

Bölüm 1

3 BOYUTLU YAZICILARIN KARACİĞER CERRAHİSİNDE VE DOKU MÜHENDİSLİĞİNDE KULLANIMI

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GİRİŞ

Karaciğer hastalıkları nedeniyle her yıl dünya genelinde yaklaşık iki milyon insan hayatını kaybetmektedir. Bu ölümlerin yarısı siroz komplikasyonlarından; kalan yarısı ise viral hepatitler ve hepatoselüler karsinomdan kaynaklanmaktadır. Siroz ve karaciğer kanseri nedeniyle gerçekleşen ölümlerin sayısı, tüm ölümlerin %3,5' ine denk gelmektedir. (1) Akut ve kronik karaciğer yetmezliğinde definitif tedavi yöntemi karaciğer naklidir. Karaciğerin ve safra yollarının primer benign ya da malign tümörleri, karaciğerin kistik hastalıkları ile karaciğer metastazları ise hepatik rezeksiyon endikasyonları arasında sayılabilir (2).

Son yıllarda bir takım öncül çalışmada, karaciğer hastalıklarının cerrahi tedavisinde 3D (üç boyutlu) yazılıların kullanımının geleneksel tedavi yöntemlerine katkılar sağladığına dair kanıtlar sunulmuştur (3,4,5). Bir takım çalışmalar ise karaciğer doku üretimi üzerine odaklanmıştır. 3D yazılıardan karaciğer cerrahisinde ve doku mühendisliği uygulamalarında yararlanmayı hedefleyen bu çalışmalar özünde iki ana gruba ayrılabilir: (6)

- 1) Hücrelerin yer almadığı 3D uygulamalar
- 2) Karaciğer hücrelerinin yer aldığı 3D biyobasım uygulamaları

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lit ettiği için ilaç araştırmalarında yararlı bulunmuştur (47,49). Özellikle hayvan modelleriyle toksisitesi değerlendirilemeyen ilaçların, insan hepatositleri barındıran hepatosit iskeleleri taşıyan farelerde denenmesi yoluyla potansiyel klinik riskler ve hepatotoksitesinin tahmin edilebilmesi mümkündür (50,51).

SONUÇ

3D baskıyla oluşturulmuş modellerin karaciğer hastalıklarının tedavisinde değişik amaçlarla kullanım şekillerine ilişkin literatür özetlenmiştir. Üç boyutlu yaklaşım; cerrahi ekiplere karaciğer cerrahisinin preoperatif aşamasında optimal cerrahi planlamayı yapma fırsatı sunmuştur. Hastalarda, cerrahi süresi kısalmış ve komplikasyon oranları düşmüştür. Bu modellerle medikal eğitimin değişik aşamasındaki öğrenciler, karaciğer anatomisini daha kolay bir şekilde öğrenebilmiştir. 3D biyoyazıcılarla oluşturulmuş iskele modelleri, doku mühendisliği uygulamalarına ciddi katkılar sunmuş ve bir gün yapay karaciğer üretimini sağlayarak donör yetersizliği kaynaklı ölümlere son vermeyi amaç edinmiş çabalara ön ayak olmuştur.

