MAYO CLINIC

SPECIAL ARTICLE

Making the Case to Study the Volume-Outcome Relationship in Hematologic Cancers

Ronald S. Go, MD; Wayne A. Bottner, MD; and Morie A. Gertz, MD

Abstract

The positive relationship between the volume of health services (hospital and physician) and health-related outcomes is established in the complex surgical treatment of cancers and certain nononcologic medical conditions. However, this topic has not been systematically explored in the medical management of cancers. We summarize the limited current state of knowledge about the volume-outcome relationship in the management of hematologic cancers and provide reasons why further research on this subject is necessary. We highlight the relatively low annual volume of hematologic cancers in the United States, the increasing complexity of making a diagnosis due to constant change in classification and prognostication, the rapid availability of novel agents with unique mechanisms of action and toxicities, and the proliferation of treatment guidelines distinct to each disease subtype. We also discuss the potential implications pertaining to medical practice and trainee education, including effects on quality of care, access and referral patterns, and subspecialty training.

 ■ Mayo Clin Proc. 2015;90(10):1393-1399

In 2000, the Institute of Medicine (IOM) convened a workshop to review the current understanding of the relationship between volume of health services and health-related outcomes.[1] It reported on its systematic review of 135 studies concerning 27 conditions and procedures that included cancer surgery. The conclusion was that for a variety of surgical procedures and certain medical conditions, higher volume (whether assessed by hospital or physician) is associated with better health outcomes even after adjusting for case-mix differences. In particular, a statistically significant positive association was found in 71% and 69% of studies of hospital and physician volumes, respectively.[2] More importantly, a significant volume effect was found in all 16 studies judged to have the soundest research methods. The 2 medical conditions included in the review showing significant volume-outcome associations were acquired immunodeficiency syndrome and myocardial infarction. The IOM report highlighted the fact that it did not find a single study that investigated the volume-outcome relationship in the medical management of cancer. One of its recommendations for new areas of research was to examine the volume-outcome relationship for chronic conditions such as cancer and nonsurgical procedures.[1]

PATIENT VOLUME AND PHYSICIAN SPECIALIZATION ASSOCIATED WITH BETTER OUTCOME IN CANCER SURGERY

For surgery, the volume-outcome relationship is particularly dramatic for certain low-frequency, high-risk, cancer surgical procedures, such as pancreatectomy and esophagectomy, with short-term mortality rates 2 to 3 times greater in low- vs high-volume hospitals.[1] Subsequent systematic reviews and population-based studies have shown similar outcomes, and the findings have been replicated in other countries.[3-7] Although there is recognition that the volume-outcome relationship has its limitations and that unmeasured processes of care are also important factors, the IOM panel concluded that volume may still be the best proxy for quality.[1]

Surgeon specialization has also been shown in multiple studies to have a positive outcome for patients with cancer undergoing surgery. A recent review revealed that of 20 of the 27 studies that examined long-term survival for 5 cancers, including colorectal, melanoma, breast, bladder, and ovarian, all but 2 found that patients operated on by specialty surgeons had

From the Division of Hematology, Mayo Clinic, Rochester, MN (R.S.G., M.A.G.); Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Rochester, MN (R.S.G.); and Section of Hematology, Gundersen Health System, La Crosse, WI (W.A.B.).

significantly better long-term survival rates. The 2 negative studies showed the same trend in favor of specialization but did not reach statistical significance. The main limitation of these findings is that not all the studies adjusted for discrepancies in volume between specialty and general surgeons.[8] This positive association was also seen in noncancer surgical procedures.[4]

