Minimally Invasive Component Separation Reduces Wound-Healing Complications from Abdominal Surgery

By Sarah Bronson

Component separation, a major advance in abdominal wall reconstruction, can prevent hernia recurrence in many patients.

Recently, a surgeon at The University of Texas MD Anderson Cancer Center developed a minimally invasive approach to component separation that reduces complications and potentially improves functional outcomes.

Component separation was introduced in 1990 for abdominal wall reconstructions in ventral hernia repair or other surgeries requiring resection along the midline of the rectus abdominis complex. Traditional, open component separation enables the surgeon to close musculofascial defects without excessive tension and without a distant transposition flap. However, the amount of dead space created and the need to transect the blood vessels that supply the overlying fat and skin during the open procedure can lead to seromas, infections, and wound-healing complications.

In minimally invasive component separation with inlay bioprosthetic mesh, subcutaneous tunnels allow access to the external oblique aponeurosis. Used with permission from Atlas of Abdominal Wall Reconstruction, Michael J. Rosen (ed.), Page 175, Copyright Elsevier Inc. 2012.
In response to these complications, Charles E. Butler, M.D., a professor in the Department of Plastic Surgery, developed minimally invasive component separation with inlay bioprosthetic mesh (MICSIB), a new technique that preserves the rectus abdominis perforator vessels and maintains the connection between the subcutaneous fat and the anterior rectus sheath.

“The minimally invasive operation was designed to be more predictable and more reliable and to achieve better outcomes with lower complication rates than open component separation. This may help cancer patients to be able to start postoperative chemotherapy or radiation therapy sooner,” Dr. Butler said.

Abdominal wall defects in cancer patients

Concurrent cancer and abdominal wall defects such as hernias can be difficult to manage because treatments for one condition can exacerbate the other. For example, complications such as an unhealed wound that persists or an infection that develops after hernia repair can delay chemotherapy or radiation therapy. Conversely, surgeons are less likely to immediately repair a hernia if treatments like chemotherapy and radiation therapy, which deplete the body’s ability to withstand and recover from hernia repair surgery, need to be given first.

Chemotherapy, radiation therapy, and cancer itself are risk factors for hernias, and cancer treatments increase the risk of wound-healing complications and hernia occurrence after abdominal surgery. By decreasing wound-healing complications, MICSIB can reduce the interference of one intervention with another.

Cancer patients have both a high rate of ventral hernias and an increased risk of hernia recurrence and wound complications after repair. Many of Dr. Butler’s patients have ventral hernias that other surgeons did not consider for elective repair because of the hernias’ severity, the high risk of complications associated with repairing the hernias, the patients’ comorbidities, or the need for extremely complex reconstructions, which sometimes require the use of a tissue flap to close the wound. MICSIB can improve these patients’ outcomes, enabling optimal cancer care. MICSIB is also used for immediate reconstruction of the abdominal wall following tumor resection.

Open component separation

Component separation reduces the muscular tension that can accompany the closure of the rectus abdominis muscle by separating the rectus abdominis muscle from the topmost of the three layers of oblique muscles to the left and right of the rectus abdominis. The surgeon creates skin flaps on each side of the semilunar line, which is just lateral to the rectus abdominis muscle. The external oblique aponeurosis is then released from the costal margin to near the pubis. This release and subsequent separation of the internal and external oblique muscles enables the surgeon to advance the rectus complex toward the midline, thus reducing the size of the defect. If the defect is narrow enough, the surgeon can perform a primary musculofascial closure reinforced with an inlay of synthetic or bioprosthetic mesh; in large defects mesh is used as a bridge between the musculofascial edges.

In traditional, open component separation, the surgeon accesses the oblique muscles and external oblique aponeurosis by elevating the skin flaps over the entire rectus abdominis muscle, thus separating the subcutaneous fat from the anterior rectus sheath and dissecting the rectus abdominis myocutaneous perforator vessels that are the main blood supply to the skin and subcutaneous fat. However, elevating the skin flaps results in subcutaneous dead space, which can lead to seromas and infections, and the reduced blood flow caused by cutting the perforator vessels inhibits wound healing. Thus, open component separation carries a risk of postoperative complications that can prolong recovery.
A BELO W  During min imally invasive component separation with inlay bioprosthetic mesh, the myocuta neous perforator vessels are preserved.

