



## BÖLÜM 19

# Pankreas Kanserinde Radyoterapi

Düriye ÖZTÜRK<sup>1</sup>

Pankreas kanserinde radyoterapi (RT), cerrahi ve kemoterapiden sonra kullanımını sınırlı olsa da uygulanmaktadır. Metastatik olmayan pankreas kanserinde cerrahi rezeksiyon, en iyi tedavi şansını sunar. Ancak, hastaların sadece %15-20'sinin tanı anında rezeksiyon şansı vardır. Yaklaşık %40'ı uzak metastazlara sahiptir ve %30-40'ı lokal olarak ilerlemiş, inoperabl olarak kabul edilir. Lokal olarak ilerlemiş, rezeke edilemeyen pankreas kanseri olan hastalarda, özellikle çölyak ve superior mezenterik arterler ve bitişik yapılara tümör invazyonu vardır. Bu hastaların optimal yönetimi tartışmalıdır ve uluslararası kabul görmüş standart bir yaklaşım yoktur. Terapötik seçenekler arasında tek başına radyasyon tedavisi, kemoradyoterapi (KRT) ve tek başına kemoterapi bulunur. Bazı durumlarda, ilk tedaviye yanıt sonrası rezeksiyon seçeneği yeterli olacaktır.

Rezektabilite değerlendirmesi preoperatif evreleme kontrastlı bilgisayarlı tomografi

(BT), manyetik rezonans (MRG) görüntüleme, endoskopik ultrason ve evreleme laparoskopisi gibi görüntüleme yöntemleriyle ve daha az sıklıkla laparotomi/laparoskopi sırasıyla yapılır. Pankreas kanserleri rezeke edilebilirlik açısından bitişik yapıların tutulumuna ve uzak metastazların varlığına göre rezeke edilebilir kanserden rezeke edilemez kansere doğru kategorize edilebilir (1). Amerikan Klinik Onkoloji Derneği kılavuzları (NCCN) (2) ve Abdominal Radyoloji Derneği/Amerikan Pankreas Dernekleri'nin konsensüs temelli kılavuzlarına göre rezektabilite kriterleri: Pankreas başı/unsinat lezyonlar için, superior mezenterik arterin (SMA)>180 derece tümör invazyonu, çölyak ekseni >180 derece tümör invazyonu, birinci jejunal SMA dalı ile solid tümör teması, tümör tutulumu oklüzyon veya yumuşak trombus nedeniyle superior mezenterik venin (SMV) tıkanması veya portal ven, SMV'ye en proksimal drenaj yapan jejunal dalı ile teması sayılabilir (3). Gövde ve kuyruk

<sup>1</sup> Dr. Öğr. Üyesi, Afyonkarahisar Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Radyasyon Onkolojisi AD., duriyeozturk07@gmail.com

malıdır. SBRT dozu 3 fraksiyon (toplam doz 30-45 Gy) veya 5 fraksiyon (toplam doz 25-45 Gy), hipofraksiyone yaklaşımla yüksek dozların verilmesidir. Deneyimli merkezlerde daha uzun süreli takiplerin bildirilmesi gereklidir (64). Daha yüksek dozlar kullanıldığında tedavi efektiftir ve normal doku kısıtlamalarına uyulmalıdır (65).