LIMITED STUDIES ON PHYSICIAN CHARACTERISTICS AND QUALITY OF MEDICAL CANCER CARE

In the years since the 2000 IOM workshop, a limited number of research papers have been published investigating physician characteristics and the outcome of medical cancer care. Using the Surveillance Epidemiology and End Results (SEER)—Medicare database, a few studies in solid tumors have shown that physician characteristics may affect the quality of medical cancer care, such as delivery of guideline-based treatments (treatments received by patients with stage III colorectal cancer who saw a medical oncologist, a radiation oncologist, and a surgeon were more likely to comply with National Comprehensive Cancer Network guidelines, odds ratio=20.6), choice of treatment (patients with localized prostate cancer who consulted with a radiation oncologist were 20 times more likely to have radiation as primary treatment as opposed to those who saw a urologist only), and cancer screening (colonoscopy performed by gastroenterologists was associated with lower risk of subsequent death from colorectal cancer compared with that performed by nongastroenterologists, odds ratio=0.6).[9-11]

Similarly, there is a paucity of studies in hematologic cancers. One study in 1987 demonstrated that patients with Hodgkin lymphoma (HL) treated in the community had mortality rates that, on average, were 1.5 times higher than those in patients treated at National Cancer Institute–designated comprehensive cancer centers.[12] A population-based study of all patients with acute myelogenous leukemia (AML) in Ontario, Canada, from 1964 through 2003 showed that referral to specialized cancer centers was associated with a longer 3-year overall survival rate (hazard ratio [HR]=1.3) independent of other relevant clinical factors.[13] However, a similar study in England and Wales consisting of adolescents and young adults with AML and acute lymphoblastic leukemia (ALL) diagnosed between 1984 and 1994 did not show a survival advantage of centralized treatment.[14] Another population-based lymphoma study in Nebraska showed that survival disparity exists among rural residents according to the type of physician. Between 1992 and 2006, individuals treated by community-based oncologists had a higher relative risk of death compared with those cared for by university-based oncologists.[15] A Mayo Clinic study in 2011 showed that disease-specific expertise influenced time to treatment and treatment outcome in patients with chronic lymphocytic leukemia (CLL). Compared with those cared for by CLL hematologists, patients who were cared for by non-CLL hematologists had shorter time to first chemotherapy (HR=2.4) and overall survival (HR=1.5), even when adjusted for pertinent clinicopathologic risk factors.[16] These studies strongly suggest that physician specialization, among other characteristics, may also have a strong effect on the outcome of medical cancer care because complex processes of treatment decision making are usually involved. However, none of these studies adjusted for the actual volume of patients seen.

COMPELLING REASONS TO PERFORM VOLUME-OUTCOME STUDIES IN HEMATOLOGIC CANCERS

In addition to the paucity of data as described previously herein, there are several compelling reasons to perform further studies in patients with hematologic cancers, as discussed in the following subsections.

Disparity in Outcome of Patients With Hematologic Cancers Is Understudied

Treatment and outcome disparities in patients diagnosed as having hematologic cancers are poorly understood. Previous studies have focused primarily on sociodemographic factors, showing inferior outcomes in minority groups in general and in adolescents and young adults with ALL treated with adult protocols.[17-22] Very few studies have investigated the actual volume-outcome relationship in hematologic patients. A study from the Center for International Blood and Marrow Transplant Research in 2005 involved patients with leukemia and lymphoma receiving autologous and human leukocyte antigen–identical sibling allogeneic

Mayo Clin Proc. ■ October 2015;90(10):1393-1399 ■ http://dx.doi.org/10.1016/j.mayocp.2015.07.003
www.mayoclinicproceedings.org

transplants. After adjusting for the clinical severity index, the 100-day mortality rate was lower in transplant physicians treating more than 20 patients annually.[23] A subanalysis of a German clinical trial in 2014 found a relationship between health care setting and survival in chronic myelogenous leukemia (CML). Patients who were treated at teaching hospitals achieved a lower mortality rate (HR=0.6), even after adjusting for comorbidities and physician experience. The number of patients enrolled in the clinical trial was used as a proxy measure for experience.[24] A retrospective study from France determined the outcome of patients with hematologic cancers who developed acute respiratory failure and were admitted to the intensive care units (ICUs) of 28 participating hospitals. Patients admitted to ICUs with more than 30 hematologic cancer patients per year treated for acute respiratory failure had lower mortality rates than those admitted to lower-volume ICUs.[25] The latter study suggests that expertise in the management of complications of hematologic cancer treatment may also be an indicator of quality care.