A BO V E  During traditional, open comp onent separation, the rectus abdominis perforating vessels are transect- ed, and a large subcutaneous dead space is created by elevating skin flaps from the anterior rectus sheath.

The minimally invasive procedure

Whereas open component separation fully separates the rectus abdominis muscle from the overlying skin, MICSIB uses narrow tunnels to access the external oblique aponeurosis and thus damages few, if any, rectus abdominis perforator vessels. With more vessels preserved, wounds can heal faster and more completely. The use of tunnels also limits the undermining of skin flaps that occurs with the separation of the anterior rectus sheath and the subcutaneous fat, which would otherwise devascularize the overlying skin fat and result in dead space.

To access the sites where the aponeurosis will be incised, the surgeon creates a tunnel 3–4 cm wide between the subcutis and the anterior rectus fascial sheath to connect the midline and semilunar line. By retracting the skin around this small tunnel, the surgeon can access and visualize a large area without the use of a laparoscope. The surgeon then makes a 1.5-cm incision in the external oblique aponeurosis just lateral to the semilunar line, inserts a suction handle (without suction) through the incision and into the avascular plane between the internal and external oblique aponeuroses (lateral to the rectus complex), and sweeps the handle inferiorly and superiorly to bluntly separate those aponeuroses and muscles. Then, the surgeon uses electrocautery and blunt dissection to create narrow vertical subcutaneous tunnels over the anticipated line along which the external oblique aponeurosis will be released.

At this point, the external oblique aponeurosis is not connected to either the inferior oblique aponeurosis or the subcutis and can be cut without injuring the overlying or underlying tissues. Scissors are used to incise the external oblique aponeurosis inferiorly toward the pubis, and scissors and electrocautery are used to incise the aponeurosis superiorly over the costal margin, where the amount of interdigitation between the aponeurosis and underlying muscle is greatest. As the surgeon incises the external oblique aponeurosis along the semilunar line, the suction handle is placed against the rectus complex between the internal and external oblique aponeuroses to guide dissection and prevent inadvertent incision of the rectus complex. The procedure is then repeated on the other side of the midline. All of this work is performed through the lateral access tunnels with use of a headlight and good retraction. No additional incisions are required, and no endoscopic equipment is involved, which makes MICSIB an efficient, fast, safe, and cost-effective procedure.

Outcomes of open component separation and MICSIB

Preserving vascularity and reducing dead space have been shown to improve wound healing. In a recent retrospective study, Dr. Butler and his colleagues compared the outcomes of complex ventral hernia repairs with open component separation in 50 patients and MICSIB in 57 patients. Significantly more patients who had undergone open component separation had wound-healing complications and skin dehiscences compared with those who had undergone MICSIB. Dr. Butler noted that, compared with the group of patients who had undergone open component separation, the group of patients who had undergone MICSIB had significantly larger defects and required significantly larger amounts of mesh for repair, indicating a possible selection bias toward patients with more severe hernias. Nevertheless, in the outcomes measured, the group that had undergone MICSIB had similar or better results compared with the group that had undergone open component separation.

“Seeing cancer patients whose sickness was made more complex by hernias stimulated me to develop a technology to address the complicated and severe cases that we see here at MD Anderson,” Dr. Butler said. “This technique is now used for challenging ventral hernia repairs regardless of whether patients have cancer.”

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FURTHER READING

The effect of bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), on overall survival in glioblastoma patients is currently being studied in two multicenter clinical trials. At the same time, basic and translational researchers are trying to better understand bevacizumab’s mechanisms of action against glioblastoma and how to use bevacizumab to more effectively treat this disease. John de Groot, M.D., an associate professor in the Department of Neuro-Oncology at The University of Texas MD Anderson Cancer Center, divides his time between caring for patients in the clinic and studying glioblastoma in the laboratory. “There are many simple questions about treating glioblastoma with bevacizumab that we don’t know the answers to,” he said.

