

Bölüm 9

HEPATOSELLÜLER KARSİNOM TANISINDA MOLEKÜLER GÖRÜNTÜLEME YÖNTEMLERİ

Göksel ALÇIN¹
Cihan GÜNDOĞAN²

GİRİŞ

Moleküler görüntüleme, moleküler biyoloji ve konvansiyonel tıbbi görüntülemenin çekirdeğinde yer alan ve fizik, kimya, biyoloji, farmakoloji, genomik ve mühendislik gibi farklı disiplinlerin oluşturduğu bir alandır. Son yıllarda laboratuvar ve klinik düzeyde iki ana faktör moleküler görüntüleme alanının yükselişini sağlamıştır; özellikle kanser olmak üzere çeşitli hastalıkların patogenezinde rol oynayan ana moleküler mekanizmaların daha iyi anlaşılması ve görüntüleme teknolojilerinin sürekli artan gelişimi. Kanser örneğinde olduğu gibi, hem hücresel hem de mikroçevresel düzeyde meydana gelen metabolik değişimler, ayrıca hastalıkların hücresel düzeyde belirteçleri moleküler görüntüleme için umut verici hedefler haline gelmiştir. Bu geniş çalışma alanında floresan görüntülemeden nükleer görüntüleme ve manyetik rezonansa kadar çok geniş bir yelpazede çeşitli görüntüleme yöntemleri geliştirilmiştir. Onkolojik nükleer tıp özelinde ise kanserleşen hücrede meydana gelen metabolik değişiklikler, reseptörlerdeki up-regülasyonlar, buna bağlı mikroçevrede meydana gelebilecek neovaskülarizasyon ya da hipoksi gibi durumlar göz önünde bulundurularak moleküler düzeyde hücreler hedeflenerek görüntü oluşturulmaktadır. Günümüzde teknolojinin hızlı ilerlemesine paralel olarak Nükleer Tıpta da birçok yeni görüntüleme ajanı, daha iyi görüntüleme yapabilen cihazlar geliştirilmekte olup Nükleer tıp

görüntüleme ve tedavi seçenekleri gün geçtikçe daha etkin rol oynamaktadır.

HEPATOSELLÜLER KARSİNOM

Primer karaciğer maligniteleri dünya çapında en sık teşhis edilen altıncı kanser ve kansere bağlı ölümlerin dördüncü önde gelen nedenidir. 2018 yılında 841.000 yeni vaka ve 782.000 kansere bağlı ölüm görülmüştür. Hepatosellüler karsinom (HCC) primer karaciğer kanser vakalarının %75-85'ini oluşturmakta olup en sık görülen tipidir. Afrika ve Asya'da en sık risk faktörü hepatit B ve hepatit C gibi kronik viral enfeksiyonlara bağlı gelişen siroz iken Amerika Birleşik Devletleri (ABD) gibi ülkelerde non-alkolik steatohepatit (NASH) önde gelen sebepler arasındadır. Alkol ve sigara tüketimi, aflatoksin maruziyeti, tip 2 DM ve obezite ise HCC gelişiminde etkenler arasında kabul edilmektedir (1,2). İnsidansı ve ölüm oranı ABD'de yıllar içerisinde artış gözlenmiştir (3).

HCC tanısı çoğunlukla görüntüleme çalışmalarına ve laboratuvar testlerine dayanmakta olup HCC hastalarının tanı, tedavi planlaması, yönetimi ve takibinin tüm aşamalarında kullanılan ultrasonografi (USG), bilgisayarlı tomografi (BT), manyetik rezonans görüntüleme (MRG) ve moleküler görüntüleme yöntemi olan pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) gibi görüntüleme yöntemleri bulunmaktadır (4). HCC'li hastaları asemptomatik iken ve karaciğer

¹ Uzm. Dr., Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi, Nükleer Tıp Kliniği, gokselalcin@hotmail.com.tr

² Uzm. Dr., Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi, Nükleer Tıp Kliniği, cihangd@hotmail.com