Hematologic Cancers Are Relatively Rare and Are Becoming More Complex to Treat

Hematologic cancers compose only approximately 10% of all cancers seen in the United States.[26] Yet, the disease classification is becoming more complex and constantly evolving. For example, there are now more than 50 subtypes of non-Hodgkin lymphoma (NHL).[27] Therefore, for a community oncologist who sees all types of cancers, for every 100 solid tumor patients seen, on average, there is only one patient with a specific subtype of hematologic cancer. To illustrate further the rarity of hematologic cancers, it is estimated that in 2015, there will be 71,850 new cases of NHL, the most common hematologic cancer. This number is less than invasive urinary bladder cancers (74,000) and just slightly more than kidney cancers (61,560), both solid tumors considered relatively uncommon in clinical practice. New cases of even less common hematologic cancers, such as AML, CML, HL, CLL, and multiple myeloma (MM), are less than or similar to those of sarcoma.[26] Moreover, knowledge on how to incorporate tumor biology has become essential not only for the diagnosis but also for treatment. In AML and MM, cytogenetics and molecular/mutational profiles are routinely used in subtype classification, risk stratification, and determination of the need for subsequent stem cell transplant.[28,29]

Increase in Novel Agents and Proliferation of Treatment Guidelines for Hematologic Cancers in the Past Decade

Between 2003 and 2014, 54 new oncology drugs were approved by the US Food and Drug Administration. Of these drugs, 21 (39%) were for hematologic cancers. Most of these drugs were novel agents (eg, ibritumomab tiuxetan, bortezomib, azacitidine, lenalidomide, vorinostat, and ibrutinib), with newly described mechanisms of actions and unique toxic effects different from traditional chemotherapeutic agents.[30] Recognizing the complexities of treating hematologic cancers, the National Comprehensive Cancer Network has expanded the number of treatment guidelines. Currently, 9 of 40 treatment guidelines (23%) are for hematologic cancers.[31] This is an understatement because the NHL treatment guideline is further subdivided into 16 different subguidelines for the various NHL subtypes.[32] Although many NHL subtypes are currently treated in the same way or with similar chemotherapeutic regimens, it is almost certain that this will not be the case in the future. In fact, the recently announced Precision Medicine Initiative, championed by the National Institutes of Health, specifically selects cancer as the model disease.[33] Therefore, we will likely see further divergence of the already complex treatment and diagnostic guidelines.

Most General Community Oncologists Who Treat Patients With Hematologic Cancer Have Limited Experience With These Diseases

The National Cancer Institute estimates that most patients with cancer (~85%) are treated at community hospitals in or near the communities in which they live.[34] In a recent American Society of Clinical Oncology national census of oncology practice covering 599 practices with 4546 oncologists, most (82%) were community oncologists and most (71%) have a combined hematology-oncology practice.[35] Therefore, community oncologists see and treat a broad spectrum of patients, including those with solid tumors, hematologic cancers, and benign blood

disorders. Keeping up-to-date with most of the hematology-oncology literature is challenging, especially in the current practice environment. In fact, many community oncology leaders have expressed the inevitable necessity of subspecialization.[36] A recent national practice survey demonstrated substantial knowledge gaps in the individualized management and interpreting the response to treatment of CML, ALL, and NHL.[37]