Bevacizumab for recurrent glioblastoma

Virginia Stark-Vance, M.D., an oncologist in private practice, was the first to report several partial responses in a small series of patients with recurrent glioblastoma treated with bevacizumab plus irinotecan. These data, presented in an abstract at the 2005 meeting of the European Association of Neuro-oncology, opened the door to clinical trials of bevacizumab for the treatment of recurrent glioblastoma—a door that previously had been firmly shut because of concerns that the drug might cause bleeding in the brain.

The subsequent studies showed that bevacizumab produced dramatic radiographic responses: contrast-enhanced magnetic resonance imaging showed a reduction in contrast enhancement, which indicated a pruning of tumor vessels and a reduction in vascular permeability, in almost all patients after administration of the drug. On the basis of two clinical trials in which patients

VEGF Inhibitors: Promise and Challenges

All of the antiangiogenic agents approved by the U.S. Food and Drug Administration for cancer treatment primarily target vascular endothelial growth factor (VEGF), a powerful regulator of the development and function of blood vessels in tumors.

Since VEGF’s discovery nearly 30 years ago, basic science and clinical researchers have been studying how blocking VEGF might slow or stop the growth of tumors, which require a blood supply to survive and expand. Lee Ellis, M.D., a professor in the Departments of Surgical Oncology and Cancer Biology, ad interim chair of the Department of Cancer Biology, and director of the Metastasis Research Center at The University of Texas MD Anderson Cancer Center, began conducting research in the field of antiangiogenic therapy in 1992. Since then, he has seen tremendous initial excitement about antiangiogenic agents give way to measured optimism, or even cynicism, based on clinical trial results. “The improvement in patient outcomes with these drugs is variable,” he said, “but it is less than we had anticipated.”

In 2003, the first phase III clinical trial of a VEGF inhibitor, bevacizumab, showed that the agent’s addition to standard chemotherapy for metastatic colorectal cancer increased overall survival by an average of 4 months. To date, it is estimated that more than 30 VEGF inhibitors have been identified and tested in more than 2,000 clinical trials.

Today, five VEGF inhibitors are approved by the U.S. Food and Drug Administration for cancer treatment: bevacizumab for non–small cell lung cancer, recurrent glioblastoma, metastatic colorectal cancer, and metastatic renal cell carcinoma (RCC); sunitinib for advanced RCC and advanced pancreatic neuroendocrine tumors; pazopanib for advanced RCC and advanced soft tissue sarcoma; axitinib for advanced RCC; and sorafenib for advanced RCC and unresectable hepatocellular carcinoma.

Bevacizumab, probably the best-known VEGF inhibitor, is a monoclonal antibody that binds to VEGF and thereby prevents VEGF from binding to VEGF receptors. It is given intravenously once every 2–3 weeks. Pazopanib, axitinib, sunitinib, and sorafenib are tyrosine kinase inhibitors that block VEGF-induced cellular signaling. These drugs are taken orally, typically once or twice a day.

Reviewing the current knowledge of VEGF inhibitor therapy, Dr. Ellis said that

By Stephanie Deming

The antiangiogenic agent bevacizumab has been shown to prolong progression-free survival and ameliorate symptoms in patients with recurrent glioblastoma. However, it remains unknown whether bevacizumab should be used to treat newly diagnosed glioblastoma and whether bevacizumab prolongs the overall survival of patients with glioblastoma.

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with recurrent glioblastoma treated with bevacizumab alone or bevacizumab plus irinotecan had higher rates of 6-month progression-free survival than historical controls treated with irinotecan alone, bevacizumab received accelerated approval from the U.S. Food and Drug Administration in 2009 for use in the treatment of recurrent glioblastoma.