KAYNAKÇA

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
- Wong R.J., Cheung R., Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology* 2014;59:2188-2195.
- Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. *BMJ* 2018;362:k2817.
- Dimitroulis D, Damaskos C, Valsami S et al. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. *World J Gastroenterol* 2017;23:5282-5294.
- Ayuso C, Rimola J, Vilana R et al. Diagnosis and staging of hepatocellular carcinoma (HCC): current guidelines. *Eur J Radiol* 2018;101:72-81.
- European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236.
- Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016;150:835-853.
- Heimbach J, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358-380.
- Dhingra VK, Mahajan A, Basu S. Emerging clinical applications of PET based molecular imaging in oncology: the promising future potential for evolving personalized cancer care. *Indian J Radiol Imaging* 2015;25:332-341.
- Rigo P, Paulus P, Kaschten BJ, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1996;23:1641-1674.
- Khan N, Islam MM, Mahmood S, et al. 18F-fluorodeoxyglucose uptake in tumor. *Mymensingh Med J* 2011;20:332-342.
- Okazumi S, Isono K, Enomoto K, et al. Evaluation of liver tumours using fluorine-18-fluorodeoxyglucose PET: characterization of tumour and assessment of effect of treatment. *J Nucl Med* 1992;33:333-339.
- Godoy A, Ulloa V, Rodriguez F, et al. Differential subcellular distribution of glucose transporters GLUT-1-6 and GLUT9 in human cancer: ultrastructural localization of GLUT-1 and GLUT-5 in breast tumour tissues. *J Cell Physiol* 2006;207:614-627.
- Younes M, Lechago LV, Somoano JR, et al. Wide expression of the human erythrocyte glucose transporter Glut-1 in human cancers. *Cancer Res* 1996;56:1164-1167.
- Gwak GY, Yoon JH, Kim KM, et al. Hypoxia stimulates proliferation of human hepatoma cells through the induction of hexokinase II expression. *J Hepatol* 2005;42:358-364.
- Shiomi S, Nishiguchi S, Ishizu H, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. *Am J Gastroenterol* 2001;96:1877-1880.
- Gallagher BM, Fowler JS, Gutterson NI, et al. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [18F] 2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 1978;19:1154-1161.
- Nelson CA, Wang JQ, Leav I, et al. The interaction among glucose transport, hexokinase, and glucose-6-phosphatase with respect to 3H-2-deoxyglucose retention in murine tumor models. *Nucl Med Biol* 1996;23:533-541.
- Hofman MS and Hicks RJ. How we read oncologic FDG PET/CT. *Cancer Imaging* 2016;16:35.
- Basu S, Hess S, Nielsen Braad PE, et al. The basic principles of FDG-PET/CT imaging. *PET Clin* 2014;9:355-370.
- Higashi T, Saga T, Nakamoto Y, et al. Relationship between retention index in dual-phase (18) F-FDG PET, and hexokinase- II and glucose transporter-1 expression in pancreatic cancer. *J Nucl Med* 2002;43:173-180.
- Borst P, Evers R, Kool M et al. A family of drug transporters: the multidrug resistance-associated proteins. *J Natl Cancer Inst* 2000;92:1295-1302.
- Chan HS, Haddad G, Thorner PS, et al. P-glycoprotein expression as a predictor of the outcome of therapy for neuroblastoma. *N Engl J Med* 1991;325:1608-1614.
- Torizuka T, Tamaki N, Inokuma T, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med* 1995;36:1811-1817.
- Yamamoto Y, Nishiyama Y, Kameyama R, et al. Detection of hepatocellular carcinoma using 11C-choline PET: comparison with 18F-FDG PET. *J Nucl Med* 2008;49:1245-1248.
- Wang XY, Chen D, Zhang XS, et al. Value of 18F-FDG-PET/CT in the detection of recurrent hepatocellular carcinoma after hepatectomy or radiofrequency ablation: a comparative study with contrast-enhanced ultrasound. *J Dig Dis* 2013;14:433-438.
- Seo S, Hatano E, Higashi T, et al. P-glycoprotein expression affects 18F-fluorodeoxyglucose accumulation in hepatocellular carcinoma in vivo and in vitro. *Int J Oncol* 2009;34:1303-1312.
- Paudyal B, Paudyal P, Oriuchi N, et al. Clinical implication of glucose transport and metabolism evaluated by 18F-FDG PET in hepatocellular carcinoma. *Int J Oncol* 2008;33:1047-1054.
- Lee JD, Yang WI, Park YN, et al. Different glucose uptake and glycolytic mechanisms between hepatocellular carcinoma and intrahepatic mass-forming cholangiocarcinoma with increased (18)F-FDG uptake. *J Nucl Med* 2005;46:1753-1759.
- Ijichi H, Shirabe K, Taketomi A, et al. Clinical usefulness of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography for patients with primary liver cancer with special reference to rare histological types, hepatocellular carcinoma with sarcomatous change and combined hepatocellular and cholangiocarcinoma. *Hepatol Res* 2013;43:481-487.
- Kawamura E, Shiomi S, Kotani K, et al. Positioning of 18F-fluorodeoxyglucose-positron emission tomography imaging in the management algorithm of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014;29:1722-1727.
- Katyal S, Oliver JH, Peterson MS, et al. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000;216:698-703.