Although there are no published data on how many of a specific type of hematologic cancer a community oncologist sees annually, one can get an estimate of this from the SEER Program and the Gundersen Health System, where one of us practices (W.A.B.). For example, it is estimated that there will be 24,000 new cases of MM in the United States this year, with a disease prevalence of 84,000.[38] Because the American Society of Clinical Oncology Workforce Information System reported 13,084 oncologists working in 2011,[39] we estimate that an oncologist in the United States on average sees 2 new MM cases a year and follows 6 patients with MM at all phases of the disease. The numbers of annual new cases for other hematologic cancers are correspondingly low (2 AMLs, 5 NHLs, and $\leq$1 CLL, CML, and HL). Gundersen Health System is a moderately sized health system in the Midwest caring for approximately 560,000 people.[40] In the past decade, the practice has, on average, had 10 full-time adult hematologist-oncologists (4 hematologists and 6 medical oncologists), and the practice volume has remained stable.[41] In 2013, the practice saw 1307 new analytical cancer cases, including 148 cases of hematologic cancers (3 ALLs, 15 AMLs, 20 CLLs, 7 CMLs, 3 hairy cell leukemias, 4 HLs, 44 NHLs, 22 MMs, 15 myelodysplastic neoplasms, and 15 myeloproliferative neoplasms). Assuming that Gundersen's case-mix approximates that of other community practices, one can estimate that the average community hematologist-oncologist sees only 1 to 2 new cases of a distinct hematologic cancer annually. Because many hematologic cancers do not require immediate therapy, the opportunity to treat is less. Recognizing this limitation, the Gundersen Health System is relatively unique among hematology-oncology community practices in this country. It has successfully sustained separate clinical services for medical oncology and hematology, with hematologists seeing virtually all patients with hematologic disorders (benign and malignant) for the past 4 decades. If the trend is toward more specialization, this practice may well serve as a paradigm for community hematology for the future.

POTENTIAL IMPLICATIONS

In the past 15 years, we have seen major advances in the understanding of the pathogenesis of hematologic cancers. Many distinct, molecularly defined pathologic subtypes have emerged from previous entities with corresponding therapeutic opportunities. These changes have dramatically increased the diagnostic and treatment complexities. For the busy general hematology-oncology practitioners, familiarity with these ever-growing changes will become increasingly difficult to sustain over time. Therefore, a case can be made to study whether a volume-outcome relationship exists in the medical management of hematologic cancers. This is very much in line with the findings and goals set forth by the 2011 IOM committee on the Learning Health Care System in America.[42] If patient volume is found to be associated with clinical outcome, then there are several potential practice and education implications, discussed in the following subsections.

Defining the Determinants of High-Quality Care

It is possible that volume is in itself a proxy for certain best practices associated with high-quality care. Therefore, identifying these practices is important because they may be translatable to lower-volume facilities. Potential examples include having a uniform care pathway,[43] adherence to national clinical practice guidelines,[44] multidisciplinary prospective case conferences,[45] tumor board discussion of challenging cases, upfront chemotherapy dose adjustments for elderly and frail patients,[46] and early identification and management of treatment toxic effects.[47]

More Appropriate Patterns of Referral to Reduce Cost of Care

Data generated from volume-outcome studies may provide an initial system to guide evidence-based facility referral and benchmarking for future qualitative analyses.

Mayo Clin Proc. ■ October 2015;90(10):1393-1399 ■ http://dx.doi.org/10.1016/j.mayocp.2015.07.003
www.mayoclinicproceedings.org

Hematologic cancers that are shown to benefit from disease expertise ideally will be referred to higher-volume facilities at least for an initial consultation. In contrast, we may find that certain cancers may not require a referral. Moreover, if we show that high-volume community practices demonstrate outcomes similar to high-volume academic facilities, this may minimize unnecessary referrals and, thus, improve access, reduce cost of care, and offer more convenience to patients and caregivers.[48]

Disease Specialization Among Community Oncologists or Practices

Community oncologists may be incentivized and encouraged to change practice patterns toward disease-specific specialization. At the minimum, each practice may need to have at least 1 dedicated care physician for hematologic cancers.[36] This model should be sustainable even in community practice for several reasons. First, because 1 in 10 cancers is of hematopoietic origin, for every 10 oncologists, there should be enough patient volume to support 1 specializing in hematologic cancers. Second, most hematologic cancers are not curable and require long-term treatment or follow-up. Therefore, the prevalence is relatively higher over time. Finally, the hematology practice would be supplemented by the care of patients with nonmalignant pathologic abnormalities (thrombosis, bleeding, cytopenias, hemoglobinopathy, etc).

