008; 26:3487–3495.
54. Stessin AM, Meyer JE, Sherr DL. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *Int J Radiat Oncol Biol Phys*. 2008; 72:1128–1133.
55. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol*. 2015;191:7–16.
56. Motoi F, Kosuge T, Ueno H, et al. Study Group of Preoperative Therapy for Pancreatic Cancer (Prep) and Japanese Study Group of Adjuvant Therapy for Pancreatic cancer (JSAP). Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol*. 2019; 49:190–194.
57. Neoptolemos JP, Stocken DD, Friess H, et al, and the European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004; 350: 1200–1210.
58. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA*. 2013; 310: 1473–1481.
59. Neoptolemos JP, Stocken DD, Bassi C, et al, European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; 304: 1073–81.
60. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389(10073):1011–1024.
61. Uesaka K, Boku N, Fukutomi A, et al. JASPAC 01 Study Group. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016; 388 :248–257.
62. Sinn M, Bahra M, Liersch T, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. *J Clin Oncol*. 2017; 35:3330–3337.
63. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA*. 2008; 299:1019–1026.
64. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol*. 2011; 18:1319–1326.
65. Li CP, Chao Y, Chi KH, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. *Int J Radiat Oncol Biol Phys* 2003; 57:98–104
66. Mukherjee S, Hurt CN, Bridgewater J et al. Gemcitabine-based or capecitabine based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2013; 14: 317–326.
67. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol*. 2016; 17:801–810.
68. Suker M, Nuyttens JJ, Groot Koerkamp B, et al. FOLFIRINOX and radiotherapy for locally advanced pancreatic cancer: A cohort study. *J Surg Oncol*. 2018; 118:1021–1026.
69. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985; 120:899–903.
70. Klinkenbijn JH, Jeekel J, Sahnoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection

- of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999; 230:776-784.
71. Neoptolemos JP, Dunn A, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001;358 :1576-1585.
 72. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation +5- fluorouracil: the Gastrointestinal Tumor Study Group. *Cancer*. 1981; 48:1705-1710.
 73. Moertel CG, Childs DS, Reitemeier RJ, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet*. 1969; 2(7626):865-867.
 74. Goodman, KA., Folkert, MR. (2013). Contouring Guidelines for Pancreatic Adenocarcinoma. In Y.L. Nancy, & J.L. Jiade (Eds.), *Target Volume Delineation and Field Setup* (1st ed., pp 127-141). Berlin: Springer.
 75. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*.2007;25:1960-1966.
 76. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-Directed Intergroup Trial S0205. *J Clin Oncol*. 2010;28:3605-3610.
 77. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2005; 23:8033-8040.
 78. Kindler HL, Niedzwiecki D, Hollis D, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis of Cancer and Leukemia Group B (CALGB). *J Clin Oncol* (Meeting Abstracts). 2007; 25:4508.
 79. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009; 27:2231-2237.
 80. Kindler HL, Richards DA, Garbo LE, et al. A randomized placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. *Ann Oncol*. 2012; 23:2834-2842.
 81. Philip PA, Goldman B, Ramanathan RK, et al. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (SWOG S0727). *Cancer*. 2014; 120:2980-2985.
 82. Sperti C, Moletta L, Patanè G. Metastatic tumors to the pancreas: The role of surgery. *World J Gastrointest Oncol*. 2014; 6:381-92.
 83. Nakamura E, Shimizu M, Itoh T, Manabe T. Secondary tumors of the pancreas: clinicopathological study of 103 autopsy cases of Japanese patients. *Pathol Int*. 2001; 51:686-90.
 84. Adler H, Redmond CE, Heneghan HM, et al. Pancreatic resection for metastatic disease: a systematic review. *Eur J Surg Oncol*. 2014 ;40:379-86.
 85. The European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut*. 2018; 67:789-804.
 86. Jana T, Shroff J, Bhutani MS. Pancreatic cystic neoplasms: Review of current knowledge, diagnostic challenges, and management options. *J Carcinog*. 2015; 14:3