

## CHAPTER 113 REFERENCES

- Muir C. Cancer of unknown primary site. Cancer 1995;75:353–356.
   Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeu. tic management of cancer of an unknown primary. Eur J Cancer 2003;39: 1990-2005
- 3. Nystrom JS, Werner JM, Heffelfinger-Juttner J, et al. Metastatic and histologic presentations in unknown primary cancer. Semin Oncol 1977;4:53–58.
  4. Gatter KC, Alcock C, Heryet A, et al. Clinical importance of analysing ma-
- lignant tumors of uncertain origin with immunohistochemical techniques. Lancet 1985;2:1302-1305.
- 5. Horning SJ, Carrier EK, Rouse RV, et al. Lymphomas presenting as histologically unclassified neoplasms: characteristics and response to treatment. J Clin Oncol 1989;7:1281-1287
- 6. Pentheroudakis G, Golfinopoulos V, Pavlidis N. Switching benchmarks in cancer of unknown primary: from autopsy to microarray. Eur J Cancer 2007;43:2026-2036.
- 7. Owen KA. Pathologic evaluation of unknown primary cancer. Semin Oncol 2009;36:8-37
- 8. Hainsworth JD, Wright EP, Gray GF Jr, Greco FA. Poorly differentiated carcinoma of unknown primary site: correlation of light microscopic findings with response to cisplatin-based combination chemotherapy. J Clin Oncol 1987:5:1272
- Dennis JL, Oien KA. Hunting the primary: novel strategies for defining the origin of tumours. *J Pathol* 2005; 205:236–247.
- 10. Oien KA, Dennis JL. Diagnostic work-up of carcinoma of unknown primary: from immunohistochemistry to molecular profiling. Ann Oncol 2012;23:271-27
- 11. Stoyianni A, Pentheroudakis G, Pavlidis, N. Neuroendocrine carcinoma of unknown primary: a systematic review of the literature and a comparative study with other neuroendocrine tumors. Cancer Treat Rev 2011;37:358-365.
- 12. Kerr SE, Schnabel CA, Sullivan PS, et al. A 92-gene cancer classifier predicts the site of origin for neuroendocrine tumors. *Modern Pathology* 2014;27:44–54.
- 13. Woltering E, Anthony LB, Diebold AE, et al. Gene expression profiling to predict site of metastatic neuroendocrine tumors presenting with an unknown primary. J Clin Oncol 2013 (suppl: abstract 4141).
- 14. Warnke RA, Gatter KC, Falini B, et al. Diagnosis of human lymphoma with monoclonal antileukocyte antibodies. N Engl J Med 1983;109:1275-1281
- 15. Battifora H, Trowbridge IS. A monoclonal antibody useful for the differential diagnosis between malignant lymphoma and nonhematopoietic neoplasms. Cancer 1983;51:816-821
- 16. Mackey B, Ordonez NG. Pathological evaluation of neoplasms with unknown primary tumor site. Semin Oncol 1993;20:206–228
- 17. Liu H, Shi H, Wilkerson ML, et al. Immunohistochemical evaluation of GATA3 expression in tumors and normal tissues. Am J Clin Pathol 2012;138:57-64.
- 18. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors; a study of 1840 cases. Am J Surg Pathol 2009; 33:1401–1408.
- Wang NP, Zee S, Zarbo RJ, et al. Coordinate expression of cytokeratins 7 and 20 defines unique subsets of carcinoma. Appl Immunohistochem 1995;3:
- 20. Tot T. Cytokeratins 20 and 7 as biomarkers: usefulness in discriminating primary from metastatic adenocarcinoma. Eur J Cancer 2002;38:758-763
- 21. Cheney L. Establishing a germ cell origin for metastatic tumors using OCT4 immunohistochemistry. Cancer 2004;101:2006-2010.
- 22. Anderson GG, Weiss LM. Determining tissue if origin for metastatic cancers: meta-analysis and literature review of immunohistochemistry performance. Appl Immunohistochem Mol Morphol 2010;18:3–8.
- 23. Arnold A, Cossman J, Bakhshi A, et al. Immunoglobulin-gene rearrangements as unique clonal markers in human lymphoid neoplasms. N Engl J Med 1983;309:1593-1599.
- 24. Rowley JD. Recurring chromosome abnormalities in leukemia and lymphoma. Semin Hematol 1990;27:122-136.
- Motzer RJ, Rodriguez E, Reuter VE, et al. Molecular and cytogenic studies in the diagnosis of patients with midline carcinomas of unknown primary site. *J Clin Oncol* 1995;13:274–282.
- Turc-Carel C, Philip I, Berger MP, et al. Chromosomal translocation in Ewing's sarcoma. N Engl J Med 1983;309:497-498.
   Whang-Peng J, Triche TJ, Knutsen T, et al. Chromosome translocation in peripheral neuroepithelioma. N Engl J Med 1984;311:584-585.
   Gerald WL, Ladanyi M, de Alava E, et al. Clinical, pathologic and molecular control of the c
- spectrum of tumors associated with t(11;22) (p13;q12): desmoplastic small round-cell tumors and its variants. J Clin Oncol 1998;16:3028-3036
- 29. French CA, Kutok JL, Faquin WC, et al. Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 2004;22:4135-4139
- Atkin NB, Baker MC. Specific chromosome change, i(12p), in testicular tumors. Lancet 1982;2:1349.
- 31. Ilson DH, Motzer RJ, Rodriguez E, et al. Genetic analysis in the diagnosis of neoplasms of unknown primary tumor site. Semin Oncol 1993;20:229-237.
- Summersgill B, Goker H, Osin P, et al. Establishing germ cell origin of undifferentiated tumors by identifying gain of 12p material using comparative genomic hybridization analysis of paraffin-embedded samples. Diagn Mol Pathol 1998;7:260-266.