Bevacizumab can also dramatically improve quality of life for patients with recurrent glioblastoma, Dr. de Groot said. Glioblastomas have leaky blood vessels, which cause brain edema, and this edema pushes on different structures in the brain and causes a variety of debilitating symptoms. The edema is typically treated with steroids, but steroids themselves cause adverse effects, including diabetes, high blood pressure, and muscle weakness. Bevacizumab decreases

Not all patients benefit from antiangiogenic therapy. A patient with recurrent glioblastoma was treated with bevacizumab but did not respond (left image). The tumor (arrows) continued to grow and invade the corpus callosum (middle and right images taken 4 and 8 weeks, respectively, from the initiation of bevacizumab).

one of the most important findings to date is that in most types of cancer, including those of the colon, breast, and lung, VEGF inhibitors confer no benefit unless they are administered in combination with chemotherapy. Another important finding is that VEGF inhibitors produce side effects such as hypertension and, rarely, bleeding problems and blood clots.

“I think we’ve kind of hit a ceiling in designing new VEGF inhibitors,” Dr. Ellis said. “There are only two ways to improve VEGF inhibitor therapy: one is to find predictive biomarkers that indicate which patients are going to respond and which are not, and the other is to figure out how best to use VEGF inhibitors in combination with other therapies. Identifying which patients are most likely to respond is important because we do not want to administer a drug to a patient if we know it will not be effective.”

Researchers are looking for biomarkers that could be measured to identify likely responders before treatment. At the European Society of Medical Oncology meeting in October 2011, researchers revealed evidence that circulating levels of a form of VEGF-A predicted response to bevacizumab in patients with glioblastoma. However, it is not clear precisely what level of VEGF-A should be used as the cutoff to distinguish which patients are likely to benefit. Furthermore, these results came from a retrospective study and need to be validated prospectively.

The search for other predictive biomarkers is made difficult by the fact that the mechanisms of action of VEGF inhibitors remain unclear. “It’s likely that the mechanisms of action are dependent on the specific tumor type,” Dr. Ellis said. A number of theories have been proposed to explain how these drugs work, including that the drugs inhibit angiogenesis, inhibit vasculogenesis, normalize the tumor vasculature, constrict blood vessels, alter the stem cell niche, or exert immunologic effects. In any case, inhibition of angiogenesis (i.e., blocking the proliferation of endothelial cells, which form blood vessels) does not appear to be the sole explanation for the drugs’ effects.

Dr. Ellis believes that VEGF inhibitors should continue to be tested in combination with various types of drugs, including other antiangiogenic therapies, signaling inhibitors, and chemotherapy drugs.

“We have to keep an open mind, but we shouldn’t use a shotgun approach,” said Dr. Ellis, who is currently studying the role of VEGF receptors on colon cancer cells. “We should take a very measured and scientific approach based on validated, preclinical data that support clinical trial development.”

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the permeability of tumor blood vessels, which reduces edema and helps patients feel better, and the drug allows tapering or discontinuing the use of steroids in some patients.

Unfortunately, the mean duration of response to bevacizumab is only about 4 months in patients with recurrent glioblastoma, and once bevacizumab stops working, oncologists have few or no options left for slowing disease progression. "When these tumors become resistant to bevacizumab," Dr. de Groot said, "they’re very hard to treat. No salvage therapy has ever been shown to help.” He is currently conducting a clinical trial to determine whether using a lower dose of bevacizumab in patients with recurrent disease may modulate or delay the development of resistance.

Bevacizumab for newly diagnosed glioblastoma

The standard therapy for newly diagnosed glioblastoma is surgery followed by a 6-week course of concurrent radiation therapy and temozolomide, followed by maintenance therapy with temozolomide for 1 year. Currently, two clinical trials are investigating whether adding bevacizumab to standard therapy will improve patient outcomes.

In the first trial, opened in 2008 by the Radiation Therapy Oncology Group (RTOG), more than 900 patients were randomly assigned to standard therapy plus either bevacizumab or placebo during chemoradiation and maintenance therapy. Mark Gilbert, M.D., a professor in the Department of Neuro-Oncology at MD Anderson, is the principal investigator. The study has completed patient accrual, and results will likely be available sometime in 2013.