33. Uka K, Aikata H, Takaki S, et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* 2007;13:414-420.
34. Ho CL, Chen S, Yeung DW, et al. Dual-tracer PET/CT imaging in evaluation of metastatic hepatocellular carcinoma. *J Nucl Med* 2007;48:902-909.
35. Lee JE, Jang JY, Jeong SW, et al. Diagnostic value for extrahepatic metastases of hepatocellular carcinoma in positron emission tomography/computed tomography scan. *World J Gastroenterol* 2012;18:2979-2987.
36. Lin CY, Chen JH, Liang JA, et al. 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Radiol* 2012;81:2417-2422.
37. Seo HJ, Kim GM, Kim JH, et al. 18F-FDG PET/CT in hepatocellular carcinoma: detection of bone metastasis and prediction of prognosis. *Nucl Med Commun* 2015;36:226-233.
38. Sugiyama M, Sakahara H, Torizuka T, et al. 18F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. *J Gastroenterol* 2004;39:961-968.
39. Cho Y, Lee DH, Lee YB, et al. Does 18F-FDG positron emission tomography-computed tomography have a role in initial staging of hepatocellular carcinoma? *PLoS One* 2014;9:e105679.
40. Yoon KT, Kim JK, Kim DY, et al. Role of 18F-fluorodeoxyglucose positron emission tomography in detecting extrahepatic metastasis in pretreatment staging of hepatocellular carcinoma. *Oncology* 2007;72: 104-110.
41. Lee M, Jeon JY, Neugent ML, et al. 18F-Fluorodeoxyglucose uptake on positron emission tomography/computed tomography is associated with metastasis and epithelial-mesenchymal transition in hepatocellular carcinoma. *Clin Exp Metastasis* 2017;34:251-260.
42. Sung PS, Park HL, Yang K, et al. 18F-fluorodeoxyglucose uptake of hepatocellular carcinoma as a prognostic predictor in patients with sorafenib treatment. *Eur J Nucl Med Mol Imaging* 2018;45:384-391.
43. Ferda J, Ferdová E, Baxa J, et al. The role of 18F-FDG accumulation and arterial enhancement as biomarkers in the assessment of typing, grading and staging of hepatocellular carcinoma using 18F-FDG-PET/CT with integrated dual-phase CT angiography. *Anticancer Res* 2015;35:2241-2246.
44. Na SJ, Oh JK, Hyun SH et al. 18F-FDG PET/CT Can Predict Survival of Advanced Hepatocellular Carcinoma Patients: A Multicenter Retrospective Cohort Study. *J Nucl Med* 2017;58:730-736.
45. Lee JW, Paeng JC, Kang KW, et al. Prediction of tumor recurrence by 18F-FDG PET in liver transplantation for hepatocellular carcinoma. *J Nucl Med* 2009;50:682-687.
46. Sun DW, An L, Wei F, et al. Prognostic significance of parameters from pretreatment (18)F-FDG PET in hepatocellular carcinoma: a meta-analysis. *Abdom Radiol* 2016;41:33-41.
47. Lee JW, Oh JK, Chung YA, et al. Prognostic Significance of ¹⁸F-FDG Uptake in Hepatocellular Carcinoma Treated with Transarterial Chemoembolization or Concurrent Chemoradiotherapy: A Multicenter Retrospective Cohort Study. *J Nucl Med* 2016;57:509-516.
