



## BÖLÜM 58

### Pankreas Adenokarsinomunda Neoadjuvan Tedavinin Yeri

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#### ÖZET

Pankreas adenokarsinomunda (PDAK) neoadjuvan tedavinin (NAT) rolü tartışmalıdır. Diğer gastrointestinal kanserlerde NAT tedavi sürecinin ayrılmaz bir parçası olmuştur. PDAK NAT'ın rutin tedavinin bir parçası olamamasının nedenleri eskiden kullanılan kemoterapi ajanlarının etkisizliği, radyolojik yöntemlerin tedavi yanıtını değerlendirmedeki yetersizlikleri, NAT sonrası patolojik tam yanıt (pTY) elde edilen hastaların az olması olarak sıralanabilir. Son dönemde gelişen kemoterapi rejimleri, NAT sonrası değerlendirmede radyomiklerin kullanımı, NAT sonrası hasta sağkalım artışı, NAT kullanımının NCCN kılavuzlarında yer almasına ve kullanımının yaygınlaşmasına yol açmaktadır.

#### Giriş

Pankreas adenokarsinomunda (PDAK) neoadjuvan tedavinin (NAT) rolü tartışmalıdır. Diğer gastrointestinal kanserlerde NAT tedavi sürecinin ayrılmaz bir parçası olmuştur. Rezektabl mide kanserinde NAT'nin sağkalım avantajı faz 3 randomize kontrollü çalışmalarda ortaya konmuştur. [1-3] Özefagus kanserinde neoadjuvan kemoradyoterapi (NKRT), rezektabl hastalık için standart tedavi yöntemidir. Bu yöntem artmış genel sağ kalım (GS), hastaliksız sağ kalım (HS), patolojik tam yanıt (pTY) ve R0 rezeksiyon oranı ile ilişkilidir.

[4-6] Rezektabl rektum kanserinde NAT standart tedavinin bir parçası olmuştur. Hastaların büyük bir kısmında ameliyat öncesi evrenin azalmasına yol açmaktadır. Yapılan çalışmalarda hastaların %10-38'in arasında bildirilen oranlarda pTYa ulaştığı gösterilmiştir.[7-11] Aynı zamanda neoadjuvan tedavi sonrası klinik olarak tam yanıt gösteren bir hasta grubu da mevcuttur[12, 13]. Bu cesaret verici veriler, rektum kanseri için organ koruyucu tedavilere bile izin veren yeni terapötik yaklaşımların geliştirilmesine yol açmış olsa da bu PDAK'a taşınmamıştır. Pankreas kanserinde çeşitli engeller NAT uygulamasını sınırlamıştır. Bu

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yan kombinasyon tedavileri, gelecekte PDAK için NAT'ta immünoterapiye bir rol verebilir.

