BÖLÜM 32

GASTROİNTESTİNAL STROMAL TÜMÖRLER

Koray KOÇHAN [1] - Erdem KOÇAK [2]

DOI: 10.37609/akya.3785.c245

GİRİŞ

Gastrointestinal Stromal Tümörler (GİST) Tanımı ve Genel Bakış

Gastrointestinal stromal tümörler (GİST), gastrointestinal sistem boyunca görülebilen mezenkimal kökenli, interstisyel Cajal hücrelerinden türediği düşünülen nadir görülen neoplazmlardır. Cajal hücreleri, gastrointestinal sistemde otonom sinir sistemi ile enterik sinir sistemi arasındaki sinyalleri ileten pacemaker hücreleridir. Diğer mezenkimal tümörlerden ayrı olarak GİST'ler bir tirozin kinaz reseptörü olan CD117 (c-kit)'in pozitif ekspresyonu ile karakterizedir (1). Gastrointestinal sistemde özellikle mide (%60-70) ve ince bağırsaklarda (%20-30) bulunup malign olma potansiyelleri de vardır ve metastaz yapabilirler (2). Bu tümörlerin temel patofizyolojik özelliği, KIT proto-onkogenindeki mutasyonlar nedeniyle meydana gelen sürekli aktif tirozin kinaz sinyalleşmesidir (3). GİST'lerin malign potansiyelinin belirlenmesinde tümörün boyutu, mitotik aktivitesi ve anatomik yerleşimi gibi faktörler kritik rol oynar (4).

GİST'lerin Keşfi ve Sınıflandırılması Üzerine Tarihsel Perspektif

Gastrointestinal stromal tümörlerin tanımlanması ve sınıflandırılması, patoloji alanında önemli bir köşetaşıdır. İlk olarak 1980'lerde tanımlanan bu tümörler, başlangıçta yanlışlıkla leiomiyomlar veya leiomiyosarkomlar gibi diğer mezenkimal tümörler olarak sınıflandırılmıştır (5). Ancak 1998 yılında Hirota ve arkadaşlarının çalışması, GİST'lerin KIT mutasyonlarına sahip olduğunu ve bu nedenle farklı bir tümör grubu olarak ele alınması gerektiğini ortaya koymuştur (1).

GİST'lerin moleküler biyolojisine dair yapılan araştırmaların sonucunda 2000'li yılların başlarında, bu tümörler için spesifik tedavi yöntemleri geliştirilmiştir. Özellikle, imatinib mesilat gibi tirozin kinaz inhibitörlerinin (TKİ) kullanımı, GİST tedavisinde devrim niteliğinde bir değişiklik oluşturmuştur (6). GİST'lerin doğru sınıflandırılması, doğru tedavi yaklaşımlarının seçilmesinde hayati öneme sahiptir ve bu da GİST'lerin klinik yönetiminde önemli bir adım olarak kabul edilir.

[1] Uzm. Dr., Biruni Üniversitesi Tıp Fakültesi, İç Hastalıkları AD., Gastroenteroloji BD., koraykochan@outlook.com, ORCID iD: 0000 0002 8150 6577

[2] Prof. Dr., İstinye Üniversitesi Tıp Fakültesi, Liv Hospital Vadi İstanbul Hastanesi, İç Hastalıkları AD., Gastroenteroloji BD., kocak67@hotmail.com, ORCID iD: 0000-0001-6675-8963