Increased Focus on Hematology Training

Currently, most adult hematology-oncology fellowship programs offer combined training in both disciplines as opposed to individual disciplines. In 2013, of the 150 hematology-oncology fellowship programs in the United States, just 14 programs (9%) offered oncology-only or hematology-only training, a 41% decline from 2007.[49,50] Increasing the opportunity to do hematology-only (combined benign and malignant diseases) fellowship training will allow for more disease-specific focus for trainees. This is the paradigm in Canada and most European countries. An alternative is to allow the option of an extra year of advanced fellowship program focusing on hematologic malignancy, similar to current stem cell transplant fellowships. With the imposition of residency work-hour restrictions, it is becoming more difficult to gain enough experience and proficiency in managing such a wide range of cancers, not to mention benign hematology. It is, therefore, a more rational approach to go from generalization to specialization, and not in the opposite direction. Subspecialization happened decades ago with internal medicine, not only in academia but also in community practice, and thrived.[51] A similar trend occurred in surgery less than a decade after the IOM report. The number of surgical subspecialty training programs, including various surgical oncology fellowships, is growing.[52] This has already impacted practice patterns (centralization of cancer surgery) and, at the same time, improved surgical outcomes in certain complex cancer operations.[53]

CONCLUSION

Owing to the relative rarity of hematologic cancers and the increasing complexity on how they are managed, we believe that the time is ripe to study whether a volume-outcome relationship exists. Not only do we have an opportunity to assess the quality of nonsurgical cancer care, we also have a chance to learn more about variations in practice that are tied to relevant outcomes. Similar to surgical volume-outcome studies performed in the past 2 decades, such investigations could be performed either at the level of the treatment facility or the oncologists by secondary analyses of large patient data sets from national cancer registries, private or public payers, and clinical trials.

Abbreviations and Acronyms: **ALL** = acute lymphoblastic leukemia; **AML** = acute myelogenous leukemia; **CLL** = chronic lymphocytic leukemia; **CML** = chronic myelogenous leukemia; **HL** = Hodgkin lymphoma; **HR** = hazard ratio; **IOM** = Institute of Medicine; **ICU** = intensive care unit; **MM** = multiple myeloma; **NHL** = non-Hodgkin lymphoma; **SEER** = Surveillance Epidemiology and End Results Program

Grant Support: This work was supported by the Mayo Clinic Division of Hematology and the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (R.S.G.).

Correspondence: Address to Ronald S. Go, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (go.ronald@mayo.edu).

REFERENCES

1. Hewitt ME, Petitti DB, eds; National Cancer Policy Board, National Research Council, and Division on Earth and Life Studies.