## Kaynaklar

- Cunningham, D., Allum, W. H., Stenning, S. P. ve ark., *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer*. *N Engl J Med*, 2006. **355**(1): p. 11-20.
- Al-Batran, S.E., Homann, N., Pauligk, C., ve ark., *Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial*. *Lancet*, 2019. **393**(10184): p. 1948-1957.
- Al-Batran, S.E., Hofheinz, R. D., Pauligk, C., ve ark., *Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial*. *Lancet Oncol*, 2016. **17**(12): p. 1697-1708.
- Oppedijk, V., Van der Gaast, A., van Lanschot, J. J., ve ark., *Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials*. *J Clin Oncol*, 2014. **32**(5): p. 385-91.
- van Hagen, P., Hulshof, M. C., van Lanschot, J. J., ve ark., *Preoperative chemoradiotherapy for esophageal or junctional cancer*. *N Engl J Med*, 2012. **366**(22): p. 2074-84.
- Shapiro, J., van Lanschot, J. J. B., Hulshof, M., ve ark., *Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial*. *Lancet Oncol*, 2015. **16**(9): p. 1090-1098.
- Das, P., Skibber, J. M., Rodriguez-Bigas, M. A., ve ark., *Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer*. *Cancer*, 2007. **109**(9): p. 1750-57.
- Collette, L., Bosset, J. F., den Dulk, M., ve ark., *Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group*. *J Clin Oncol*, 2007. **25**(28): p. 4379-86.
- Smith, K.D., Tan, D., Das, P., ve ark., *Clinical significance of acellular mucin in rectal adenocarcinoma patients with a pathologic complete response to preoperative chemoradiation*. *Ann Surg*, 2010. **251**(2): p. 261-4.
- Shivnani, A.T., Small, W., Jr., Stryker, S. J., ve ark., *Preoperative chemoradiation for rectal cancer: results of multimodality management and analysis of prognostic factors*. *Am J Surg*, 2007. **193**(3): p. 389-93; discussion 393-4.
- Petrelli, F., Trevisan, F., Cabiddu, M., ve ark., *Total Neoadjuvant Therapy in Rectal Cancer: A Systematic Review and Meta-analysis of Treatment Outcomes*. *Ann Surg*, 2020. **271**(3): p. 440-448.
- Habr-Gama, A., Perez, R. O., Nadalin, W., ve ark., *Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results*. *Ann Surg*, 2004. **240**(4): p. 711-7; discussion 717-8.
- Smith, J.J., Strombom, P., Chow, O. S., ve ark., *Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy*. *JAMA Oncol*, 2019. **5**(4): p. e185896.
- Burriss, H.A., 3rd, Moore, M. J., Andersen, J., ve ark., *Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial*. *J Clin Oncol*, 1997. **15**(6): p. 2403-13.
- Ferrone, C.R., Marchegiani, G., Hong, T. S., ve ark., *Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer*. *Ann Surg*, 2015. **261**(1): p. 12-7.
- Wagner, M., Antunes, C., Pietrasz, D., ve ark., *CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma*. *Eur Radiol*, 2017. **27**(7): p. 3104-3116.
- He, J., Blair, A. B., Groot, V. P., ve ark., *Is a Pathological Complete Response Following Neoadjuvant Chemoradiation Associated With Prolonged Survival in Patients With Pancreatic Cancer?* *Ann Surg*, 2018. **268**(1): p. 1-8.
- Ychou, M., Conroy, T., Seitz, J. F., ve ark., *An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/ 5-fluorouracil every 2 weeks in patients with advanced solid tumors*. *Ann Oncol*, 2003. **14**(3): p. 481-9.
- Macedo, F.I., Ryon, E., Maithel, S. K., ve ark., *Survival Outcomes Associated With Clinical and Pathological Response Following Neoadjuvant FOLFIRINOX or Gemcitabine/Nab-Paclitaxel Chemotherapy in Resected Pancreatic Cancer*. *Ann Surg*, 2019. **270**(3): p. 400-413.
- Tempero, M.A., Malafa, M. P., Al-Hawary, M., ve ark., *Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology*. *J Natl Compr Canc Netw*, 2021. **19**(4): p. 439-457.
- Li, D., Xie, K., Wolff, R., ve ark., *Pancreatic cancer*. *Lancet*, 2004. **363**(9414): p. 1049-57.
- Conroy, T., Paillet, B., François, E., ve ark., *Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study*. *J Clin Oncol*, 2005. **23**(6): p. 1228-36.
- Conroy, T., Desseigne, F., Ychou, M., ve ark., *FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer*. *N Engl J Med*, 2011. **364**(19): p. 1817-25.
- Von Hoff, D.D., Ramanathan, R. K., Borad, M. J., ve ark., *Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial*. *J Clin Oncol*, 2011. **29**(34): p. 4548-54.
- Von Hoff, D.D., Ervin, T., Arena, F. P., ve ark., *Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine*. *N Engl J Med*, 2013. **369**(18): p. 1691-703.
- Chiorean, E.G., Von Hoff, D. D., Reni, M., ve ark., *CA19-9 decrease at 8 weeks as a predictor of overall survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in*