In the RTOG trial, if patients randomly assigned to placebo experience disease progression, they can cross over and receive bevacizumab. Thus, according to Dr. de Groot, the trial may not show a survival difference between the two arms even if a survival difference would have been observed without crossover. “This trial is investigating whether giving bevacizumab at the time of progression will have the same survival benefit as giving it from the time of diagnosis,” he said. “And that’s an important question.”

The second trial, called AVAglio, is sponsored by Roche and is similar in design to the RTOG study. However, AVAglio is being conducted in Europe, where bevacizumab is not approved in all countries, and therefore it is expected that fewer patients who experience disease progression while receiving placebo will subsequently switch to bevacizumab. If this prediction is borne out, this trial will be better able to answer the question of whether bevacizumab promotes tumor invasion.

Dr. de Groot cautioned against the use of bevacizumab to treat newly diagnosed glioblastoma in the period before results from these two trials become available. There is some preliminary evidence, he said, that bevacizumab may promote tumor resistance to therapy. In addition, there is controversy in the literature about whether antiangiogenic therapy promotes tumor invasion.

Dr. de Groot noted that a significant portion of practicing physicians currently add bevacizumab to the standard treatment for newly diagnosed glioblastoma. However, he said, “Because we don’t have any evidence to suggest that adding bevacizumab up front improves outcomes compared with standard therapy, and because there are data suggesting that it could make matters worse, we don’t recommend adding antiangiogenic therapy to the standard of care for newly diagnosed patients outside of a clinical trial.”

Other clinical and laboratory studies

“Some glioblastoma patients respond to bevacizumab for long periods of time,” he said. “If we had a biomarker that identified those patients who were most likely to benefit, we could justify using the drug in that subgroup of patients—that’s sort of the holy grail of personalized medicine.” In collaboration with John Heymach, M.D., Ph.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology, Dr. de Groot is trying to identify such a marker.

Dr. de Groot is also conducting preclinical studies of various combinations of bevacizumab plus new drugs as well as studying whether antiangiogenesis therapy promotes tumor invasion. “That’s something that you can reproduce in the laboratory,” he said, “but it’s not clear what effect these therapies have on tumor biology in patients.”

Dr. de Groot and his colleagues are also studying mechanisms of resistance to antiangiogenesis therapy. In a recent study, the researchers compared cells from xenografts of human glioblastoma in untreated mice and in mice with glioblastomas that had become resistant to a VEGF inhibitor. The treatment-resistant cells had increased expression of mesenchymal and proinflammatory genes and were more invasive in vitro. In collaboration with Amy Heimberger, M.D., an associate professor in the Department of Neurosurgery, Dr. de Groot recently found that the upregulation of the signal transducer and activator of transcription 3 (STAT3) protein plays a role in resistance to anti–VEGF therapy. They also found that, in a mouse model of glioblastoma, cotreatment with a VEGF inhibitor and a Janus kinase (JAK)/STAT3 inhibitor reduced tumor volume more than treatment with either agent alone did.

“I think we need to work harder to better understand how these drugs work,” Dr. de Groot said, “in order to use them more effectively.”

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“We don’t recommend adding antiangiogenic therapy to the standard of care for newly diagnosed patients outside of a clinical trial.”

– Dr. John de Groot
Hospice Care

Patients and families have choices for care and comfort

When patients are told they likely have less than 6 months to live, hospice arrangements are usually suggested.

In hospice care—either at a facility or in patients’ homes—medical attention shifts from treating the disease to making the patients as comfortable as possible. Quality of life becomes the ultimate concern, and pain management and social, spiritual, and psychological support for the patients and their families are addressed. Studies have shown that the earlier a terminally ill patient engages in palliative care or hospice services, the better the patient’s quality of life will be.

What is hospice care?