48. Lee JW, Hwang SH, Kim DY, et al. Prognostic Value of FDG Uptake of Portal Vein Tumor Thrombosis in Patients With Locally Advanced Hepatocellular Carcinoma. *Clin Nucl Med* 2017;42:e35-e40.
49. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transplant* 2011;17:S44-S57.
50. Viveiros A, Zoller H, Finkenstedt A. Hepatocellular carcinoma: when is liver transplantation oncologically futile? *Transl Gastroenterol Hepatol* 2017;2:63.
51. Ling LL, Hsu CC, Yong CC, et al. FDG-PET predicted unfavorable tumor histology in living donor liver transplant recipients: a retrospective cohort study. *Int J Surg* 2019;69:124-131.
52. Zeisel SH. Choline phospholipids: signal transduction and carcinogenesis. *Faseb J* 1993;7:551-557.
53. Chotipanich C, Kunawudhi A, Promteangtrong C, et al. Diagnosis of Hepatocellular Carcinoma Using C11 Choline PET/CT: Comparison with F18 FDG, ContrastEnhanced MRI and MDCT. *Asian Pac J Cancer Prev* 2016;17:3569-3573.
54. Kuang Y, Salem N, Corn DJ, et al. Transport and metabolism of radiolabeled choline in hepatocellular carcinoma. *Mol Pharm* 2010;7:2077-2092.
55. Castilla-Lievre MA, Franco D, Gervais P, et al. Diagnostic value of combining 11C-choline and 18F-FDG PET/CT in hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging* 2016;43:852-859.
56. Wong SC, Ngai WT, Choi FPT. Update on Positron Emission Tomography for Hepatocellular Carcinoma. *Hong Kong J Radiol* 2017;20:192-204.
57. Wu HB, Wang QS, Li BY, et al. F-18 FDG in conjunction with 11C-choline PET/CT in the diagnosis of hepatocellular carcinoma. *Clin Nucl Med* 2011;36:1092-1097.
58. Talbot JN, Gutman F, Fartoux L, et al. PET/CT in patients with hepatocellular carcinoma using [18F] fluorocholine: preliminary comparison with [18F] FDG PET/CT. *Eur J Nucl Med Mol Imaging*. 2006;33:1285-1289.
59. Lanza E, Donadon M, Felisaz P, et al. Refining the management of patients with hepatocellular carcinoma integrating 11C-choline PET/CT scan into the multidisciplinary team discussion. *Nucl Med Commun* 2017;38:826-836.
60. Hartenbach M, Weber S, Albert NL, et al. Evaluating Treatment Response of Radioembolization in Intermediate-Stage Hepatocellular Carcinoma Patients Using 18F-Fluoroethylcholine PET/CT. *J Nucl Med* 2015;56:1661-1666.
61. Chalaye J, Costentin CE, Luciani A, et al. Positron emission tomography/computed tomography with 18F-fluorocholine improve tumour staging and treatment allocation in patients with hepatocellular carcinoma. *J Hepatol* 2018;69:336-344.
62. Park JW, Kim JH, Kim SK, et al. A prospective evaluation of 18F-FDG and 11C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. *J Nucl Med* 2008;49:1912-1921.