## Kaynaklar

- Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med*. 2014; 371:1039-1049. doi: 10.1056/NEJMra1404198.
- National Comprehensive Cancer Network (NCCN) (2021). NCCN clinical practice guidelines in oncology. 20/12/2021 tarihinde [https://www.nccn.org/guidelines/category\\_1](https://www.nccn.org/guidelines/category_1) adresinden ulaşılmıştır.
- Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. *Radiology*. 2014;270(1):248-260. doi: 10.1148/radiol.13131184.
- Seufferlein T, Bachet JB, Van Cutsem E, et al. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(7):VII33-VII40. doi: 10.1093/annonc/mds224.
- Khorana AA, Mangu PB, Berlin J, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(21):2541-2556. doi: 10.1200/JCO.2016.67.5553.
- Yamada S, Fujii T, Sugimoto H, et al. Aggressive surgery for borderline resectable pancreatic cancer: evaluation of National Comprehensive Cancer Network guidelines. *Pancreas*. 2013;42(6):1004-1010. doi: 10.1200/JCO.2016.67.5553.
- Balaban EP, Mangu PB, Khorana AA, et al. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(22):2654-2668. doi: 10.1200/JCO.2016.67.5553.
- Tsai S, George B, Wittmann D, et al. Importance of Normalization of CA19-9 Levels Following Neoadjuvant Therapy in Patients With Localized Pancreatic Cancer. *Ann Surg*. 2020;271(4):740-747. doi: 10.1097/SLA.0000000000003049.
- Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm--general principles. *Nat Clin Pract Oncol*. 2007;4:86-100. doi: 10.1038/ncponc0714.
- Palta M, Godfrey D, Goodman KA, et al. Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol*. 2019;9(5):322-332. doi: 10.1016/j.prro.2019.06.016.
- Marthey L, Sa-Cunha A, Blanc JF, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. *Ann Surg Oncol*. 2015;22(1):295-301. doi: 10.1245/s10434-014-3898-9.
- 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(6):801-810. doi: 10.1016/S1470-2045(16)00172-8.
- 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(8):1705-1710. doi:10.1002/1097-0142(19811015)48:8<1705::aid-cnrc2820480803>3.0.co;2-4.
- Cohen SJ, Dobelbower R Jr, Lipsitz S, et al. A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. *Int J Radiat Oncol Biol Phys*. 2005;62(5):1345-1350. doi: 10.1016/j.ijrobp.2004.12.074.
- Sultana A, Tudur Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer*. 2007;96(8):1183-1190. doi: 10.1038/sj.bjc.6603719.
- Huguët F, Girard N, Guerche CS-E, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. *J Clin Oncol*. 2009;27(13):2269-2277. doi: 10.1200/JCO.2008.19.7921.
- Krzyzanowska MK, Weeks JC, Earle CC. Treatment of locally advanced pancreatic cancer in the real world: population-based practices and effectiveness. *J Clin Oncol*. 2003;21(18):3409-3414. doi: 10.1200/JCO.2003.03.007.
- Hurt CN, Falk S, Crosby T, et al. Long-term results and recurrence patterns from SCALOP: a phase II randomised trial of gemcitabine- or capecitabine-based chemoradiation for locally advanced pancreatic cancer. *Br J Cancer*. 2017;116:1264-1270. doi: 10.1038/bjc.2017.95.
- Brasiuniene B, Juozaityte E. The effect of combined treatment methods on survival and toxicity in patients with pancreatic cancer. *Medicina (Kaunas)*. 2007; 43(9):716-725. PMID: 17986845.
- 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(4):317-326. doi: 10.1016/S1470-2045(13)70021-4.
- 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(9):1592-1599. doi: 10.1093/annonc/mdn281.
22. Hammel P, Huguet F, van Laethem JL, et al. 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):1844-1853. doi: 10.1001/jama.2016.4324.
  23. Reyngold M, O'Reilly EM, Varghese AM, et al. Association of Ablative Radiation Therapy With Survival Among Patients With Inoperable Pancreatic Cancer. *JAMA Oncol.* 2021;7(5):735-738. doi: 10.1001/jamaoncol.2021.0057.
  24. 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):326-331. doi: 10.1200/JCO.2006.07.5663.
  25. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer.* 2007;110(1):47-55. doi: 10.1002/cncr.22735.
  26. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2008;72(3):678. doi: 10.1016/j.ijrobp.2008.01.051.
  27. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2010;78(3):735-742. doi: 10.1016/j.ijrobp.2009.08.046.
  28. Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J Gastrointest Surg.* 2010;14(10):1547-1559. doi: 10.1007/s11605-010-1323-7.
  29. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys.* 2013;86(3):516-522. doi: 10.1016/j.ijrobp.2013.02.022.
  30. Polistina F, Costantin G, Casamassima F, et al. Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. *Ann Surg Oncol.* 2010;17(8):2092-2101. doi: 10.1245/s10434-010-1019-y.
  31. MHG, Shi Q, Meyers JP, et al. Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. *J Clin Oncol.* 2021;39S:ASCO #377
  32. Ghaneh P, Palmer DH, Cicconi S, et al. ESPAC-5F: Four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer. *J Clin Oncol.* 2020;38S:ASCO #4505.
  33. Moningi S, Marciscano AE, Rosati LM, et al. Stereotactic body radiation therapy in pancreatic cancer: the new frontier. *Expert Rev Anticancer Ther.* 2014;14(12):1461-1475. doi: 10.1586/14737140.2014.952286.
  34. Reni M, Panucci MG, Ferreri AJ, et al. Effect on local control and survival of electron beam intraoperative irradiation for resectable pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2001; 50(3):651-658. doi: 10.1016/s0360-3016(01)01470-5.
  35. Cai S, Hong TS, Goldberg SI, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. *Cancer.* 2013;119(23):4196-4204. doi: 10.1002/cncr.28329.
  36. Ruano-Ravina A, Almazán Ortega R, Guedea F. Intraoperative radiotherapy in pancreatic cancer: a systematic review. *Radiother Oncol.* 2008; 87(3):318-325. doi: 10.1016/j.radonc.2007.12.002.
  37. Gunderson LL, Martin JK Jr, Earle JD, et al. Intraoperative and external beam irradiation with or without resection: Mayo pilot experience. *Mayo Clin Proc.* 1984;59(10):691-699. doi: 10.1016/s0025-6196(12)62058-8.
  38. Mohiuddin M, Regine WF, Stevens J, et al. Combined intraoperative radiation and perioperative chemotherapy for unresectable cancers of the pancreas. *J Clin Oncol.* 1995;13(11):2764-2768. doi:10.1200/JCO.1995.13.11.2764.
  39. Roldan GE, Gunderson LL, Nagorney DM, et al. External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. *Cancer.* 1988;61(6):1110-1116. doi: 10.1002/1097-0142(19880315)61:6<1110::aid-cncr2820610610>3.0.co;2-6.
  40. Ashman JB, Moss AA, Rule WG, et al. Preoperative chemoradiation and IOERT for unresectable or borderline resectable pancreas cancer. *J Gastrointest Oncol.* 2013;4(4):352-360. doi: 10.3978/j.issn.2078-6891.2013.006.
  41. Jingu K, Tanabe T, Nemoto K, et al. Intraoperative radiotherapy for pancreatic cancer: 30-year experience in a single institution in Japan. *Int J Radiat Oncol Biol Phys.* 2012;83(4):e507-511. doi: 10.1016/j.ijrobp.2012.01.024.
  42. Palta M, Willett C, Czito B. The role of intraoperative radiation therapy in patients with pancreatic cancer. *Semin Radiat Oncol.* 2014;24(2):126-131. doi: 10.1016/j.semradonc.2013.11.004.
  43. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg.* 1985;120(8):899-903. doi: 10.1001/archsurg.1985.01390320023003.

44. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004;350(12):1200-1210. doi: 10.1056/NEJMoa032295.
45. Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. *Int J Radiat Oncol Biol Phys.* 2005;61(4):965-966. doi: 10.1016/j.ijrobp.2004.11.018.
46. Van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol.* 2010;28(29):4450-4456. doi: 10.1200/JCO.2010.30.3446.
47. Klinkenbijnl 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(6):776-782. doi: 10.1097/0000658-199912000-00006.
48. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol.* 2008;26(21):3503-3510. doi: 10.1200/JCO.2007.15.8469.
49. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). *J Clin Oncol.* 2008;26(21):3511-3516. doi: 10.1200/JCO.2007.15.8782.
50. CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol.* 2010;17(4):981-990. doi: 10.1245/s10434-009-0743-7.
51. Zimmermann FB, Jeremic B, Lersch C, et al. Dose escalation of concurrent hypofractionated radiotherapy and continuous infusion 5-FU- chemotherapy in advanced adenocarcinoma of the pancreas. *Hepatogastroenterology.* 2005;52(61):246-250. PMID: 15783041.
52. Combs SE, Habermehl D, Kessel K, et al. Intensity modulated radiotherapy as neoadjuvant chemoradiation for the treatment of patients with locally advanced pancreatic cancer. Outcome analysis and comparison with a 3D-treated patient cohort. *Strahlenther Onkol.* 2013;189(9):738-744. doi: 10.1007/s00066-013-0391-5.
53. Crane CH, Antolak JA, Rosen II, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. *Int J Gastrointest Cancer.* 2001;30(3):123-132. doi: 10.1385/IJGC:30:3:123.
54. Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys.* 2004;59(2):445-453. doi: 10.1016/j.ijrobp.2003.11.003.
55. Spalding AC, Jee KW, Vineberg K, et al. Potential for dose- escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. *Med Phys.* 2007;34(2):521-529. doi: 10.1118/1.2426403.
56. Bittner MI, Grosu AL, Brunner TB. Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer - a systematic review. *Radiother Oncol.* 2015;114(1):117-121. doi: 10.1016/j.radonc.2014.11.043.
57. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys.* 2011;79(1):158-162. doi: 10.1016/j.ijrobp.2009.10.043.
58. 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(9):1019-1026. doi: 10.1001/jama.299.9.1019.
59. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2007;68(3):801-808. doi: 10.1016/j.ijrobp.2006.12.053.
60. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol.* 2020;38(16):1763-1773. doi: 10.1200/JCO.19.02274.
61. Katz MH, Crane CH, Varadhachary G. Management of borderline resectable pancreatic cancer. *Semin Radiat Oncol.* 2014;24(2):105-112. doi: 10.1016/j.semradonc.2013.11.006.
62. Katz MH, Shi Q, Ahmad SA, et al. 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):e161137. doi: 10.1001/jamasurg.2016.1137.
63. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: A phase 2 clinical trial. *JAMA Oncol.* 2018;4(7):963-969. doi: 10.1001/jamaoncol.2018.0329.
64. Koay EJ, Hanania AN, Hall WA, et al. Dose-escalated radiation therapy for pancreatic cancer: a simultaneous integrated boost approach. *Pract Radiat Oncol.* 2020;10(6):e495-e507. doi: 10.1016/j.prro.2020.01.012.
65. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer.* 2009;115(3):665-672. doi: 10.1002/cncr.24059.