KAYNAKLAR

- Asrani SK, Devarbhavi H, Eaton J, Burden of liver diseases in the world. *J Hepatol.* 2019 Jan;70(1):151-171. doi: 10.1016/j.jhep.2018.09.014.
- Shishir K, Maithel, William R, Jarnagin, Jacques Belghiti.(2012) Chapter 90B - Hepatic resection for benign disease and for liver and biliary tumors. In William R. Jarnagin, Leslie H. Blumgart (Eds.), *Blumgart's Surgery of the Liver, Pancreas and Biliary Tract* (5th ed.), s. 1461-1511 W.B. Saunders,
- Zein NN, Hanouneh IA, Bishop PD, et al. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. *Liver Transpl* 2013;19:1304-1310. doi: 10.1002/lt.23729
- Igami T, Nakamura Y, Hirose T, et al. Application of a three-dimensional print of a liver in hepatectomy for small tumors invisible by intraoperative ultrasonography: Preliminary experience. *World J Surg* 2014;38:3163–3166. doi: 10.1007/s00268-014-2740-7.
- Watson RA. A low-cost surgical application of additive fabrication. *J Surg Educ* 2014;71:14–17. doi:10.1016/j.jsurg.2013.10.012
- Jing-Zhang Wang, Nan-Yan Xiong, Li-Zhen Zhao. Review fantastic medical implications of 3D-printing in liver surgeries, liver regeneration, liver transplantation and drug hepatotoxicity testing: A review, *International Journal of Surgery*, Volume 56, 2018, Pages 1-6, ISSN 1743-9191, <https://doi.org/10.1016/j.ijsu.2018.06.004>.
- Saeideh Kholgh Eshkalak, Erfan Rezvani Ghomi, Yunqian Dai, et al. The role of three-dimensional printing in healthcare and medicine, *Materials & Design*, Volume 194, 2020, 108940, ISSN 0264-1275, <https://doi.org/10.1016/j.matdes.2020.108940>.

8. O.G. Bhusnure, V.S. Gholve, B.K. Sugave, et al. 3D Printing & Pharmaceutical Manufacturing: Opportunities and Challenges, *International Journal of Bioassays*, 5 (2016) 4723. doi:10.21746/ijbio.2016.01.006.
9. J. Groll, T. Boland, T. Blunk, J.A. Burdick, et al. Biofabrication: Reappraising the definition of an evolving field, *Biofabrication*. 8 (2016). doi:10.1088/1758-5090/8/1/013001.
10. Y.Y. Yang, C.Q. Zhao, L.S. Wang, et al. A novel biopolymer device fabricated by 3D printing for simplifying procedures of pancreaticojejunostomy, *Mater. Sci. Eng. C*. 103 (2019) 109786. doi:10.1016/j.msec.2019.10978
11. Şahin, Kemal , Turan, Bülent Onur .Üç boyutlu yazıcı teknolojilerinin karşılaştırmalı analizi. *Stratejik ve Sosyal Araştırmalar Dergisi* 2 / 2 (Ağustos 2018): 97-116 . <https://doi.org/10.30692/sisad.441648>
12. Gross, BC, Erkal JL, Lockwood SY, et al. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. *Anal Chem* 2014;86(7):3240–3253. doi: 10.1021/ac403397r
13. Cui X, Boland T, D'Lima DD, Lotz MK. Thermal inkjet printing in tissue engineering and regenerative medicine. *Recent Pat Drug Deliv Formul* 2012;6(2):149 – 155. doi:10.2174/18722112800672949
14. Schubert C, van Langeveld MC, Donoso LA. Innovations in 3D printing: a 3D overview from optics to organs. *Br J Ophthalmol* 2014;98(2):159–161 doi: 10.1136/bjophthalmol-2013-304446
15. Banks J. Adding value in additive manufacturing: Researchers in the United Kingdom and Europe look to 3D printing for customization. *IEEE Pulse* 2013;4(6):22–26 doi: 10.1109/MPUL.2013.2279617
16. Hoy MB. 3D printing: making things at the library. *Med Ref Serv Q* 2013;32(1):94–99. doi: 10.1080/02763869.2013.749139
17. Klein GT, Lu Y, Wang MY. 3D printing and neurosurgery—ready for prime time? *World Neurosurg* 2013;80(3–4):233–235 doi: 10.1016/j.wneu.2013.07.009
18. Ventola CL. Medical Applications for 3D Printing: Current and Projected Uses. *P T. a peer-reviewed journal for formulary management* 2014 Oct;39(10):704-11. PMID: 25336867; PMCID: PMC4189697.
19. Mertz L. Dream it, design it, print it in 3-D: What can 3-D printing do for you? *IEEE Pulse* 2013;4(6):15–21 doi: 10.1109/MPUL.2013.2279616
20. 3D Print Exchange. National Institutes of Health (11/11/2020 tarihinde <https://3dprint.nih.gov/discover> adresinden ulaşılmıştır).
21. Benzoni E, Molaro R, Cedolini C, et al. Liver resection for HCC: analysis of causes and risk factors linked to postoperative complications. *Hepatogastroenterology* 2007; 54:186–189. PMID: 17419257
22. Cescon M, Vetrone G, Grazi GL, et al. Trends in perioperative outcome after hepatic resection: analysis of 1500 consecutive unselected cases over 20 years. *Ann Surg* 2009; 249:995–1002. doi:10.1097/sla.0b013e3181a63c74
23. Z. Baimakhanov, A. Soyama, M. Takatsuki, et al., Preoperative Simulation With a 3-Dimensional Printed Solid Model for One-Step Reconstruction of Multiple Hepatic Veins During Living Donor Liver Transplantation, *Liver TransPlant* 21 (2) (2015) 266-268. <https://doi.org/10.1002/lt.24019>
24. Xiang N, Fang C, Fan Y, Yang J, Zeng N, et al. Application of liver three-dimensional printing in hepatectomy for complex massive hepatocarcinoma with rare variations of portal vein: preliminary experience. *Int J Clin Exp Med*. 2015 Oct 15;8(10):18873-8. PMID: 26770510; PMCID: PMC4694410.