- 33. Yuge NK, Mochiki M, Nibu K, et al. Detection of Epstein-Barr virus in metastatic lymph nodes of patients with nasopharyngeal carcinoma and a primary unknown cancer. Arch Otolaryngol Head Neck Surg 2003;129:338-340.
- 34. Feinmesser R, Miyazaki I, Chenng R, et al. Diagnosis of nasopharyngeal carcinoma by DNA amplification of tissue obtained by fine-needle aspiration. N Engl J Med 1992;326:17–21.
- 35. Lipshultz RJ, Morris D, Chee M, et al. Using oligonucleotide probe arrays to access genetic diversity. Biotechniques 1995;19:442-447.
- Schena M, Shalon D, Davis RW, et al. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science 1995;270:467–470.
- Golub TR, Slonim DK, Tamayo P, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 1999; 286:531-537
- 38. Greco FA, Erlander MG. Molecular classification of unknown primary cancer site. Mol Diagn Ther 2009;13:367-373
- Li X, Quigg RJ, Zhou J, et al. Clinical utility of microassays: current status, existing challenges and future outlook. Curr Genomics 2008;9:466-474
- Sotiriou C, Piccart MJ. Taking gene-expression profiling to the clinic: when will molecular signatures become relevant to patient care? Nature Rev Cancer 2007;7:545-553.
- 41. Ramaswamy S, Tamayo P, Rifkin R, et al. Multiclass cancer diagnosis using tumor gene expression signatures. Proc Natl Acad Sci U S A 2001;98: 15149-15154.
- MacConaill LE. Existing and emerging technologies for genomic profiling. J Clin Oncol 2013;31:1815-1824.
- Abaan OD, Polley EC, Davis SR, et al. The exomes of the NCI-60 panel: a genomic resource for cancer biology and systems pharmacology. *Cancer Res* 2013;73:4372–4382.
- Su AI, Welsh JB, Sapinoso LM, et al. Molecular classification of human carcinomas by use of gene expression signatures. *Cancer Res* 2001;61:7388–7393.
   Bloom G, Yang IV, Boulware D, et al. Multi-platform, multi-site, microarray-based human tumor classification. *Am J Path* 2004;164:9–16.
- Tothill RW, Kowalczyk A, Rischin D, et al. An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. Cancer Res 2005;65:4031-4040
- 47. Talantov D, Baden J, Jatkoe T. A quantitative reverse transcriptase-polymerase chain reaction array to identify metastatic carcinoma tissue of origin. J Mol Diag 2006;8:320.
- 48. Rosenfeld N, Aharonov R, Meiril E, et al. MicroRNAs accurately identify cancer tissue origin. *Nature Biotech* 2008;26:462–469.
- Monzon FA, Lyons-Weiler M, Buturovic LJ, et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. Clin Oncol 2009;27:2503-2508.
- Ma X-J, Pate R, Wang X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction array. Arch Path Lab Med 2006;130:465-473
- 51. Pillai R, Deeter R, Rigl CT, et al. Validation of a microarray-based gene expression test for tumors with uncertain origins using formalin-fixed paraffinembedded (FFPE) specimens. *J Mol Diagn* 2011;13:48–56.