63. Grassi I, Nanni C, Allegri V, et al. The clinical use of PET with (11)C-acetate. *Am J Nucl Med Mol Imaging* 2012;2:33-47.
64. Haug AR. Imaging of primary liver tumors with positron-emission tomography. *Q J Nucl Med Mol Imaging* 2017;61:292-300.
65. Filippi L, Schillaci O, Bagni O. Recent advances in PET probes for hepatocellular carcinoma characterization. *Expert Rev Med Devices* 2019;16:341-350.
66. Li S, Peck-Radosavljevic M, Ubl P, et al. The value of [11C]-acetate PET and [18F]-FDG PET in hepatocellular carcinoma before and after treatment with transarterial chemoembolization and bevacizumab. *Eur J Nucl Med Mol Imaging* 2017;44:1732-1741.
67. Ho CL, Yu SC, Yeung DW. 11C-acetate PET imaging in hepatocellular carcinoma and other liver masses. *J Nucl Med* 2003;44:213-221.
68. Larsson P, Arvidsson D, Björnstedt M, et al. Adding 11C-acetate to 18F-FDG at PET examination has an incremental value in the diagnosis of hepatocellular carcinoma. *Mol Imaging Radionucl Ther.* 2012;21:6-12.
69. Alçın G, Gündoğan C, Mutlu İN, et al. 68Ga-Prostate-Specific Membrane Antigen-11 PET/CT: Incidental Finding of a Vestibular Schwannoma. *Clin Nucl Med* 2019;44:883-885.
70. Kunikowska J, Kuliński R, Muylle K2, et al. 68Ga-Prostate-Specific Membrane Antigen-11 PET/CT: A New Imaging Option for Recurrent Glioblastoma Multiforme? *Clin Nucl Med* 2020;45:11-18.
71. Marafi F, Sasikumar A, Alfeeli M, et al. 18F-PSMA 1007 Uptake in Brain Metastases From Breast Cancer. *Clin Nucl Med* 2020;45:e77-e79.
72. Arçay A, Aydın F, Kutlu Ö, et al. Heterogeneous 68Ga-Prostate-Specific Membrane Antigen Uptake in the Left Upper Abdomen: Mesenchymal Tumor. *Clin Nucl Med* 2020;45:e108-e109.
73. Pozzessere C, Bassanelli M, Ceribelli A, et al. Renal Cell Carcinoma: the Oncologist Asks, Can PSMA PET/CT Answer? *Curr Urol Rep* 2019;20:68.
74. Lütje S, Gomez B, Cohnen J, et al. Imaging of Prostate-Specific Membrane Antigen Expression in Metastatic Differentiated Thyroid Cancer Using 68Ga-HBED-CC-PSMA PET/CT. *Clin Nucl Med* 2017;42:20-25.
75. Evans J, Malhotra M, Cryan J, et al. The therapeutic and diagnostic potential of the prostate specific membrane antigen/glutamate carboxypeptidase II (PSMA/GC-PII) in cancer and neurological disease. *Br J Pharmacol* 2016;173:3041-3079.
76. Virgolini I, Decristoforo C, Haug A, et al. Current status of theranostics in prostate cancer. *EJNMMI* 2018;45:471-495.
77. Kuyumcu S, Has-Simsek D, Iliaz R, et al. Evidence of Prostate-Specific Membrane Antigen Expression in Hepatocellular Carcinoma Using 68Ga-PSMA PET/CT. *Clin Nucl Med* 2019;44:702-706.
78. Kesler M, Levine C, HersHKovitz D, et al. 68Ga-PSMA is a novel PET-CT tracer for imaging of hepatocellular carcinoma: A prospective pilot study. *J Nucl Med* 2019;60:185-191.
79. Tolkach Y, Goltz D, Kremer A, et al. Prostate-specific membrane antigen expression in hepatocellular carcinoma: potential use for prognosis and diagnostic imaging. *Oncotarget* 2019;10:4149-4160.
80. Van de Wiele C, Sathekge M, de Spiegeleer B, et al. PSMA-Targeting Positron Emission Agents for Imaging Solid Tumors Other Than Non-Prostate Carcinoma: A Systematic Review. *Int J Mol Sci* 2019;20:4886.