

Simultaneous Resection of Liver and Lung Metastases from Colorectal Cancer Eliminates Need for Second Surgery

By Bryan Tutt

Patients with colorectal cancer metastases to the liver and one or both lungs often face the unwelcome prospect of two

operations and two recovery periods. But a novel surgical approach enables the liver and lung lesion resections to be performed during the same operation.

To reduce the sequelae that result from separate operations for patients with metastatic disease in both the liver and lungs—the two most common sites of colorectal cancer metastases—surgeons at The University of Texas MD Anderson Cancer Center developed a technique to resect the lung metastases using a trans-diaphragmatic approach immediately following the liver resection.

A surgical team performs a simultaneous resection of liver and lung metastases in a patient with colorectal cancer. In this procedure, the liver lesions are resected first, and the lung lesions are resected through an incision in the diaphragm. Image courtesy of Dr. Yoshihiro Mise.

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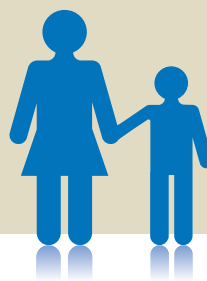
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Simultaneous Resection of Liver and Lung Metastases

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“We can combine the thoracic and hepatic procedures under one anesthesia induction for the benefit of the patient,” said Reza Mehran, M.D., a professor in the Department of Thoracic and Cardiovascular Surgery.

Benefits of complete metastasectomy

“For patients with colorectal cancer metastases in the liver and lungs, complete resection of the metastases in both organs offers the best survival outcomes,” said Jean-Nicolas Vauthey, M.D., a professor and chief of the liver and pancreas section in the Department of Surgical Oncology. This survival advantage was demonstrated in a recent study in which Drs. Mehran and Vauthey collaborated with Yoshihiro Mise, M.D., Ph.D., and other MD Anderson researchers. The retrospective study compared 3- and 5-year overall survival rates among patients with liver and lung metastases from colorectal cancer. Patients who underwent chemotherapy plus resection of only the liver metastases had higher survival rates than did patients who underwent chemotherapy only but lower survival rates than did patients who underwent chemotherapy plus resection of both the lung and liver metastases.

Although that study included patients whose liver and lung lesion resections were done as separate sur-

“The benefit is that the patient doesn’t have to undergo a second surgery, a second anesthesia induction, and a second source of pain.”

– Dr. Reza Mehran

geries, another MD Anderson study showed that patients who underwent simultaneous liver and transdiaphragmatic wedge lung resections had similar operative outcomes but less blood loss compared with patients who underwent separate resections.

“The novelty of the new approach is that we can do both resections at the same time with a single incision, avoiding a thoracic incision,” Dr. Vauthey said.

Patient selection

All patients with colorectal cancer metastases in the liver and one or both lungs whose liver metastases are completely resectable are considered for simultaneous resection of their lung metastases. This includes patients whose liver disease requires a two-stage

resection; the lung lesion resection could be performed during either stage.

Although liver resections may be performed on patients who are not candidates for lung metastasis resections, lung metastasis resections usually are not performed on patients with unresectable liver metastases because of the patients’ poor prognosis.

At MD Anderson, patients with colorectal cancer metastases in the liver and lungs typically receive chemotherapy for 2–3 months before surgery. Computed tomography (CT) scans taken before and after chemotherapy help determine whether a patient is a candidate for liver resection and/or lung metastasectomy.

“We diagnose the lung metastases based on their change in size and appearance on CT following chemotherapy,” Dr. Vauthey said.

Patients whose liver or lung metastases have grown during chemotherapy have a poor prognosis and are not typically candidates for metastasectomy. In 70%–80% of patients, however, the lung lesions respond to chemotherapy or are stable. Patients whose disease responds are candidates for surgery.

Patients whose lung lesions remain stable after chemotherapy present a dilemma because the lesions could be tumors or merely scar tissue. These cases are reviewed by a multidisciplinary

During a transdiaphragmatic lung resection, a surgeon palpates the lung to locate the metastatic lesion (left) and then resects it using a surgical stapler (right). Image courtesy of Dr. Yoshihiro Mise.

nary team of physicians, and the decision whether to resect the lung lesions is made on a case-by-case basis. "If the tumors are large and not calcified, we will likely decide to operate," Dr. Vauthey said. "The complication rate for the transdiaphragmatic procedure is low, so you can make the case for removing a suspicious lung lesion even though you're not 100% sure that it's cancer."

Small lung tumors are less likely to be resected. "If the tumor is too small for the surgeon to palpate, we prefer to wait," Dr. Mehran said. "We tell the patient to come back in a year for another CT study, and if the tumor has grown, then we take it out."

The location of the lung lesions also affects the decision whether to operate. "If the tumor is too deep for wedge resection, we prefer to use radiation therapy," Dr. Mehran said.

Simultaneous resection

During a simultaneous resection of liver and lung metastases, a double-lumen endotracheal tube is used to allow one-lung ventilation. The hepatic surgeon makes an abdominal incision and performs an open hepatectomy. Dr. Vauthey said that this part of the procedure is done exactly as it would be done if the lung surgery were not planned.

When the liver resection is finished, the thoracic surgeon takes over. The lung with the metastases is deflated, and the surgeon makes an incision in the diaphragm large enough to reach through. The thoracic surgeon then cuts the inferior pulmonary ligament to mobilize the lung.

Next, the thoracic surgeon, who knows the locations of the tumor or tumors from CT scans, reaches through the diaphragm incision and palpates the lung to find each tumor. Working by touch, the surgeon then performs a wedge resection using a surgical stapler. "I hold the tumor with my fingers and staple around it to free it from the surrounding tissue," Dr. Mehran said.

