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Understanding the Relationship Between Care Volume and Clinical Outcomes in Multiple Myeloma

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For decades, a relationship between patient volume and clinical outcomes has been recognized for certain procedures and conditions.[1–4] The strongest and most consistent associations exist for less common conditions requiring high-risk procedures, such as pancreatic, gastric, and esophageal cancer resection, abdominal aortic aneurysm repair, and pediatric cardiac surgery.[1–4] More modest and less consistent associations have been reported for more common conditions and those treated with lower risk procedures, such as lung, bladder, colorectal, and prostate cancer.[1, 5, 6] Among medically treated malignancies, associations between facility volume and long-term survival have recently been identified for complex conditions requiring high-risk treatment regimens, including acute myeloid leukemia, non-Hodgkin lymphoma, and advanced melanoma and renal cell cancer treated with high-dose interleukin-2.[7–10]

In the article that accompanies this editorial, Go et al[11] also identify volume-outcome associations in multiple myeloma (MM), a relatively rare hematologic malignancy that has seen profound increases in diagnostic and therapeutic complexity over the past 20 years. Analyzing data from the National Cancer Database on 94,722 patients cared for at 1,333 facilities between 2003 and 2011, the authors found that patients who received their initial treatment at higher volume centers had better all-cause, long-term survival. Compared with patients initially treated by the highest volume quartile providers (10 or more patients with MM per year), those seen at the lowest quartile sites (less than four patients with MM per year) had a 22% higher risk of death. The effect appeared linear, with no obvious threshold, as has been seen in other conditions.

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The study by Go et al[11] meets most of the criteria of a methodologically strong volume-outcome study.[1, 2] They examined a national data set containing a large number of patients treated in diverse settings (more than half of patients were from nonacademic centers). They calculated the average annual volumes over 9 years, which will smooth out short-term fluctuations. They analyzed facility volume across quartiles and as a continuous variable. Because high-volume providers are often referred different kinds of patients, they adjusted for several factors that may influence survival including patient age, sex, race, ethnicity, education, income, insurance, and comorbidity, as well as receipt of an initial stem-cell transplantation. Finally, they focused on the most important long-term outcome of overall survival.

Nevertheless, the study has a few important limitations. The investigators did not have patient-level data on MM stage, cytogenetic features, or performance status. They also did not have data on case volumes of the treating clinician, a key factor that often influences outcomes more than hospital volume. They were not able to adjust for the use of specific chemotherapeutic agents or immunomodulatory drugs, although controlling for time period may have partly factored in the impact of newer agents. Because all facilities were Commission on Cancer–accredited programs, they may have higher volume, be more technologically sophisticated, and have greater oncology support services than facilities not included in the study. As a result, this means that Go et al[11] probably underestimate the magnitude of the volume-outcome relationship because the lowest volume facilities were not included.

What might explain the volume-outcome association in MM? One possibility is that healthier patients sought care at high-volume centers. Prior studies have identified referral biases in both directions.[12] For some conditions, the sickest, most complex patients are referred to specialty centers. For others, the best functioning, most socioeconomically privileged patients travel to centers of excellence. In the current study, both trends were observed. High-volume facilities treated more patients with favorable characteristics (eg, younger age, better insurance, fewer comorbidities), but they also cared for more minority and lower income individuals. Although the authors adjusted for these potential confounders, there could be unmeasured factors such as patient frailty and patient engagement causing residual bias.[13] Referral bias is unlikely to explain the finding because most patients were treated within 9 miles of home, and the authors controlled for travel distance. They also attributed cases to the facility where patients were initially treated, so any benefits that accrued from lower-volume sites referring patients to higher-volume centers for further treatment, evaluation for stem-cell transplantation, or enrollment onto clinical trials would get credited to that initial lower-volume site.

In the absence of significant referral bias, high volume must be a proxy for other factors such as the skills, experience, diagnostic and therapeutic decision making, and care processes of the treatment team. Prior studies showed that specialization of the treating physician can influence cancer outcomes.[2] Among patients with chronic lymphocytic leukemia treated within a single center of excellence, those managed by hematologist-oncologists with expertise in chronic lymphocytic leukemia had earlier time to treatment and better survival.[14] In contrast to solid tumors, for which diagnosis is based on tissue biopsy,

rendering a diagnosis of MM requires interpretation of numerous criteria including serum protein electrophoresis, immunofixation, light chain assays, bone marrow plasmacytosis, cytogenetics, radiographic studies, renal function, and hematologic parameters. Furthermore, diagnostic and staging criteria in MM continue to evolve. Highly specialized physicians may diagnose individuals sooner, which would lengthen survival as a result of lead-time bias.