KAYNAKLAR

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* [Internet]. 1998 Jan 23 [cited 2024 Nov 18];279(5350):577–80. Available from: https://pubmed.ncbi.nlm.nih.gov/9438854/
2. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* [Internet]. 2002 [cited 2024 Nov 18];33(5):459–65. Available from: https://pubmed.ncbi.nlm.nih.gov/12094370/
3. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol [Internet]*. 2003 Dec 1 [cited 2024 Nov 18];21(23):4342–9. Available from: https://pubmed.ncbi.nlm.nih.gov/14645423/
4. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol [Internet]*. 2006 May [cited 2024 Nov 18];23(2):70–83. Available from: https://pubmed.ncbi.nlm.nih.gov/17193820/
5. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol [Internet]*. 1983 [cited 2024 Nov 18];7(6):507–19. Available from: https://pubmed.ncbi.nlm.nih.gov/6625048/
6. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med [Internet]*. 2002 Aug 15 [cited 2024 Nov 18];347(7):472–80. Available from: https://pubmed.ncbi.nlm.nih.gov/12181401/
7. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. *Cancer [Internet]*. 2005 Feb 15 [cited 2024 Nov 18];103(4):821–9. Available from: https://pubmed.ncbi.nlm.nih.gov/15648083/
8. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer [Internet]*. 2005 Nov 1 [cited 2024 Nov 18];117(2):289–93. Available from: https://pubmed.ncbi.nlm.nih.gov/15900576/
9. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol [Internet]*. 2005 Jan [cited 2024 Nov 18];100(1):162–8. Available from: https://pubmed.ncbi.nlm.nih.gov/15654796/
10. Søreide K, Sandvik OM, Søreide JA, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. *Cancer Epidemiol [Internet]*. 2016 Feb 1 [cited 2024 Nov 18];40:39–46. Available from: https://pubmed.ncbi.nlm.nih.gov/26618334/
11. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. *Lancet [Internet]*. 2007 May 19 [cited 2024 Nov 18];369(9574):1731–41. Available from: https://pubmed.ncbi.nlm.nih.gov/17512858/
12. Nishida T, Hirota S, Taniguchi M, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. *Nat Genet [Internet]*. 1998 [cited 2024 Nov 18];19(4):323–4. Available from: https://pubmed.ncbi.nlm.nih.gov/9697690/
13. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch [Internet]*. 2001 [cited 2024 Nov 18];438(1):1–12. Available from: https://pubmed.ncbi.nlm.nih.gov/11213830/
14. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg [Internet]*. 2000 Jan [cited 2024 Nov 18];231(1):51–8. Available from: https://pubmed.ncbi.nlm.nih.gov/10636102/
15. Janeway KA, Weldon CB. Pediatric gastrointestinal stromal tumor. *Semin Pediatr Surg [Internet]*. 2012 Feb [cited 2024 Nov 18];21(1):31–43. Available from: https://pubmed.ncbi.nlm.nih.gov/22248968/
16. Cho MY, Sohn JH, Kim JM, et al. Current trends in the epidemiological and pathological characteristics of gastrointestinal stromal tumors in Korea, 2003-2004. *J Korean Med Sci [Internet]*. 2010 Jun [cited 2024 Nov 18];25(6):853–62. Available from: https://pubmed.ncbi.nlm.nih.gov/20514305/
17. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol [Internet]*. 2012 Oct [cited 2024 Nov 18];23 Suppl 7(SUPPL. 7). Available from: https://pubmed.ncbi.nlm.nih.gov/22997454/
18. Sawaki A, Yamada Y, Komatsu Y, et al. Phase II study of motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate. *Cancer Chemother Pharmacol [Internet]*. 2010 Apr [cited 2024 Nov 18];65(5):961–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19690858/
19. Kindblom LG, Remotti HE, Aldenborg F, et al. Gastrointestinal Pacemaker Cell Tumor (GIPACT) Gastrointestinal Stromal Tumors Show Phenotypic Characteristics of the *Interstitial Cells of Cajal*. Vol. 152, American Journal ofPathology. 1998.
20. Sanders KM, Ward SM. Interstitial cells of Cajal: a new perspective on smooth muscle function. *J Physiol [Internet]*. 2006 Nov [cited 2024 Nov 18];576(Pt 3):721–6. Available from: https://pubmed.ncbi.nlm.nih.gov/16873406/
21. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science [Internet]*. 1998 Jan 23 [cited 2024 Nov 18];279(5350):577–80. Available from: https://pubmed.ncbi.nlm.nih.gov/9438854/
22. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch [Internet]*. 2001 [cited 2024 Nov 18];438(1):1–12. Available from: https://pubmed.ncbi.nlm.nih.gov/11213830/
23. Xie F, Luo S, Liu D, et al. Genomic and transcriptomic landscape of human gastrointestinal stromal tumors. *Nat Commun*. 2024 Dec 1;15(1):9495.

24. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol [Internet]*. 2004 [cited 2024 Nov 18];22(18):3813–25. Available from: https://pubmed.ncbi.nlm.nih.gov/15365079/
25. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol [Internet]*. 2008 Nov 20 [cited 2024 Nov 18];26(33):5352–9. Available from: https://pubmed.ncbi.nlm.nih.gov/18955458/
26. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology [Internet]*. 2008 Sep [cited 2024 Nov 18];53(3):245–66. Available from: https://pubmed.ncbi.nlm.nih.gov/18312355/
27. Antonescu CR, DeMatteo RP. CCR 20th Anniversary Commentary: A Genetic Mechanism of Imatinib Resistance in Gastrointestinal Stromal Tumor-Where Are We a Decade Later? *Clin Cancer Res.* 2015 Aug 1;21(15):3363–5.
28. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res [Internet]*. 2005 Jun 1 [cited 2024 Nov 18];11(11):4182–90. Available from: https://pubmed.ncbi.nlm.nih.gov/15930355/
29. Erkan M, Kleeff J, Gorbachevski A, et al. Periostin creates a tumor-supportive microenvironment in the pancreas by sustaining fibrogenic stellate cell activity. *Gastroenterology [Internet]*. 2007 [cited 2024 Nov 18];132(4):1447–64. Available from: https://pubmed.ncbi.nlm.nih.gov/17408641/
30. Yoon DH, Ryu MH, Ryoo BY, et al. Sunitinib as a second-line therapy for advanced GISTs after failure of imatinib: *Relationship between efficacy and tumor genotype in Korean patients. Invest New Drugs.* 2012 Apr;30(2):819–27.
31. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol [Internet]*. 2005 Jan [cited 2024 Nov 18];29(1):52–68. Available from: https://pubmed.ncbi.nlm.nih.gov/15613856/
32. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science [Internet]*. 2003 Jan 31 [cited 2024 Nov 18];299(5607):708–10. Available from: https://pubmed.ncbi.nlm.nih.gov/12522257/
33. Alvarez CS, Piazuelo MB, Fleitas-Kanonnikoff T, et al. Incidence and Survival Outcomes of Gastrointestinal Stromal Tumors. *JAMA Netw Open.* 2024;e2428828.
34. Haller V, Reiff C, Hamacher R, et al. Overall survival of patients with KIT-mutant metastatic GIST in the era of multiple kinase inhibitor availability. *J Cancer Res Clin Oncol* [Internet]. 2024 Nov 9 [cited 2024 Nov 18];150(11):489. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39516299
35. Haller V, Reiff C, Hamacher R, et al. Overall survival of patients with KIT-mutant metastatic GIST in the era of multiple kinase inhibitor availability. *J Cancer Res Clin Oncol [Internet]*. 2024 Nov 9 [cited 2024 Nov 18];150(11):489. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39516299
36. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol [Internet]*. 2005 Jan [cited 2024 Nov 18];29(1):52–68. Available from: https://pubmed.ncbi.nlm.nih.gov/15613856/
37. Fletcher CDM, Berman JJ, Corless C, Gorstein F, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol [Internet]*. 2002 [cited 2024 Nov 18];33(5):459–65. Available from: https://pubmed.ncbi.nlm.nih.gov/12094370/
38. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med [Internet]*. 2002 Aug 15 [cited 2024 Nov 18];347(7):472–80. Available from: https://pubmed.ncbi.nlm.nih.gov/12181401/
39. Zhang H, Liu Q. Prognostic Indicators for Gastrointestinal Stromal Tumors: *A Review. Transl Oncol [Internet]*. 2020 Oct 1 [cited 2024 Nov 18];13(10):100812. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32619820
40. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg [Internet]*. 2000 Jan [cited 2024 Nov 18];231(1):51–8. Available from: https://pubmed.ncbi.nlm.nih.gov/10636102/
41. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol [Internet]*. 2006 May [cited 2024 Nov 18];23(2):70–83. Available from: https://pubmed.ncbi.nlm.nih.gov/17193820/
42. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol [Internet]*. 2004 [cited 2024 Nov 18];22(18):3813–25. Available from: https://pubmed.ncbi.nlm.nih.gov/15365079/
43. Yang J, Guo P, Zhang Z, et al. The impact of gender on survival outcomes in patients with small intestinal stromal tumors: a comprehensive analysis using the SEER database. *Surg Endosc.* 2024 Jul 1;38(7):3905–16.
44. Amin M, Nageeb A, Abuhashem S, Saleh A, Awad E, Raed R. Common Symptoms and a Rare Diagnosis: A Case of Duodenal Gastrointestinal Stromal Tumor Presenting as Gastrointestinal Bleeding. *Cureus [Internet]*. 2024 Sep 20 [cited 2024 Nov 18];16(9):e69814. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39429312
45. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. *Cancer [Internet]*. 2005 Feb 15 [cited 2024 Nov 18];103(4):821–9. Available from: https://pubmed.ncbi.nlm.nih.gov/15648083/
46. Italiano A, Cioffi A, Coco P, et al. Patterns of care, prognosis, and survival in patients with metastatic gastrointestinal stromal tumors (GIST) refractory to first-line imatinib and second-line sunitinib. *Ann Surg Oncol.* 2012 May;19(5):1551–9.
47. Chiappa A, Zbar AP, Biffi R, et al. Prognostic factors and outcome of resected patients for gastrointestinal stromal tumors. *Hepatogastroenterology.* 2007 Apr;54(75):693–6.
48. Han IW, Jang JY, Lee KB, et al. Clinicopathologic analysis of gastrointestinal stromal tumors in duodenum and small intestine. *World J Surg.* 2015 Apr 1;39(4):1026–33.