  52. Pentheroudakis G, Greco FA, Pavlidis N. Molecular assignment of tissue of
- origin in cancer of unknown primary may not predict response to therapy or outcome: a systematic literature review. Cancer Treat Rev 2009;35:221-227.
- Varadhachary G, Talantov D, Raber M, et al. Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. J Clin Oncol 2008:26:4442-4448
- 54. Bridgewater J, van Laar R, Floore A, et al. Gene expression profiling may improve diagnosis in patients with carcinoma of unknown primary. Br J Cancer 2008;98:1425–1430.
- 55. Horlings HM, van Laar R, Kerst J-M, et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. J Clin Oncol 2008;26:4435-4441.
- van Laar RK, Ma XJ, de Jong D, et al. Implementation of a novel microarray-based diagnostic test for cancer of known primary. Int J Cancer 2009;125:1390-1397
- Monzon FA, Medeiros F, Lyons-Weiler M, Henner WD. Identification of tissue of origin in carcinoma of unknown primary with a microarray-based gene expression test. Diagn Pathol 2010;5:3
- 58. Greco FA, Spigel DR, Yardley DA, et al. Molecular profiling in unknown primary cancer: tissue of origin prediction. Oncologist 2010;15:500-506.
- Erlander MG, Ma XJ, Kesty NC, et al. Performance and clinical evaluation of the 92-gene real-time PCR assay for tumor classification. J Mol Diagn 2011:13:493-503
- Kerr SE, Schnabel CA, Sullivan PS, et al. Multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier. Clin Cancer Res 2012;18:3952–3960.
- Meiri E, Mueller WC, Rosenwald S, et al. A second-generation microRNAbased assay for diagnosing tumor tissue origin. The Oncologist 2012;17:
- 62. Weiss LM, Cha PG, Schroeder BE, et al. Blinded comparator study of immunohistochemistry analysis versus 92-gene cancer classifier in the diagnosis of the primary site in metastatic tumors. J Molecular Diagn. 2013;15:263-269.







- 63. Handorf CR, Kulkarni A, Grenut JD, et al. A multisite study directly comparing the diagnostic accuracy of the gene expression profiling and immunohistochemistry for primary site identification in metastatic tumors. *Am J Surg Pathol.* 2013;37:1067–1075.
- Gross-Goupil M, Massard C, Lesimple T, et al. Identifying the primary site using gene expression profiling in patients with carcinoma of unknown primary; a feasibility study from the GEFCAPI. Onkologie 2011;35:54–55.
- 65. Pentheroudakis G, Pavlidis N, Fountzilas G, et al. Novel microRNA-based assay demonstrates 92% agreement with diagnosis based on clinicopathologic and management data in a cohort of patients with carcinoma of unknown primary. Molecular Cancer 2013; 12:57.
- Nystrom SJ, Hornberger JC, Varadhachary GR, et al. Clinical utility of geneexpression profiling for tissue-site origin in patients with metastatic or poorly differentiated cancer: impact on diagnosis, treatment and survival. *Oncotar*get 2012;3:620–628.
- 67. Varadhachary Gr, Spector Y, Abbruzzese JL, et al. Propective gene signature study using microRNA to identify the tissue of origin in patients with carcinoma of unknown primary. Clin Cancer Res 2011;17:4063–4070.
  68. Ferracin M, Pedriali M, Veronese A, et al. Micro RNA profiling for the
- Ferracin M, Pedriali M, Veronese A, et al. Micro RNA profiling for the identification of cancers with unknown primary tissue of origin. J Pathol 2011;225:43–53.
- Greco FA, Lennington WJ, Spigel DR, et al. Molecular profiling diagnosis in unknown primary cancer; accuracy and ability to complement standard pathology. J Natl Cancer Inst 2013;105:782–790.
- Morawietz L, Floore A, Stork-Sloats L, et al. Comparison of histopathological and gene expression-based typing of cancer on unknown primary. Virchows Arch 2010; 456:23–29.
- Greco FA, Spigel DR, Hainsworth JD. Molecular tumor profiling of poorly differentiated neoplasms of unknown primary site. J Clin Oncol 2013;31: 217–223.
- Sorscher SM, Greco FA. Papillary renal carcinoma presenting as a cancer of unknown primary and diagnosed through gene expression profiling. Case Rep Oncol 2012;5;229–232.
- Choi YR, Han HS, Lee OJ, et al. Metastatic renal cell carcinoma in a supraclavicular lymph node with no known primary; a case report. Cancer Res Treat 2012; 44:215–218.
- Hainsworth JD, Spigel DR, Greco FA. Renal cell carcinoma presenting as cancer of unknown primary: diagnosis by molecular tumor profiling. *J Clin Oncol* 2013;31:abstract e15501.
- Seve P, Billotey C, Broussulle C, et al. The role of 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography in disseminated carcinoma of unknown primary site. Cancer 2007;109:292–299.
- Moller AK, Loft A, Berthelsen AK, et al. A prospective comparison of 18F-FDG PET/CT and CT as diagnostic tools to identify the primary tumor site in patients with extracervical cancer of unknown primary site. Oncologist 2012;17:1146–1154.
- 77. Welborn J, Jenks H, Taplett J, et al. High-grade neuroendocrine carcinomas display unique cytogenetic aberrations. *Cancer Genet Cytogenet* 2004;155:33–41.
- Swarts DR, Ramackers FC, Speel EJ, et al. Molecular and cellular biology of neuroendocrine tumors: evidence for separate biological entities. *Biochim Biophys Acta* 2012;1826:255–271.
- Moertel CG, Kovals LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991;68:227–232.
- van der Gaast A, Verwey J, Prins E, Splinter TAW. Chemotherapy as treatment of choice in extrapulmonary undifferentiated small cell carcinoma. Cancer 1990;65:422–424.
- 81. Kasimis BS, Wuerker RB, Malefatto JP, Moran EM. Prolonged survival of patients with extrapulmonary small cell carcinoma arising in the neck. *Med Pediatr Oncol* 1983;11:27–32.
- Rusthoven KE, Koshy M, Pauline AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. Cancer 2004;101:2641–2649.
- Califano J, Westra WH, Koch W, et al. Unknown primary head and neck squamous carcinoma: molecular identification of the site of origin. J Natl Cancer Inst 1999;91:599–604.
- 84. Jones AS, Cook JA, Phillips DE, et al. Squamous carcinoma presenting as an enlarged cervical lymph node. *Cancer* 1993;72:1756–1761.
- Varadhachary GR, Abbruzzese JL, Lenzi R. Diagnostic strategies for unknown primary cancer. Cancer 2004;100:1776–1785.
- known primary cancer. Cancer 2004;100:1776–1785.
  86. Lapeyre M, Malissard L, Peiffert D, et al. Cervical lymph node metastasis from an unknown primary: is a tonsillectomy necessary? Int J Radiat Oncol Biol Phys 1997;39:291–296.
- Tobacman JK, Greene MH, Tucker MA, et al. Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian cancer-prone families. *Lancet* 1982;2:795–797.
- Schorge JO, Muto MG, Welch WR et al. Molecular evidence for multifocal papillary serous carcinoma of the peritoneum in patients with germ-line BRCA1 mutations. I Natl Cancer Inst 1998-90:841–845
- BRCA1 mutations. J Natl Cancer Inst 1998;90:841–845.
  89. Roh MH, Kindelberger D, Crum CP. Serous tubal intraepithelial carcinoma and the dominant ovarian mass: clues to a serous tumor origin? Am J Surg Pathol 2009;33:376–383.