A typical team providing hospice care will include, at the minimum, a physician, a nurse, and a counselor, although it may include other health care professionals, social workers, and chaplains. Together, the team will work to ensure that patients receive medical attention as well as medicine required to manage pain.

Hospice workers strive to help patients reduce stress as much as possible by providing a home-like environment or providing care in the patients’ homes. Hospice workers address patients’ psychological, social, and spiritual needs by providing counseling and companionship and sometimes by helping them reminisce about the life they have lived. Combined, the two-pronged approach of pain management and psychosocial care ensures that patients enjoy as dignified and comfortable an end-of-life experience as possible.

Hospice care options

Hospice programs are becoming increasingly available as awareness grows of the benefits of attention to a patient’s comfort in his or her last months of life. With nearly 5,000 hospice facilities in the United States alone, patients and their families have many options for hospice care and can select a provider that best aligns with their individual needs.

If patients still require medical attention, it may be provided within the hospital or in a nursing home that offers advanced medical care, with special attention paid to maintaining their level of comfort. In some cases, a facility specifically designed for hospice care may be available.

Typical facility hospice programs include:

- 24-hour medical care through one’s physician or a specialty hospice doctor and a staff of nurses, therapists, and aides;
- easy access to various treatments or medical equipment;
- counseling services for mental well-being;
- spiritual comfort from onsite or visiting clergy;
- help for personal needs through social services; and
- visitation hours that allow family members to come at any time.

If the life-threatening disease does not require constant medical care, patients may choose to return to their homes and receive treatment from mobile specialists trained to provide hospice care. While in-home care usually will not provide around-the-clock assistance, help is always available when it is needed.

Typical in-home hospice programs include:

- in-home medical care as well as 24-hour access to nursing support;
- hospital or doctor visits as needed;
- help with getting required medical supplies or equipment;
- help with day-to-day necessities such as cooking, cleaning, or personal care;
- information for the patient’s family about how to give medical care between care team visits;
- time spent with the patient to provide family members much-needed physical and social relief from full-time caregiving; and
- counseling for both the patient and family during the illness and after the patient has died.

Each option has its merits. Choosing a hospice program should involve identifying one that aligns with a patient’s specific needs and beliefs as well as investigating the agency’s credentials. A patient’s insurance coverage may affect his or her choice, but most insurance plans and Medicaid now cover hospice care, and Medicare offers the Medicare Hospice Benefit.

Knowing their options can help patients and their families find the hospice program that best suits their needs.

—L. Jorewicz

FOR MORE INFORMATION

- Talk to your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
- Call MD Anderson’s Department of Social Work at 713-792-6195
- Contact the National Hospice and Palliative Care Organization at 703-837-1500 or www.nhpco.org
- Contact the Hospice Foundation of America at 800-854-3402 or www.hospicefoundation.org
IN BRIEF

Panobinostat Elicits Durable Response in Hodgkin Lymphoma

The experimental drug panobinostat can elicit durable disease responses in Hodgkin lymphoma (HL) patients who have relapsed disease or disease that is refractory to autologous stem-cell transplantation, a multicenter, international phase II study has found.

The prospective study, which was conducted in part at The University of Texas MD Anderson Cancer Center, enrolled 129 HL patients who had progressive disease despite having received high-dose autologous stem-cell transplantation. The patients received 40 mg of panobinostat 3 times per week in a 21-day cycle. Therapy was stopped when patients experienced progressive disease or intolerable toxicity, began new therapy, or withdrew from the study. Panobinostat was also stopped if the investigator believed it to no longer benefit the patient.

Panobinostat reduced tumor size in 96 patients (74%). Based on the investigators’ assessment of the patients’ computed tomography or magnetic resonance imaging studies, 30 patients’ tumors had a partial response, 5 patients had a complete response, partial response, or stable disease, respectively; however, patients with progressive disease did not have a change in TARC levels. Further analysis revealed that patients with a lower-than-median reduction of TARC were at greater risk of disease progression than were patients with a higher-than-median reduction of TARC.

The study’s report was published online (ahead of print) on April 30 by the Journal of Clinical Oncology.