- patients with metastatic pancreatic cancer. *Ann Oncol*, 2016. **27**(4): p. 654-60.
27. Oettle, H., Neuhaus, P., Hochhaus, A., ve ark., *Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial*. *Jama*, 2013. **310**(14): p. 1473-81.
  28. Conroy, T., Hammel, P., Hebbar, M., ve ark., *FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer*. *N Engl J Med*, 2018. **379**(25): p. 2395-2406.
  29. Mayo, S.C., Gilson, M. M., Herman, J. M., ve ark., *Management of patients with pancreatic adenocarcinoma: national trends in patient selection, operative management, and use of adjuvant therapy*. *J Am Coll Surg*, 2012. **214**(1): p. 33-45.
  30. Merkow, R.P., Bilimoria, K. Y., Tomlinson, J. S., ve ark., *Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer*. *Ann Surg*, 2014. **260**(2): p. 372-7.
  31. Tee, M.C., Krajewski, A. C., Groeschl, R. T., ve ark., *Indications and Perioperative Outcomes for Pancreatectomy with Arterial Resection*. *J Am Coll Surg*, 2018. **227**(2): p. 255-269.
  32. Del Chiaro, M., Rangelova, E., Halimi, A., ve ark., *Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer*. *HPB (Oxford)*, 2019. **21**(2): p. 219-225.
  33. Michelakos, T., Pergolini, I., Castillo, C. F., ve ark., *Predictors of Resectability and Survival in Patients With Borderline and Locally Advanced Pancreatic Cancer who Underwent Neoadjuvant Treatment With FOLFIRINOX*. *Ann Surg*, 2019. **269**(4): p. 733-740.
  34. Rangelova, E., Wefer, A., Persson, S., ve ark., *Surgery Improves Survival After Neoadjuvant Therapy for Borderline and Locally Advanced Pancreatic Cancer: A Single Institution Experience*. *Ann Surg*, 2021. **273**(3): p. 579-586.
  35. Yoo, C., Shin, S. H., Kim, K. P., ve ark., *Clinical Outcomes of Conversion Surgery after Neoadjuvant Chemotherapy in Patients with Borderline Resectable and Locally Advanced Unresectable Pancreatic Cancer: A Single-Center, Retrospective Analysis*. *Cancers (Basel)*, 2019. **11**(3).
  36. Satoi, S., Yamamoto, T., Yamaki, S., ve ark., *Surgical indication for and desirable outcomes of conversion surgery in patients with initially unresectable pancreatic ductal adenocarcinoma*. *Ann Gastroenterol Surg*, 2020. **4**(1): p. 6-13.
  37. Hackert, T., Sachsenmaier, M., Hinz, U., ve ark., *Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With FOLFIRINOX Results in Resectability in 60% of the Patients*. *Ann Surg*, 2016. **264**(3): p. 457-63.
  38. Hosein, P.J., Macintyre, J., Kawamura, C., ve ark., *A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma*. *BMC Cancer*, 2012. **12**: p. 199.
  39. Boone, B.A., Steve, J., Krasinskas, A. M., ve ark., *Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer*. *J Surg Oncol*, 2013. **108**(4): p. 236-41.