49. Hashimoto T, Nakamura Y, Komatsu Y, et al. Different efficacy of tyrosine kinase inhibitors by KIT and PGFRA mutations identified in circulating tumor DNA for the treatment of refractory gastrointestinal stromal tumors. *BJC reports [Internet]*. 2024 Jul 25 [cited 2024 Nov 18];2(1). Available from: https://pubmed.ncbi.nlm.nih.gov/39516322/
50. Lee CK, Chung IK, Lee SH, et al. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). *Gastrointest Endosc [Internet]*. 2010 Jan [cited 2024 Nov 18];71(1):188–94. Available from: https://pubmed.ncbi.nlm.nih.gov/19879567/
51. De La Serna-Higuera C, Pérez-Miranda M, Díez-Redondo P, et al. EUS-guided single-incision needle-knife biopsy: Description and results of a new method for tissue sampling of subepithelial GI tumors (with video). *Gastrointest Endosc.* 2011 Sep;74(3):672–6.
52. Du B, Zhu Z, Pu J, Zhao Y, Wang S. Analysis of the diagnostic value of CT radiomics models in differentiating GIST and other mesenchymal tumors. *Hell J Nucl Med [Internet]*. 2024 May 1 [cited 2024 Nov 18];27(2):141–8. Available from: https://pubmed.ncbi.nlm.nih.gov/39190613/
53. Fishman EK, Chu LC. Imaging of Gastrointestinal Stromal Tumors: The Next Wave of Radiology. *Can Assoc Radiol J [Internet]*. 2024 Feb 1 [cited 2024 Nov 18];75(1):24–5. Available from: https://pubmed.ncbi.nlm.nih.gov/37531213/
54. Polkowski M. Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. Endoscopy. 2005 Jul;37(7):635–45.
55. Verloop CA, Goos JAC, Bruno MJ, et al. Diagnostic yield of endoscopic and EUS-guided biopsy techniques in subepithelial lesions of the upper GI tract: a systematic review. *Gastrointest Endosc.* 2024 Jun 1;99(6):895-911.e13.
56. Varanese M, Spadaccini M, Facciorusso A, et al. Endoscopic Ultrasound and Gastric Sub-Epithelial Lesions: Ultrasonographic Features, Tissue Acquisition Strategies, and Therapeutic Management. Medicina (Kaunas) [Internet]. 2024 Oct 1 [cited 2024 Nov 18];60(10). Available from: https://pubmed.ncbi.nlm.nih.gov/39459482/
57. Sekine M, Miura T, Fujiwara J, et al. Utility of endoscopic ultrasonography-guided fine-needle biopsy (EUS-FNB) for diagnosing small subepithelial lesions (< 20 mm). J *Ultrasound.* 2022 Mar 1;25(1):35–40.
58. Chen Y, Chen M, Wang Z, et al. Correlation of preoperative CT features with intra- and postoperative parameters of endoscopic resection in patients with gastric submucosal tumor (1~3 cm). *Surg Endosc [Internet]*. 2024 Nov 11 [cited 2024 Nov 18]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/39528660
59. Tanaka H, Kamata K, Ishihara R, et al. Value of artificial intelligence with novel tumor tracking technology in the diagnosis of gastric submucosal tumors by contrast-enhanced harmonic endoscopic ultrasonography. J *Gastroenterol Hepatol [Internet]*. 2022 May 1 [cited 2024 Nov 18];37(5):841–6. Available from: https://pubmed.ncbi.nlm.nih.gov/35043456/