25. M.H. Samaan, B. Eghtesad, C. Quintini, et al., 3D printed liver models for precise resection of complex hepatic tumors, *Hepatology* 62 (2015) 626A.
26. Y. Oshiro, J. Mitani, T. Okada, et al., A novel three-dimensional print of liver vessels and tumors in hepatectomy, *Surg. Today* 47 (4) (2017) 521–524. <https://doi.org/10.1007/s00595-016-1383-8>
27. T. Igami, Y. Nakamura, T. Hirose, et al., Application of a three-dimensional print of a liver in hepatectomy for small tumors invisible by intraoperative ultrasonography: preliminary experience, *World J. Surg.* 38 (12) (2014) 3163–3166. <https://doi.org/10.1007/s00268-014-2740-7>
28. Witowski, J., Budzyński, A., Grochowska, A. et al. Decision-making based on 3D printed models in laparoscopic liver resections with intraoperative ultrasound: a prospective observational study. *Eur Radiol* 30, 1306–1312 (2020). <https://doi.org/10.1007/s00330-019-06511-2>
29. Soler L, Nicolau S, Pessaux P, et al. Real-time 3D image reconstruction guidance in liver resection surgery. *Hepatobiliary Surg Nutr.* 2014;3(2):73-81. doi:10.3978/j.issn.2304-3881.2014.02.03
30. Oldani G, Lacotte S, Orci LA, et al. Efficient nonarterialized mouse liver transplantation using 3-dimensional-printed instruments. *Liver Transpl.* 2016 Dec;22(12):1688-1696. doi: 10.1002/lt.24637. PMID: 27616447.
31. Damiati S, Küpcü S, Peacock M, et al. Acoustic and hybrid 3D-printed electrochemical biosensors for the real-time immunodetection of liver cancer cells (HepG2). *Biosens Bioelectron.* 2017 Aug 15;94:500-506. doi: 10.1016/j.bios.2017.03.045. Epub 2017 Mar 21. PMID: 28343102.
32. Gou, M., Qu, X., Zhu, W. et al. Bio-inspired detoxification using 3D-printed hydrogel nanocomposites. *Nat Commun* 5, 3774 (2014). <https://doi.org/10.1038/ncomms4774>
33. Yang T, Lin S, Xie Q, et al. Impact of 3D printing technology on the comprehension of surgical liver anatomy. *Surg Endosc.* 2019 Feb;33(2):411-417. doi: 10.1007/s00464-018-6308-8. Epub 2018 Jun 25. PMID: 29943060.
34. Kong X, Nie L, Zhang H, et al. Do 3D Printing Models Improve Anatomical Teaching About Hepatic Segments to Medical Students? A Randomized Controlled Study. *World J Surg.* 2016 Aug;40(8):1969-76. doi: 10.1007/s00268-016-3541-y. PMID: 27172803.
35. Yang T, Tan T, Yang J, et al. The impact of using three-dimensional printed liver models for patient education. *Journal of International Medical Research.* April 2018:1570-1578. doi:10.1177/0300060518755267
36. Guillemot F, Mironov V, Nakamura M, et al. Bioprinting is coming of age: report from the international conference on bioprinting and biofabrication in Bordeaux (3B'09) ,*Biofabrication* 2 <https://doi.org/10.1088/1758-5082/2/1/010201>
37. Bülbül A İl, Küçük S. Üç Boyutlu (3B) Biyobasına Bir Bakış ve Organ Basımı. *Turkiye Klinikleri Journal of Health Sciences* doi: 10.5336/healthsci.2019-72026
38. JB R, V G, P M, BR S, SC. P. A novel in vitro three-dimensional bioprinted liver tissue system for drug development. FASEB journal : official publication of the *Federation of American Societies for Experimental Biology* 2013;27(Meeting Abstract Supplement):872.12.
39. Robert C, Kamal E, Honglu W, Wei S. Biofabrication of a three-dimensional liver micro-organ as an in vitro drug metabolism model. *Biofabrication* 2010;2:045004.
40. Lee SY, Kim HJ, Choi D. Cell sources, liver support systems and liver tissue engineering: alternatives to liver transplantation. *Int J. Stem Cells* 2015;8:36–47 <https://doi.org/10.1038/pr.2017.252>
41. Faulkner-Jones A, Fyfe C, Cornelissen DJ, et al. Bioprinting of human pluripotent stem cells and their directed differentiation into hepatocyte-like cells for the generation of mini-livers in 3D. *Biofabrication* 2015;7:044102.