- 90. Semmel DR, Folkins AK, Hirsch MS, et al. Intercepting early pelvic serous carcinoma by routine pathological examination of the fimbria. *Mod Pathol* 2009-27-085-088
- 91. Ransom DT, Patel SR, Kenney GL, et al. Papillary serous carcinoma of the peritoneum: a review of 33 cases treated with cisplatin-based chemotherapy. *Cancer* 1990;66:1091–1094.
- Piver MS, Eltabbakh GH, Hempling RE, et al. Two sequential studies for primary peritoneal carcinoma: induction with weekly cisplatin followed by either cisplatin/doxorubicin/cyclophosphamide or paclitaxel/cisplatin. Gynecol Oncol 1997:67:141–146.
- Pentheroudakis G, Pavidis N. Serous papillary peritoneal carcinoma: unknown primary tumor ovarian cancer counterpart or a distinct entity? A systematic review. Crit Rev Oncol Hematol 2010;75:27–42.
- 94. Shah IA, Jayram L, Gani OJ, et al. Papillary serous carcinoma of the peritoneum in a man. *Cancer* 1998;82:860–866.
- 95. Pentheroudakis G, Lazaridis G, Pavlidis N. Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. *Breast Cancer Res Treat* 2010;119:1–11.
- evidence. *Breast Cancer Res Treat* 2010;119:1–11.

  96. Bhatia SK, Saclarides TJ, Witt TR, et al. Hormone receptor studies in axillary metastases from occult breast cancer. *Cancer* 1987;59:1170–1172.
- Block EF, Meyer MA. Positron emission tomography in diagnosis of occult adenocarcinoma of the breast. Am Surg 1998;64:906–908.
- Schorn C, Fischer U, Luftner-Nagel Š, et al. MRI of the breast in patients with metastatic disease of unknown primary. Eur Radiol 1999;9:470–473.
- 99. Henry-Tillman RS, Fischer U, Luftner-Nagel S, et al. MRI of the breast in pa-
- tients with metastatic disease of unknown primary. Eur Radiol 1999;9:470–473.