  40. Faris, J.E., Blaszkowsky, L. S., McDermott, S., ve ark., *FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience*. *Oncologist*, 2013. **18**(5): p. 543-8.
  41. Christians, K.K., Tsai, S., Mahmoud, A., ve ark., *Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm?* *Oncologist*, 2014. **19**(3): p. 266-74.
  42. Panizza, A., Edil, B. H., Schulick, R. D., ve ark., *Neoadjuvant FOLFIRINOX application in borderline resectable pancreatic adenocarcinoma: a retrospective cohort study*. *Medicine (Baltimore)*, 2014. **93**(27): p. e198.
  43. Blazer, M., Wu, C., Goldberg, R. M., ve ark., *Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas*. *Ann Surg Oncol*, 2015. **22**(4): p. 1153-9.
  44. Khushman, M., Dempsey, N., Maldonado, J. C., ve ark., *Full dose neoadjuvant FOLFIRINOX is associated with prolonged survival in patients with locally advanced pancreatic adenocarcinoma*. *Pancreatol*, 2015. **15**(6): p. 667-73.
  45. Marthey, L., Sa-Cunha, A., Blanc, J. F., ve ark., *FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort*. *Ann Surg Oncol*, 2015. **22**(1): p. 295-301.
  46. Nanda, R.H., El-Rayes, B., Maithel, S. K., ve ark., *Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability*. *J Surg Oncol*, 2015. **111**(8): p. 1028-34.
  47. Sadot, E., Doussot, A., O'Reilly, E. M., ve ark., *FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma*. *Ann Surg Oncol*, 2015. **22**(11): p. 3512-21.
  48. Katz, M.H., Shi, Q., Ahmad, S. A., ve ark., *Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101*. *JAMA Surg*, 2016. **151**(8): p. e161137.
  49. Suker, M., Beumer, B. R., Sadot, E., ve ark., *FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis*. *Lancet Oncol*, 2016. **17**(6): p. 801-810.
  50. Peddi, P.F., Lubner, S., McWilliams, R., ve ark., *Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma*. *Jop*, 2012. **13**(5): p. 497-501.
  51. Gunturu, K.S., Yao, X., Cong, X., ve ark., *FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity*. *Med Oncol*, 2013. **30**(1): p. 361.
  52. Tinchon, C., Hubmann, E., Pichler, A., ve ark., *Safety and efficacy of neoadjuvant FOLFIRINOX treatment in a series of patients with borderline resectable pancreatic ductal adenocarcinoma*. *Acta Oncol*, 2013. **52**(6): p. 1231-3.
  53. Nitsche, U., Wenzel, P., Siveke, J. T., ve ark., *Resectability After First-Line FOLFIRINOX in Initially Unresectable Locally Advanced Pancreatic Cancer: A Single-Center Experience*. *Ann Surg Oncol*, 2015. **22** Suppl 3: p. S1212-20.
  54. Yoo, C., Kang, J., Kim, K. P., ve ark., *Efficacy and safety of neoadjuvant FOLFIRINOX for borderline resectable pancreatic adenocarcinoma: improved efficacy compared with gemcitabine-based regimen*. *Oncotarget*, 2017.