Interpreting the Volume-Outcome Relationship in the Context of Cancer Care. Washington, DC: National Academy Press; 2001.
2. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? a systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137(6):511-520.
3. Killeen SD, O'Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. *Br J Surg*. 2005;92(4):389-402.
4. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. *Br J Surg*. 2007;94(2):145-161.
5. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. *CA Cancer J Clin*. 2009;59(3):192-211.
6. Chang CM, Huang KY, Hsu TW, et al. Multivariate analyses to assess the effects of surgeon and hospital volume on cancer survival rates: a nationwide population-based study in Taiwan. *PLoS One*. 2012;7(7):e40590.
7. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med*. 2011;364(22):2128-2137.
8. Bilimoria KY, Phillips JD, Rock CE, Hayman A, Prystowsky JB, Bentrem DJ. Effect of surgeon training, specialization, and experience on outcomes for cancer surgery: a systematic review of the literature. *Ann Surg Oncol*. 2009;16(7):1799-1808.
9. Goulart BH, Reyes CM, Fedorenko CR, et al. Referral and treatment patterns among patients with stages III and IV non-small-cell lung cancer. *J Oncol Pract*. 2013;9(1):42-50.
10. Jang TL, Bekelman JE, Liu Y, et al. Physician visits prior to treatment for clinically localized prostate cancer. *Arch Intern Med*. 2010;170(5):440-450.
11. Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol*. 2012;30(21):2664-2669.
12. Davis S, Dahlberg S, Myers MH, Chen A, Steinhorn SC. Hodgkin's disease in the United States: a comparison of patient characteristics and survival in the Centralized Cancer Patient Data System and the Surveillance, Epidemiology, and End Results Program. *J Natl Cancer Inst*. 1987;78(3):471-478.
13. Alibhai SM, Leach M, Minden MD, Brandwein J. Outcomes and quality of care in acute myeloid leukemia over 40 years. *Cancer*. 2009;115(13):2903-2911.
14. Stiller CA, Benjamin S, Cartwright RA, et al. Patterns of care and survival for adolescents and young adults with acute leukaemia: a population-based study. *Br J Cancer*. 1999;79(3-4):658-665.
15. Loberiza FR Jr, Cannon AJ, Weisenburger DD, et al. Survival disparities in patients with lymphoma according to place of residence and treatment provider: a population-based study. *J Clin Oncol*. 2009;27(32):5376-5382.
16. Shanafelt TD, Kay NE, Rabe KG, et al. Hematologist/oncologist disease-specific expertise and survival: lessons from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). *Cancer*. 2012;118(7):1827-1837.
17. Mandal R, Bolt DM, Shah BK. Disparities in chronic myeloid leukemia survival by age, gender, and ethnicity in pre- and post-imatinib eras in the US. *Acta Oncol*. 2013;52(4):837-841.
18. Komrokji RS, Al Ali NH, Beg MS, et al. Outcome of diffuse large B-cell lymphoma in the United States has improved over time but racial disparities remain: review of SEER data. *Clin Lymphoma Myeloma Leuk*. 2011;11(3):257-260.
19. Evens AM, Antillon M, Aschebrook-Kilfoy B, Chiu BC. Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. *Ann Oncol*. 2012;23(8):2128-2137.
20. Goggins WB, Lo FF. Racial and ethnic disparities in survival of US children with acute lymphoblastic leukemia: evidence from the SEER database 1988-2008. *Cancer Causes Control*. 2012;23(5):737-743.
21. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood*. 2010;116(25):5501-5506.
22. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? a comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood*. 2008;112(5):1646-1654.
23. Loberiza FR Jr, Zhang MJ, Lee SJ, et al. Association of transplant center and physician factors on mortality after hematopoietic stem cell transplantation in the United States. *Blood*. 2005;105(7):2979-2987.
24. Lauseker M, Hasford J, Pfirrmann M, Hehlmann R. The impact of health care settings on survival time of patients with chronic myeloid leukemia. *Blood*. 2014;123(16):2494-2496.
25. Lecuyer L, Chevret S, Guidet B, et al. Case volume and mortality in haematological patients with acute respiratory failure. *Eur Respir J*. 2008;32(3):748-754.
26. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5-29.
27. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology Am Soc Hematol. Educ Program*. 2009:523-531.
28. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute myeloid leukemia, version 2.2013. *J Natl Compr Cancer Netw*. 2013;11(9):1047-1055.
29. Anderson KC, Alsina M, Bensinger W, et al. Multiple myeloma, version 1.2013. *J Natl Compr Cancer Netw*. 2013;11(1):11-17.
30. Drug and Biologic Approval and IND Activity Reports. US Food and Drug Administration website. http://www.fda.gov/Drugs/InformationOnDrugs/default.htm. Accessed December 31, 2014.
31. National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed December 31, 2014.
32. Zelenetz AD, Gordon LI, Wierda WG, et al. Non-Hodgkin's lymphomas, version 4.2014. *J Natl Compr Cancer Netw*. 2014;12(9):1282-1303.
33. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372(9):793-795.
34. Zaren HA, Nair S, Go RS, et al. Early-phase clinical trials in the community: results from the national cancer institute community cancer centers program early-phase working group baseline assessment. *J Oncol Pract*. 2013;9(2):e55-e61.
35. Forte GJ, Hanley A, Hagerty K, Kurup A, Neuss MN, Mulvey TM. American Society of Clinical Oncology National Census of Oncology Practices: preliminary report. *J Oncol Pract*. 2013;9(1):9-19.
36. Gesme DH, Wiseman M. Subspecialization in community oncology: option or necessity? *J Oncol Pract*. 2011;7(3):199-201.
37. Murray S, Obholz KL, Bowser AD, et al. Practice gaps and barriers to optimal care of hematologic malignancies in the United States. *J Community Support Oncol*. 2014;12(9):329-338.
38. SEER Cancer Statistics Review, 1975-2011. Surveillance, Epidemiology, and End Results Program website. http://seer.cancer.gov/csr/1975_2011/sections.html. Updated December 17, 2014. Accessed March 14, 2015.
39. Kirkwood MK, Kosty MP, Bajorin DF, Bruinooge SS, Goldstein MA. Tracking the workforce: the American Society of Clinical Oncology workforce information system. *J Oncol Pract*. 2013;9(1):3-8.
40. Gundersen Health System website. http://www.gundersenhealth.org. Accessed December 5, 2014.
41. Go RS, Frisby KA, Lee JA, et al. Clinical trial accrual among new cancer patients at a community-based cancer center. *Cancer*. 2006;106(2):426-433.
42. Smith M, Saunders R, Stuckhardt L, McGinnis JM, eds. *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*. Washington, DC: National Academies Press; 2013.