42. J.W. Lee, Y.J. Choi, W.J. Yong, et al., Development of a 3D cell printed construct considering angiogenesis for liver tissue engineering, *Biofabrication* 8 (1) (2016) 015007
43. E. Foster, J. You, C. Siitanen, et al., Heparin hydrogel sandwich cultures of primary hepatocytes, *Eur. Polym. J.* 72 (2015) 726-735
44. X. Ma, X. Qu, W. Zhu, et al., A 3D Printed Human iPSC-derived Hepatic Model than can Improve In Vitro Liver Functional Maturation, *Tissue Eng. Part A* 21 (2015) S77-S77
45. H. Jeon, K. Kang, S.A. Park, et al., Generation of Multilayered 3D Structures of HepG2 Cells Using a Bio-printing Technique, *Gut. Liver* 11 (1) (2017) 121-128.
46. H. Lee, W. Han, H. Kim, et al., Development of Liver Decellularized Extracellular Matrix Bio-ink for Three-Dimensional Cell Printing-Based Liver Tissue Engineering, *Biomacromolecules* 18 (4) (2017) 1229-1237.
47. J.B. Robbins, V. Gorgen, P. Min, et al., A novel in vitro three-dimensional bioprinted liver tissue system for drug development, *Faseb. J.* 27 (2013) 872.812
48. J.S. Lee, H. Yoon, D. Yoon, et al., Development of hepatic blocks using human adipose tissue-derived stem cells through three-dimensional cell printing techniques, *Journal of Materials Chemistry B* 5 (5) (2017) 1098-1107.
49. D. Nguyen, J. Robbins, C. Crogan-Grundy, et al., Functional Characterization of Three-dimensional (3D) Human Liver Tissues Generated by an Automated Bioprinting Platform, *Faseb. J.* 29 (Supplement 1) (2015) LB424
50. D. Visk, Will Advances in Preclinical In Vitro Models Lower the Costs of Drug Development?, *Appl. In Vitro Toxicol.* 1 (1) (2015) 79-82.
51. H. Kamimura, S. Ito, Assessment of chimeric mice with humanized livers in new drug development: generation of pharmacokinetics, metabolism and toxicity data for selecting the final candidate compound, *Xenobiotica*.46 (6) (2016) 557-569.