- 8(28): p. 46337-46347.
55. Barenboim, A., Lahat, G., Geva, R., ve ark., *Neoadjuvant FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer: An intention to treat analysis*. Eur J Surg Oncol, 2018. **44**(10): p. 1619-1623.
  56. Byun, Y., Han, Y., Kang, J. S., ve ark., *Role of surgical resection in the era of FOLFIRINOX for advanced pancreatic cancer*. J Hepatobiliary Pancreat Sci, 2019. **26**(9): p. 416-425.
  57. Kunzmann, V., Hartlapp, I., Scheurlen, M., ve ark., *Sequential neoadjuvant chemotherapy with nab-paclitaxel plus gemcitabine and FOLFIRINOX in locally advanced pancreatic cancer (LAPC): A PILOT study*. Journal of Clinical Oncology, 2013. **31**(15\_suppl): p. e15193-e15193.
  58. Reni, M., Balzano, G., Zanon, S., ve ark., *Phase 1B trial of Nab-paclitaxel plus gemcitabine, capecitabine, and cisplatin (PAXG regimen) in patients with unresectable or borderline resectable pancreatic adenocarcinoma*. Br J Cancer, 2016. **115**(3): p. 290-6.
  59. Hammel, P., Lacy, J., Portales, F., ve ark., *Phase II LAPACT trial of nab-paclitaxel (nab-P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPC)*. Journal of Clinical Oncology, 2018. **36**(4\_suppl): p. 204-204.
  60. Reni, M., Zanon, S., Balzano, G., ve ark., *A randomised phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma*. Eur J Cancer, 2018. **102**: p. 95-102.
  61. Takahashi, H., Akita, H., Ioka, T., ve ark., *Phase I Trial Evaluating the Safety of Preoperative Gemcitabine/nab-Paclitaxel With Concurrent Radiation Therapy for Borderline Resectable Pancreatic Cancer*. Pancreas, 2018. **47**(9): p. 1135-1141.
  62. Lee, J.L., Kim, S. C., Kim, J. H., ve ark., *Prospective efficacy and safety study of neoadjuvant gemcitabine with capecitabine combination chemotherapy for borderline-resectable or unresectable locally advanced pancreatic adenocarcinoma*. Surgery, 2012. **152**(5): p. 851-62.
  63. Katz, M.H., Fleming J.B., Bhosale, P., ve ark., *Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators*. Cancer, 2012. **118**(23): p. 5749-56.
  64. Kim, E.J., Ben-Josef, E., Herman, J. M., ve ark., *A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer*. Cancer, 2013. **119**(15): p. 2692-700.
  65. Motoi, F., Ishida, K., Fujishima, F., ve ark., *Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective multi-institutional phase 2 trial*. Ann Surg Oncol, 2013. **20**(12): p. 3794-801.
  66. Rose, J.B., Rocha, F. G., Alseidi, A., ve ark., *Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival*. Ann Surg Oncol, 2014. **21**(5): p. 1530-7.
  67. Sherman, W.H., Chu, K., Chabot, J., ve ark., *Neoadjuvant gemcitabine, docetaxel, and capecitabine followed by gemcitabine and capecitabine/radiation therapy and surgery in locally advanced, unresectable pancreatic adenocarcinoma*. Cancer, 2015. **121**(5): p. 673-80.
  68. Hammel, P., Huguët, F., van Laethem, J. L., ve ark., *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**(17): p. 1844-53.
  69. Fiore, M., Ramella, S., Valeri, S., ve ark., *Phase II study of induction chemotherapy followed by chemoradiotherapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer*. Sci Rep, 2017. **7**: p. 45845.
  70. Busquets, J., Fabregat, J., Verdagué, H., ve ark., *Initial Experience in the Treatment of "Borderline Resectable" Pancreatic Adenocarcinoma*. Cir Esp, 2017. **95**(8): p. 447-456.
  71. Eguchi, H., Yamada, D., Iwagami, Y., ve ark., *Prolonged Neoadjuvant Therapy for Locally Advanced Pancreatic Cancer*. Dig Surg, 2018. **35**(1): p. 70-76.
  72. Saito, K., Isayama, H., Sakamoto, Y., ve ark., *A phase II trial of gemcitabine, S-1 and LV combination (GSL) neoadjuvant chemotherapy for patients with borderline resectable and locally advanced pancreatic cancer*. Med Oncol, 2018. **35**(7): p. 100.