  100. Ellerbroek N, Holmes F, Singletary E, et al. Treatment of patients with isolated axillary nodal metastases from an occult primary carcinoma consistent with breast origin. Cancer 1990;66:1461–1467.
- Tell DT, Khoury JM, Taylor HG, et al. Atypical metastasis from prostate cancer: clinical utility of the immunoperoxidase technique for prostate-specific antigen. JAMA 1985;253:3574–3575.
- 102. Gentile PS, Carloss HW, Huang T-Y, et al. Disseminated prostate carcinoma simulating primary lung cancer. *Cancer* 1988;62:711–715.
- 103. Richardson RL, Greco FA, Wolff S, et al. Extragonadal germ cell malignancy: value of tumor markers in metastatic carcinoma of young males. *Proc Am Assoc Clin Oncol Am Assoc Clin Res* 1979;20 (abstr 204).
  104. Hainsworth JD, Greco FA. Poorly differentiated carcinoma of unknown prima-
- 104. Hainsworth JD, Greco FA. Poorly differentiated carcinoma of unknown primary site. In: Fer MF, Greco FA, Oldham R, eds. Poorly Differentiated Neoplasms and Tumors of Unknown Origin. Orlando, FL: Grune Stratton; 1986:189.
- Fox RM, Woods RL, Tattersall MHN. Undifferentiated carcinoma in young men: the atypical teratoma syndrome. *Lancet* 1979;1:1316–1318.
- Rades D, Kuhnel G, Wildfang I, et al. Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management. Ann Oncol 2001;12:1605–1609.
- individual therapeutic management. *Ann Oncol* 2001;12:1605–1609.

  107. Nguyen LN, Maor, MH, Oswald MJ. Brain metastases as the only manifestation of an undetected primary tumor. *Cancer* 1998;83:2181–2184.
- 108. Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer Principles and Practice of Oncology, 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:2363.
- Fernandez JA, Suanz C, Martinez JA, et al. Metastatic squamous cell carcinoma in cervical lymph nodes from an unknown primary tumor: prognostic factors. Clin Otolaryngol 1998;23:158–163.
- De Braud F, Heilbrun LK, Ahmed K, et al. Metastatic squamous cell carcinoma of an unknown primary localized to the neck: advantages of an aggressive treatment. Cancer 1989;64:510–515.
- 111. Guarischi A, Keane TJ, Elkahim T. Metastatic inguinal nodes from an unknown primary neoplasm: a review of 56 cases. *Cancer* 1987;59:572–577.
- 112. Rinke Á, Muller HH, Schade-Brittinger C, et al. Placebo-controlled double-blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27:4656.
- Hainsworth JD, Johnson DH, Greco FA. Poorly differentiated neuroendocrine carcinoma of unknown primary site: a newly recognized clinicopathologic entity. Ann Intern Med 1988;109:364–371.
- 114. Hainsworth JD, Spigel DR, Litchy S, Greco FA. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J Clin Oncol 2006;24:3548–3554.
- Richardson RL, Schoumacher RA, Fer MF, et al. The unrecognized extragonadal germ cell cancer syndrome. Ann Intern Med 1981:94:181–186.
- nadal germ cell cancer syndrome. *Ann Intern Med* 1981;94:181–186.

  116. Greco FA, Vaughn WK, Hainsworth JD. Advanced poorly differentiated carcinoma of unknown primary site: recognition of a treatable syndrome. *Ann Intern Med* 1986;104:547–553.
- 117. Hainsworth JD, Greco FA. Treatment of patients with cancer of an unknown primary site. N Engl J Med 1995;329:257–263.
- 118. Hainsworth JD, Johnson DH, Greco FA. Cisplatin-based combination chemotherapy in the treatment of poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary site: results of a 12 year experience at a single institution. J Clin Oncol 1992;10:912–922.
- 119. Falkson CI, Cohen GL. Mitomycin C, epirubicin and cisplatin versus mitomycin C alone as therapy for carcinoma of unknown primary origin. *Oncology* 1998,55:116–121.







- Briasoulis E, Kalofonos H, Bafaloukos D, et al. Carboplatin plus paclitaxel in unknown primary cancer: a phase II Hellenic Cooperative Oncology Group study. J Clin Oncol 2000;18:3101–2107.
- Raber MN, Faintuch J, Abbruzzese J, et al. Continuous infusion 5-fluorouracil, etoposide and cis-diamminedichloroplatinum in patients with metastatic carcinoma of unknown primary site. Ann Oncol 1991;2:519–520.
- Pavlidis N, Kosmidis P, Skaros D, et al. Subsets of tumors responsive to cisplatin or combinations in patients with carcinoma of unknown primary site. Ann Oncol 1992;3:631–634.
- 123. van der Gaast A, Verweij J, Henzen-Logmans SC, et al. Carcinoma of unknown primary; identification of a treatable subset. Ann Oncol 1990;1: 119–127
- 124. Briasoulis E, Tsavaris N, Fountzilas G, et al. Combination regimen with carboplatin, epirubicin and etoposide in metastatic carcinomas of unknown primary site: a Hellenic Cooperative Oncology Group phase II trial. Oncology 1998;55:426–430.
- 125. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013–2019.
  126. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first pro-
- 126. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008;26:5326–5334.
- Varadhachary GR, Raber MN, Matamoros A, Abbruzzese JL. Carcinoma of unknown primary with a colon cancer-profile changing paradigm and emerging definitions. *Lancet Oncol* 2008;9:596–599.
- Varadhachary GR, Karanth S, Qiao W, et al. Carcinoma of unknown primary with gastrointestinal profile: immunohistochemistry and survival data for this favorable subset. In J Clin Oncol 2014;19:479