43. DeMartino JK, Larsen JK. Equity in cancer care: pathways, protocols, and guidelines. *J Natl Compr Cancer Netw*. 2012;10(suppl 1):S1-S9.
44. Chagpar R, Xing Y, Chiang YJ, et al. Adherence to stage-specific treatment guidelines for patients with colon cancer. *J Clin Oncol*. 2012;30(9):972-979.
45. Fennell ML, Das IP, Clauser S, Petrelli N, Salner A. The organization of multidisciplinary care teams: modeling internal and external influences on cancer care quality. *J Natl Cancer Inst Monogr*. 2010;2010(40):72-80.
46. Zweegman S, Palumbo A, Bringhen S, Sonneveld P. Age and aging in blood disorders: multiple myeloma. *Haematologica*. 2014;99(7):1133-1137.
47. Vij R. Treatment-related adverse events in patients with relapsed/refractory multiple myeloma. *Oncology*. 2011; 25(suppl 2):45-55.
48. Hayanga AJ, Mukherjee D, Chang D, et al. Teaching hospital status and operative mortality in the United States: tipping point in the volume-outcome relationship following colon resections? *Arch Surg*. 2010;145(4):346-350.
49. Brotherton SE, Etzel SI. Graduate medical education, 2013-2014. *JAMA*. 2014;312(22):2427-2445.
50. Brotherton SE, Etzel SI. Graduate medical education, 2007-2008. *JAMA*. 2008;300(10):1228-1243.
51. Anderson RJ. Subspecialization in internal medicine: a historical review, an analysis, and proposals for change. *Am J Med*. 1995; 99(1):74-81.
52. Greenberg CC, Ashley SW, Schrag D. Centralization of cancer surgery: what does it mean for surgical training? *J Clinl Oncol*. 2009;27(28):4637-4639.
53. Stitzenberg KB, Meropol NJ. Trends in centralization of cancer surgery. *Ann Surg Oncol*. 2010;17(11):2824-2831.