  73. Neoptolemos, J.P., Dunn, J. A., Stocken, D. D., ve ark., *Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial*. Lancet, 2001. **358**(9293): p. 1576-85.
  74. Keane, F.K., Wo, J. Y., Ferrone, C. R., ve ark., *Intraoperative Radiotherapy in the Era of Intensive Neoadjuvant Chemotherapy and Chemoradiotherapy for Pancreatic Adenocarcinoma*. Am J Clin Oncol, 2018. **41**(6): p. 607-612.
  75. Chapman, B.C., Gleisner, A., Rigg, D., ve ark., *Perioperative outcomes and survival following neoadjuvant stereotactic body radiation therapy (SBRT) versus intensity-modulated radiation therapy (IMRT) in pancreatic adenocarcinoma*. J Surg Oncol, 2018. **117**(5): p. 1073-1083.
  76. Kaissis, G., Ziegelmayer, S., Lohöfer, F., ve ark., *A machine learning model for the prediction of survival and tumor subtype in pancreatic ductal adenocarcinoma from preoperative diffusion-weighted imaging*. European Radiology Experimental, 2019. **3**(1): p. 41.
  77. Tanaka, M., Heckler, M., Mihaljevic, A. L., ve ark., *CT response of primary tumor and CA19-9 predict resectability of metastasized pancreatic cancer after FOLFIRINOX*. Eur J Surg Oncol, 2019. **45**(8): p. 1453-1459.
  78. Khorana, A.A., Mangu, P. B., Berlin, J., ve ark., *Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update*. J Clin Oncol, 2017. **35**(20): p. 2324-2328.
  79. Oettle, H., Post, S., Neuhaus, P., ve ark., *Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial*. Jama, 2007. **297**(3): p. 267-77.
  80. Neoptolemos, J.P., Palmer, D. H., Ghaneh, P., ve ark., *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): p. 1011-1024.
81. Mackay, T.M., Smits, F. J., Roos, D., ve ark., *The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis*. *HPB (Oxford)*, 2020. **22**(2): p. 233-240.
  82. Haeberle, L. ve I. Esposito, *Pathology of pancreatic cancer*. *Transl Gastroenterol Hepatol*, 2019. **4**: p. 50.
  83. Kitano, M., Yoshida, T., Itonaga, M., ve ark., *Impact of endoscopic ultrasonography on diagnosis of pancreatic cancer*. *J Gastroenterol*, 2019. **54**(1): p. 19-32.
  84. Verbeke, C., Löhr, M., Karlsson, J. S., ve ark., *Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties*. *Cancer Treat Rev*, 2015. **41**(1): p. 17-26.
  85. Mellon, E.A., Jin, W. H., Frakes, J. M., ve ark., *Predictors and survival for pathologic tumor response grade in borderline resectable and locally advanced pancreatic cancer treated with induction chemotherapy and neoadjuvant stereotactic body radiotherapy*. *Acta Oncol*, 2017. **56**(3): p. 391-397.
  86. Golcher, H., Brunner, T. B., Witzigmann, H., ve ark., *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**(1): p. 7-16.
  87. Talamonti, M.S., Small, W., Jr., Mulcahy, M. F., ve ark., *A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma*. *Ann Surg Oncol*, 2006. **13**(2): p. 150-8.
  88. Evans, D.B., Varadhachary, G. R., Crane, C. H., ve ark., *Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head*. *J Clin Oncol*, 2008. **26**(21): p. 3496-502.
  89. Heinrich, S., Pestalozzi, B. C., Schäfer, M., ve ark., *Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head*. *J Clin Oncol*, 2008. **26**(15): p. 2526-31.
  90. Turrini, O., Viret, F., Moureau-Zabotto, L., ve ark., *Neoadjuvant 5 fluorouracil-cisplatin chemoradiation effect on survival in patients with resectable pancreatic head adenocarcinoma: a ten-year single institution experience*. *Oncology*, 2009. **76**(6): p. 413-9.
  91. Tajima, H., Ohta, T., Kitagawa, H., ve ark., *Pilot study of neoadjuvant chemotherapy with gemcitabine and oral S-1 for resectable pancreatic cancer*. *Exp Ther Med*, 2012. **3**(5): p. 787-792.
  92. Sahani, D.V., Kambadakone, A., Macari, M., ve ark., *Diagnosis and management of cystic pancreatic lesions*. *AJR Am J Roentgenol*, 2013. **200**(2): p. 343-54.