MM experts may also be more familiar with guideline recommendations influencing the selection, sequencing, and combination of a growing number of newer therapies. They might also have access to new therapeutics through clinical trials before they are available in the community. Consistent with this hypothesis, Go et al[11] found that the volume-outcome effect was strongest in the most recent time period, when newer and better tolerated agents became available. In addition, MM specialists may be more familiar with disease-specific treatment-related complications, allowing them to maintain greater therapeutic dose-intensity when appropriate or modify therapy before toxicity escalates to the point of foregoing further treatment. Monitoring response to therapy in MM is nuanced, incorporating various parameters with separate response threshold determinations. Early recognition and management of rare MM complications such as amyloidosis could also impact survival. The selection and ongoing management of patients undergoing stem-cell transplantation may also drive long-term survival. Although Go et al[11] adjusted for receipt of initial stem-cell transplantation, they were not able to account for the downstream care needed by transplantation recipients.

At an institutional level, high-volume centers may have more skilled multidisciplinary teams to comanage disease and treatment complications, including radiation oncology, orthopedics, nephrology, onco-cardiology, and infectious disease consultants. Having advanced practice providers and nurses experienced in caring for patients with MM and patients who have received stem-cell transplantations could also be important. The 24/7 availability of intensivists and house staff and dedicated transplantation units might be other assets of higher-volume facilities. In the surgical literature, high volume hospitals derive much of their short-term survival advantage from their ability to successfully manage perioperative complications, thereby preventing someone from dying from a potentially life-threatening adverse event.[15] Similar variation in ability to manage complications could also play a role in patients with hematologic malignancies.

Because one in four patients with MM dies in the first year, and half of deaths happen in the first 3 months, the stakes are high to get the early management decisions right. The current study confirms this observation, because the greatest survival benefit attributable to higher-volume sites occurred during the first year. Therefore, trying to facilitate a referral to an MM specialist during the early months of diagnosis and treatment selection would be beneficial. For pancreatic and esophageal cancer surgery, policymakers and payers have advocated for selective referral to high-volume centers. This strategy may be impractical for MM because there are few centers that see a sufficient caseload to be considered a center of excellence. Moreover, major surgical procedures and perioperative care are completed within days, whereas MM management lasts years. At a minimum, it would make sense to strive for selective avoidance, so patients are not managed by the lowest-volume providers.[16] In addition, insurers and accountable care organizations could encourage and pay for second

opinions from high-volume providers. Referring clinicians and patients can identify MM specialists in their area by contacting the local MM patient support group (sponsored by the International Myeloma Foundation) or local chapter of the Leukemia and Lymphoma Society. If no local or regional experts meet these criteria, an alternative would be to obtain a virtual second opinion via an electronic consult with an MM expert to review the diagnosis, suggest an initial treatment plan, and assess appropriateness for stem-cell transplantation and clinical trials.

A quality improvement approach may also be fruitful. If researchers and experts can identify the specific processes of care used by high-volume providers that are associated with better outcomes, then evidence-based guidelines and best practice protocols can be disseminated and implemented across facilities. Because the management of MM will likely continue to change rapidly, it might make sense to link local hematologist-oncologists with experts through learning cooperatives. This kind of collaborative, virtual comanagement model between local providers and distant specialists has shown promise in improving treatment in hepatitis C.[17] As oncology groups and accountable care organizations become larger regional entities, there could be increasing opportunities for disease-specific specialization within a network, as well as facilitating virtual linkages with national experts and enrollment in appropriate clinical trials.

It is often said that “geography is destiny.” Because most patients with complex cancers like MM will be diagnosed and treated close to home, the challenge for oncologists, payers, and policymakers is to come up with creative, feasible ways to provide expert care to patients regardless of where they live. If there was a new drug that improved overall survival in MM by 22%, everyone would prescribe it. Pursuing this goal ought to be as much a priority for our field as developing the next new agent.

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