  –484.
- Greco FA, Lennington WJ, Spigel DR, et al. Carcinoma of unknown primary site: outcomes in patients with colorectal profile treated with site-specific chemotherapy. J Cancer Ther 2012;3:37–43.
- Hainsworth JD, Schnabel CA, Erlander MG, et al. A retrospective study of treatment outcomes in patients with carcinoma of unknown primary site and a colorectal cancer molecular profile. Clin Colorectal Cancer 2012;11: 112–118.
- 131. Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon Research Institute. *J Clin Oncol* 2012; 31:217–223.
- Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Lawrence TS, Rosenberg SA, eds, Cancer Principles and Practice of Oncolory. 9th ed. Philadelphia: Lipping of Williams and Wilkins. 2011; 2033.
- ogy, 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2011: 2033.

  133. Greco FA, Pavlidis N. Treatment for patienmts with unknown primary carcinoma and unfavorable prognostic factors. Semin Oncol 2009;36:65–74.
- noma and unfavorable prognostic factors. *Semin Oncol* 2009;36:65–74.

  134. Lee J, Hahn S, Kim D-W, et al Evaluation of survival benefits by platinums and taxanes for unfavorable subset of carcinoma of unknown primary; a systematic review and meta-analysis. *Br J Cancer* 2013;108:39–48.
- Altman E, Cadman E. An analysis of 1,539 patients with cancer of unknown primary site. Cancer 1986;57:120–124.
- Hess KR, Abbruzzese MC, Lenzi R, et al. Classification and regression free analysis of 1000 consecutive patients with unknown primary carcinoma. Clin Cancer Res 1999;5:3403–3410.
- Holmes FT, Fouts TL. Metastatic cancer of unknown primary site. Cancer 1970;26:816–820.
- 138. Krementz ET, Cerise EJ, Foster DC, et al. Metastases of undetermined source. *Curr Probl Cancer* 1979;4:4–37.
- Markman M. Metastatic adenocarcinoma of unknown primary site: analysis of 245 patients seen at the Johns Hopkins Hospital from 1965–1979. Med Pediatr Oncol 1982;10:569–574.
- Moertel CG, Reitmeier RJ, Schutt AJ, et al. Treatment of the patient with adenocarcinoma of unknown primary site. Cancer 1972;30:1469–1472.
- Van de Wouw AJ, Janssen-Heijnen MLC, Coebergh JWW, et al. Epidemiology of unknown primary tumors; incidence and population-based survival of 1285 patients in Southeast Netherlands 1984–1992. Eur J Cancer 2002;38:409–413.
- 142. Levi F, Te VC, Erler G, et al. Epidemiology of unknown primary tumors. *Eur J Cancer* 2002;38:1810–1812.
- Greco FA. Therapy of adenocarcinoma of unknown primary: are we making progress? J Natl Compr Conc Netw 2008;6:1061–1067.
- 144. Hainsworth JD, Erland JB, Kalman CA, et al. Carcinoma of unknown primary site: treatment with one-hour paclitaxel, carboplatin and extended schedule etoposide. *J Clin Oncol* 1997;15:2385–2393.
  145. Greco FA, Gray J, Burris HA, et al. Taxane-based chemotherapy with carcinomarchical control of the control of the
- 145. Greco FA, Gray J, Burris HA, et al. Taxane-based chemotherapy with carcinoma of unknown primary site. *Cancer J* 2001;7:203–212.
  146. Greco FA, Erland JB, Morrissey LH, et al. Phase II trials with docetaxel plus
- Greco FA, Erland JB, Morrissey LH, et al. Phase II trials with docetaxel plus cisplatin or carboplatin. Ann Oncol 2000;11:211–215.
- 147. Greco FA, Burris HA, Litchy S, et al. Gemcitabine, carboplatin, and paclitaxel for patients with unknown primary site: a Minnie Pearl Cancer Research Network study. J Clin Oncol 2002;20:1651–1656.
- 148. Hainsworth JD, Burris HA, Calvert SW, et al. Gemeitabine in the secondline therapy of patients with carcinoma of unknown primary site: a phase II trial of the Minnie Pearl Cancer Research Network. Cancer Invest 2001;19:335–339.