60. Seven G, Silahtaroglu G, Kochan K, et al. Use of Artificial Intelligence in the Prediction of Malignant Potential of Gastric Gastrointestinal Stromal Tumors. *Dig Dis Sci [Internet]*. 2022 Jan 1 [cited 2024 Nov 18];67(1):273–81. Available from: https://pubmed.ncbi.nlm.nih.gov/33547537/
61. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). *Mod Pathol [Internet]*. 2000 [cited 2024 Nov 18];13(10):1134–42. Available from: https://pubmed.ncbi.nlm.nih.gov/11048809/
62. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. *Am J Pathol [Internet]*. 2004 [cited 2024 Nov 18];165(1):107–13. Available from: https://pubmed.ncbi.nlm.nih.gov/15215166/
63. Moga DFC, Vlădoiu G, Frățilă AM, et al. Understanding Gastric GIST: From Pathophysiology to Personalized Treatment. J Clin Med [Internet]. 2024 Jul 1 [cited 2024 Nov 18];13(14). Available from: https://pubmed.ncbi.nlm.nih.gov/39064037/
64. Jilg S, Rassner M, Maier J, et al. Circulating cKIT and PDGFRA DNA indicates disease activity in Gastrointestinal Stromal Tumor (GIST). *Int J Cancer.* 2019 Oct 15;145(8):2292–303.
65. Rassner M, Waldeck S, Follo M, et al. Development of Highly Sensitive Digital Droplet PCR for Detection of cKIT Mutations in Circulating Free DNA That Mediate Resistance to TKI Treatment for Gastrointestinal Stromal Tumor (GIST). *Int J Mol Sci [Internet]*. 2023 Mar 1 [cited 2024 Nov 18];24(6). Available from: https://pubmed.ncbi.nlm.nih.gov/36982486/
66. Li J, Guo S, Sun Z, Fu Y. Noncoding RNAs in Drug Resistance of Gastrointestinal Stromal Tumor. *Front Cell Dev Biol [Internet]*. 2022 Jan 31 [cited 2024 Nov 18];10:808591. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35174150
67. Floris G, Debiec-Rychter M, Wozniak A, et al. The heat shock protein 90 inhibitor IPI-504 induces KIT degradation, tumor shrinkage, and cell proliferation arrest in xenograft models of gastrointestinal stromal tumors. *Mol Cancer Ther [Internet]*. 2011 Oct [cited 2024 Nov 18];10(10):1897–908. Available from: https://pubmed.ncbi.nlm.nih.gov/21825009/
68. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer [Internet]*. 2011 Dec [cited 2024 Nov 18];11(12):865–78. Available from: https://pubmed.ncbi.nlm.nih.gov/22089421/
69. Kim MC, Yook JH, Yang HK, et al. Long-Term Surgical Outcome of 1057 Gastric GISTs According to 7th UICC/AJCC TNM System: Multicenter Observational Study From Korea and Japan. *Medicine [Internet]*. 2015 [cited 2024 Nov 18];94(41). Available from: https://pubmed.ncbi.nlm.nih.gov/26469894/
70. Park CH, Kim GH, Lee BE, et al. Two staging systems for gastrointestinal stromal tumors in the stomach: Which is better? *BMC Gastroenterol.* 2017 Dec 6;17(1).
71. Rutkowski P, Wozniak A, D-biec-Rychter M, et al. Clinical utility of the new American Joint Committee on Cancer staging system for gastrointestinal stromal tumors:

Current overall survival after primary tumor resection. *Cancer*. 2011 Nov 1;117(21):4916–24.
72. Gold JS, Gönen M, Gutiérrez A, Broto JM, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol [Internet]*. 2009 Nov [cited 2024 Nov 18];10(11):1045–52. Available from: https://pubmed.ncbi.nlm.nih.gov/19793678/
73. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol [Internet]*. 2008 Oct [cited 2024 Nov 18];39(10):1411–9. Available from: https://pubmed.ncbi.nlm.nih.gov/18774375/
74. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol [Internet]*. 2003 Dec 1 [cited 2024 Nov 18];21(23):4342–9. Available from: https://pubmed.ncbi.nlm.nih.gov/14645423/
75. DeMatteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer [Internet]*. 2008 Feb 1 [cited 2024 Nov 18];112(3):608–15. Available from: https://pubmed.ncbi.nlm.nih.gov/18076015/
76. Polkowski M, Larghi A, Weynand B, et al. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline. *Endoscopy [Internet]*. 2012 [cited 2024 Nov 18];44(2):190–205. Available from: https://pubmed.ncbi.nlm.nih.gov/22180307/
77. Nishida T, Goto O, Raut CP, Yahagi N. Diagnostic and treatment strategy for small gastrointestinal stromal tumors. *Cancer [Internet]*. 2016 Oct 15 [cited 2024 Nov 18];122(20):3110–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27478963/
78. Tang X, Ren Y, Huang S, et al. Endoscopic Submucosal Tunnel Dissection for Upper Gastrointestinal Submucosal Tumors Originating from the Muscularis Propria Layer: A Single-Center Study. *Gut Liver [Internet]*. 2017 Sep 1 [cited 2024 Nov 18];11(5):620–7. Available from: https://pubmed.ncbi.nlm.nih.gov/28335098/
79. Pollack SM, Pillarisetty VG, Padia SA, et al. The use of radiofrequency ablation in gastrointestinal stromal tumor. Journal of Vascular and Interventional Radiology. 2013 May;24(5):751.
80. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. *Gastric Cancer [Internet]*. 2016 Jan 1 [cited 2024 Nov 18];19(1):3–14. Available from: https://pubmed.ncbi.nlm.nih.gov/26276366/
81. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg [Internet]*. 2000 Jan [cited 2024 Nov 18];231(1):51–8. Available from: https://pubmed.ncbi.nlm.nih.gov/10636102/
82. Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. *Ann Surg Oncol [Internet]*. 2007 [cited 2024 Nov 18];14(7):2018–27. Available from: https://pubmed.ncbi.nlm.nih.gov/17473953/
83. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol [Internet]*. 2008 Nov 20 [cited 2024 Nov 18];26(33):5352–9. Available from: https://pubmed.ncbi.nlm.nih.gov/18955458/
84. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet [Internet]*. 2013 [cited 2024 Nov 18];381(9863):295–302. Available from: https://pubmed.ncbi.nlm.nih.gov/23177515/
85. Joensuu H, Eriksson M, Hall KS, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA [Internet]*. 2012 Mar 21 [cited 2024 Nov 18];307(12):1265–72. Available from: https://pubmed.ncbi.nlm.nih.gov/22453568/
86. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol [Internet]*. 2020 Jul 1 [cited 2024 Nov 18];21(7):923–34. Available from: https://pubmed.ncbi.nlm.nih.gov/32511981/
87. Bauer S, Duensing A, Demetri GD, et al. KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. *Oncogene [Internet]*. 2007 Nov 29 [cited 2024 Nov 18];26(54):7560–8. Available from: https://pubmed.ncbi.nlm.nih.gov/17546049/
88. D'Angelo SP, Shoushtari AN, Keohan ML, et al. Combined KIT and CTLA-4 Blockade in Patients with Refractory GIST and Other Advanced Sarcomas: A Phase Ib Study of Dasatinib plus Ipilimumab. *Clin Cancer Res [Internet]*. 2017 Jun 15 [cited 2024 Nov 18];23(12):2972–80. Available from: https://pubmed.ncbi.nlm.nih.gov/28007774/
89. Blanke CD, Demetri GD, Von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol [Internet]*. 2008 Feb 1 [cited 2024 Nov 18];26(4):620–5. Available from: https://pubmed.ncbi.nlm.nih.gov/18235121/
90. Komatsu Y, Doi T, Sawaki A, et al. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. *Int J Clin Oncol [Internet]*. 2015 Oct 3 [cited 2024 Nov 18];20(5):905–12. Available from: https://pubmed.ncbi.nlm.nih.gov/25655899/
91. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol [Internet]*. 2009 Jan 1 [cited 2024 Nov 18];99(1):42–7. Available from: https://pubmed.ncbi.nlm.nih.gov/18942073/
92. Gits CMM, Van Kuijk PF, Jonkers MBE, et al. MiR-17-92 and miR-221/222 cluster members target KIT and ETV1 in human gastrointestinal stromal tumours. *Br J Cancer [Internet]*. 2013 Sep 17 [cited 2024 Nov 18];109(6):1625–35. Available from: https://pubmed.ncbi.nlm.nih.

gov/23969726/
93. He C, Wang Z, Yu J, Mao S, Xiang X. Current Drug Resistance Mechanisms and Treatment Options in Gastrointestinal Stromal Tumors: Summary and Update. *Curr Treat Options Oncol [Internet]*. 2024 Nov 1 [cited 2024 Nov 18];25(11):1390–405. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39441520
94. Fujii H, Hirano H, Shiraishi K, et al. Comprehensive Genomic Assessment of Advanced-Stage GI Stromal Tumors Using the Japanese National Center for Cancer Genomics and Advanced Therapeutics Database. *JCO Precis Oncol [Internet]*. 2024 Oct [cited 2024 Nov 18];8(8):e2400284. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39447098
95. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature [Internet]*. 2017 Feb 2 [cited 2024 Nov 18];542(7639):115–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28117445/