  93. O'Reilly, E.M., Perelshteyn, A., Jarnagin, W. R., ve ark., *A single-arm, nonrandomized phase II trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma*. *Ann Surg*, 2014. **260**(1): p. 142-8.
  94. Grose, D., McIntosh, D., Jamieson, N., ve ark., *The role of induction chemotherapy + chemoradiotherapy in localised pancreatic cancer: initial experience in Scotland*. *J Gastrointest Oncol*, 2017. **8**(4): p. 683-695.
  95. Okano, K., Suto, H., Oshima, M., ve ark., *A Prospective Phase II Trial of Neoadjuvant S-1 with Concurrent Hypofractionated Radiotherapy in Patients with Resectable and Borderline Resectable Pancreatic Ductal Adenocarcinoma*. *Ann Surg Oncol*, 2017. **24**(9): p. 2777-2784.
  96. Motoi, F., Kosuge, T., Ueno, H., ve ark., *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**(2): p. 190-194.
  97. Varadhachary, G.R., Wolff, R. A., Crane, C. H., ve ark., *Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head*. *J Clin Oncol*, 2008. **26**(21): p. 3487-95.
  98. Casadei, R., Di Marco, M., Ricci, C., ve ark., *Neoadjuvant Chemoradiotherapy and Surgery Versus Surgery Alone in Resectable Pancreatic Cancer: A Single-Center Prospective, Randomized, Controlled Trial Which Failed to Achieve Accrual Targets*. *J Gastrointest Surg*, 2015. **19**(10): p. 1802-12.
  99. Tienhoven, G.V., Versteijne, E., Suker, M., ve ark., *Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial*. *Journal of Clinical Oncology*, 2018. **36**(18\_suppl): p. LBA4002-LBA4002.
  100. Labori, K.J., Lassen, K., Hoem, D., ve ark., *Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial*. *BMC Surg*, 2017. **17**(1): p. 94.
  101. Hozaeel, W., Pauligk, C., Homann, N., ve ark., *Randomized multicenter phase II/III study with adjuvant gemcitabine versus neoadjuvant/adjuvant FOLFIRINOX in resectable pancreatic cancer: The NEPAFOX trial*. *Journal of Clinical Oncology*, 2015. **33**(15\_suppl): p. TPS4152-TPS4152.
  102. Heinrich, S., Pestalozzi, B., Lesurtel, M., ve ark., *Adjuvant gemcitabine versus Neoadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study)*. *BMC Cancer*, 2011. **11**: p. 346.
  103. Sohal, D., McDonough, S. L., Ahmad, S. A., ve ark., *SWOG S1505: A randomized phase II study of perioperative mFOLFIRINOX vs. gemcitabine/nab-paclitaxel as therapy for resectable pancreatic adenocarcinoma*. *Journal of Clinical Oncology*, 2017. **35**(15\_suppl): p. TPS4152-TPS4152.
  104. Brahmer, J.R., Tykodi, S. S., Chow, L. Q., ve ark., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer*. *N Engl J Med*, 2012. **366**(26): p. 2455-65.
  105. Jiang, Y., Y. Li, ve B. Zhu, *T-cell exhaustion in the tumor microenvironment*. *Cell Death Dis*, 2015. **6**(6): p. e1792.
  106. Luo, G., Lu, Y., Jin, K., ve ark., *Pancreatic cancer: BRCA mutation and personalized treatment*. *Expert Rev Anti-cancer Ther*, 2015. **15**(10): p. 1223-31.
  107. Humphris, J.L., Patch, A. M., Nones, K., ve ark., *Hypermutation In Pancreatic Cancer*. *Gastroenterology*, 2017. **152**(1): p. 68-74.e2.

108. Nevala-Plagemann, C., M. Hidalgo, ve I. Garrido-Laguna, *From state-of-the-art treatments to novel therapies for advanced-stage pancreatic cancer*. Nat Rev Clin Oncol, 2020. **17**(2): p. 108-123.
109. Le, D.T., Durham, J. N., Smith, K. N., ve ark., *Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade*. Science, 2017. **357**(6349): p. 409-413.
110. Sohal, D.P.S., Kennedy, E. B., Khorana, A., ve ark., *Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update*. J Clin Oncol, 2018. **36**(24): p. 2545-2556.
111. Golan, T., Hammel, P., Reni, M., ve ark., *Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer*. N Engl J Med, 2019. **381**(4): p. 317-327.
112. Torphy, R.J., Y. Zhu, ve R.D. Schulick, *Immunotherapy for pancreatic cancer: Barriers and breakthroughs*. Ann Gastroenterol Surg, 2018. **2**(4): p. 274-281.