- 149. Hainsworth JD, Spigel DR, Raefsky EL, et al. Combination chemotherapy with gemeitabine and irinotecan in patients with previously treated carcinoma of an unknown primary site. Cancer 2005;104:1992–1997.
- 150. Greco FA, Hainsworth JD, Yardley DA, et al. Sequential paclitaxel/carboplat-in/etoposide followed by irinotecan/gemcitabine for patients with carcinoma of unknown primary site: a Minnie Pearl Cancer Research Network phase II trial. Oncologist 2004;9:644–652.
- 151. Hainsworth JD, Spigel DR, Farley C, et al. Bevacizumab and erlotinib in the treatment of patients with carcinoma of unknown primary site: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2007;25:1747–1752.
  152. Hainsworth JD, Spigel DR, Burris HA 3rd, et al. Oxaliplatin and capecitabine
- 152. Hainsworth JD, Spigel DR, Burris HA 3rd, et al. Oxaliplatin and capecitabine in the treatment of patients with recurrent or refractory carcinoma of unknown primary site: a phase 2 trial of the Sarah Cannon Oncology Research Consortium. Cancer 2010;116:2448–2454.
- 153. Hainsworth JD, Spigel DR, Clark BL, et al. Paclitaxel/carboplatin/etoposide versus gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial. Cancer J 2010;16:70–75.
- Dowell JE, Garrett AM, Shyr Y, et al. A randomized phase II trial in patients with carcinoma of an unknown primary site. Cancer 2001;91:592–597.
- 155. Pittman KB, Oliver IN, Koczwara R, et al. Gemcitabine and carboplatin in carcinoma of unknown primary site: a phase 2 Adelaide cancer-trials and education collaborative study. Br J Cancer 2006;95:1309–1313.
- Balana C, Manzano JL, Moreno L, et al. A phase II study of cisplatin, etoposide and gemcitabine in an unfavorable group of patients with carcinoma of unknown primary site. Ann Oncol 2003;14:1425–1429.
- Piga A, Nortilli R, Cetto GL, et al. Carboplatin, doxorubicin and etoposide in the treatment of tumors of unknown primary site. Br J Cancer 2004;90: 1898–1904.
- 158. Park YH, Ryoo BY, Choi SJ, et al. A phase II study of paclitaxel plus cisplatin chemotherapy in an unfavorable group of patients with cancer of unknown primary site. *Jpn J Clin Oncol* 2004;34:681–685.
- Pouessel D, Culine S, Becht C, et al. Gemcitabine and docetaxel as frontline chemotherapy inpatients with carcinoma of an unknown primary site. Cancer 2004;100:1257–1261.
- 160. Briasoulis E, Fountzilas G, Bamias A, et al. Multicenter phase II trial of irinotecan plus oxaliplatin [IROX regimen] in patients with poor-prognosis cancer of unknown primary: a Hellenic Cooperative Group study. Cancer Chemother Pharmacol 2008;62:277–284.
- El-Rayes BF, Shields AF, Zalupski M, et al. A phase II study of carboplatin and paclitaxel in adenocarcinoma of unknown primary site. Am J Clin Oncol 2005;28:152–156
- Palmeri S, Lorusso V, Palmeri L, et al. Cisplatin and gemcitabine with either vinorelbine or paclitaxel in the treatment of carcinoma of unknown primary site. Cancer 2006;1007:2898–2905.
- Schneider BJ, El-Reyes B, Muler JH, et al. Phase II trial of carboplatin, gencitabine and capecitabine in patients with carcinoma of unknown primary site cancer. Cancer 2007;110:770–775.
- 164. Berry W, Elkordy M, O'Rourke M, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in advanced carcinoma of unknown primary origin: a reasonable regimen for the community-based clinic? Cancer Invest 2007;3:77-21.
- 165. Hainsworth JD, Spigel DR, Thompson DS, et al. Paclitaxel/carboplatin plus bevacizumab/erlotinib in the first-line treatment of patients with carcinoma of unknown primary site. Oncologist 2009;14:1189–1197.
  166. Tan DSW, Montoya J, Ng DS, et al. Molecular profiling for druggable
- 166. Tan DSW, Montoya J, Ng DS, et al. Molecular profiling for druggable genetic abnormalities in carcinoma of unknown primary. J Clin Oncol 2013;1:e273–239.
- Penley WC, Spigel Dr, Greco FA, et al. Confirmation of non-small cell lung cancer diagnosis using ALK testing and genetic profiling in patients presenting with carcinoma of unknown primary site. J Clin Oncol 2013;31:abstract e115004.
- 168. Gatalica Z, Millis S, Bender R, et al. Molecular profiling cancers of unknown primary: paradigm shift in management of CUP. Presented at: 2013 European Cancer Conference; September 30, 2013; Amsterdam.
- Abbruzzese JL, Abbruzzese MC, Hess KR, et al. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. J Clin Oncol 1994;12:1272–1280.
- Lenzi R, Hess KR, Abbruzzese MC, et al. Poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary origin: favorable subsets of patients with unknown primary cancer? J Clin Oncol 1997;15:2056–2066.
- 171. van der Gaast A, Verweij J, Planting AST, et al. Simple prognostic model to predict survival in patients with undifferentiated carcinoma of unknown primary site. *J Clin Oncol* 1995;13:1720–1725.
- Culine S, Kramar A, Saghatchian M, et al. Development and validation of a prognostic model to predict the length of survival in patients with carcinoma of unknown primary site. J Clin Oncol 2002;20:4679–4683.
- 173. Seve P, Ray-Coquard I, Trillet-Lenoir V, et al. Low serum albumin levels and liver metastasis are powerful prognostic markers for survival in patients with carcinomas of unknown primary site. Cancer 2006;107:2698–2705
- carcinomas of unknown primary site. Cancer 2006;107:2698–2705.

  174. Wood LA, Venner PM, Pabst HF. Monozygotic twin brothers with primary immunodeficiency presenting with metastatic adenocarcinoma of unknown primary. Acta Oncol 1998;37:771–772.







- 175. Korbling M, Katz RL, Khanna A, et al. Hepatocytes and epithelial cells of donor origin in recipients of peripheral blood stem cells. N Engl J Med 2002;346:738–746.
- 176. McCulloch EA. Stem cells and diversity. Leukemia 2003;17:1042-1048.
- Young HE, Duplaa C, Romera-Ramos M, et al. Adult reserve stem cells and their potential for tissue engineering. Cell Biochem Bio Phys 2004;40:1-80.
- 2004;40:1–80.
  178. Dieterien-Lievre F. [Lineage-switching by pluripotent cells derived from adults.] *J Soc Biol* 2001;195:39–46.
  179. De Coppi P, Bartsch G, Siddiqui MM, et al. Isolation of amniotic stem cells with potential for therapy. *Nat Biotechnol* 2007;25:100–106.
  180. Abbruzzese JL, Lenzi R, Raber MN, et al. The biology of unknown primary tumors. *Semin Oncol* 1993;20:238–243.

- 181. Ramaswamy S, Ross KN, Lander ES, Golab TR. A molecular signature of metastasis in primary solid tumors. Nat Genet 2003;33:49-54.
- 182. Bar-Eli M, Abbruzzese JL, Lee-Jackson D, et al. P53 gene mutation spectrum in human unknown primary tumors. Anticancer Res 1993;13:1619–1623.
- 183. Briasoulis E, Tsakos M, Fountzilas G, et al. Bc12 and p53 protein expression in metastatic carcinoma of unknown primary origin; biological and clinical implications. A Hellenic Cooperative Oncology Group study. *Anticancer Res* 1998;18:1907.

- 184. Pavlidis N, Briasoulis E, Baj M, et al. Overexpression of C-myc, Ras and Cerb-2 oncoproteins in carcinoma of unknown primary origin. Anticancer Res
- 185. Hainsworth JD, Lennington WJ, Greco FA. Overexpression of Her-2 in patients with poorly differentiated carcinoma or poorly differentiated adenocarcinoma of unknown primary site. J Clin Oncol 2000;18:632-635
- 186. Golfinopoulos V, Pentheroudakis G, Goussia A, et al. Intercellular signaling via the AKT axis and downstream effectors is active and prognostically significant in cancer of unknown primary; a study of 100 cases. Ann Oncol 2012;23:2725–2730.
- 187. Stella GM, Benvenutis S, Gramaglia D, et al. MET mutations in cancers of unknown origin. *Hum Mutat* 2010; 32:44–50.
- Koo JS, Kim H. Hypoxia-related protein expression and its clinicopathologic implication in carcinomas of unknown primary. *Tumour Biol* 2011;32:893–904.
- 189. Bonnefoi H, Smith IE. How should cancer presenting as a malignant pleural effusion be managed? Br J Cancer 1996;74:832-835.
- 190. Kuttesch JF, Parham DM, Kaste SC, et al. Embryonal malignancies of unknown primary origin in children. *Cancer* 1995;75:115–121.
  191. Bauer DE, Mitchell CM, Strait KM, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. *Clin Cancer Res* 2012;18;5773-5779.