Dr. Vauthey added that the transdi-

In an analysis of patients with colorectal cancer metastases to the liver and lungs, patients who underwent chemotherapy plus resection of the liver and lung metastases had a longer median overall survival than did patients who underwent chemotherapy plus liver resection or patients who underwent chemotherapy only ($P < .01$). Adapted from Mise Y, et al., Ann Surg Oncol. 2014.

aphragmatic approach has been done in patients with bilateral lung metastases. "We make an incision in the right side of the diaphragm and remove the lesions in the right lung, and then we close the diaphragm, re-inflate the right lung, and deflate the left lung and make an incision in the left side of the diaphragm," he said.

Once the resection is complete, a chest tube is inserted, the diaphragm is closed, and the abdominal incision is closed.

The chest tube usually is removed the day after surgery. The typical hospital stay is the same as that for a liver resection alone, which is about 6 days.

"We've had no complications so far in patients who have undergone simultaneous resections of liver and lung metastases. The procedure is very well tolerated," Dr. Mehran said. "Simultaneous resection is very patient friendly. The benefit is that the patient doesn't have to undergo a second surgery, a second anesthesia induction,

and a second source of pain to achieve the same objective, which is to make the patient cancer-free." ■

FOR MORE INFORMATION

Dr. Reza Mehran.....713-563-3908
Dr. Jean-Nicolas Vauthey.....713-792-2022

FURTHER READING

Mise Y, Mehran RJ, Aloia TA, et al. Simultaneous lung resection via a transdiaphragmatic approach in patients undergoing liver resection for synchronous liver and lung metastases. *Surgery*. 2014;156:1197-203.

Mise Y, Kopetz S, Mehran RJ, et al. Is complete liver resection without resection of synchronous lung metastases justified? *Ann Surg Oncol*. 2014. doi: 10.1245/s10434-014-4207-3. [Epub ahead of print]

Some Breast Cancer Patients May Benefit from Shortening of Whole-Breast Irradiation

By Markeda Wade

A shorter course of radiation therapy at higher doses per fraction than the standard regimen could reduce side effects and improve quality of life for some patients with breast cancer.

For patients with early-stage breast cancer who undergo breast-conserving therapy, the standard treatment regimen includes 6 weeks of whole-breast irradiation (WBI). However, the results of a recent clinical trial suggest that hypofractionated WBI, which involves fewer radiation fractions at higher doses per fraction but a lower total dose, causes fewer short-term side effects and lower rates of fatigue.

Hypofractionated WBI

The efficacy of hypofractionated WBI is well established. In the early 2000s, four large randomized controlled trials in Canada and the United Kingdom compared 3–4-week courses of hypofractionated WBI with 5–6-week courses of conventionally fractionated WBI and showed that the outcomes were similar with regard to tumor control, patient survival, and side effect profiles. At 10 years' follow-up, the outcomes were still comparable.

Because the protocols of some of the trials did not include a radiation boost—which is standard in the United States—there were concerns about the applicability of the results to U.S. patients. Thus, hypofractionated WBI has not been widely adopted, and only 20% of eligible patients in the United States currently receive hypofractionated WBI



“In addition to the benefits of reduced side effects and improved overall quality of life, the treatment plan is decreased by 2 weeks.”

– Dr. Benjamin Smith

instead of the longer course of conventionally fractionated WBI.

The slow adoption of hypofractionated WBI continues despite the 2011 publication of guidelines for the use of hypofractionated WBI. The guidelines, developed by a task force from the American Society for Radiation Oncology (ASTRO), were based on prior clinical studies showing that hypofractionated WBI was equivalent to conventionally fractionated WBI for patients 50 years or older who had pathologic stage T1–2 N0 breast cancer and had not received systemic chemotherapy.

The authors of the ASTRO guidelines noted that more research was needed to determine the role of hypofractionated WBI for patients with other characteristics and whether toxic effects differ between conventional and hypofractionated WBI delivered in conjunction with chemotherapy or a radiation boost.

Clinical trial

To clarify the appropriate use of hypofractionated WBI, researchers at The University of Texas MD Anderson Cancer Center established a clinical trial comparing long-term cosmetic outcomes and short-term toxic effects between hypofractionated and conventionally fractionated WBI.

The study population was more diverse than those of previous studies from Canada and the United Kingdom and included patients who were undergoing chemotherapy with anthracy-

clines or taxanes, had received neoadjuvant chemotherapy, or had ductal carcinoma in situ.

Eligible patients were women 40 years and older with ductal carcinoma in situ or early invasive breast cancer that was defined pathologically as Tis, T1, or T2 and N0, N1mi, or N1a. All patients had undergone breast-conserving surgery with negative surgical margins. Patients with more than three involved axillary lymph nodes were ineligible, as were those for whom regional lymph node irradiation was planned via the addition of a third field.

A total of 287 patients were enrolled from 2011 to early 2014 and randomly assigned to receive conventionally fractionated WBI (50 Gy in 25 fractions followed by a tumor bed boost of 10–14 Gy in 5–7 fractions) or hypofractionated WBI (42.56 Gy in 16 fractions followed by a tumor bed boost of 10.0–12.5 Gy in 4–5 fractions).

“Dogma suggests that low daily doses that accumulate to a high total dose give the best result, but what we’ve proposed is a higher dose per treatment for a lower total dose,” said Benjamin Smith, M.D., an associate professor in the Department of Radiation Oncology and the trial’s principal investigator. Co-investigators on the trial were Simona Shaitelman, M.D., an assistant professor in the Department of Radiation Oncology, and Thomas Buchholz, M.D., MD Anderson’s Executive Vice President and Physician-in-Chief, who is also a professor in the

Shorter Course

Department of Radiation Oncology.

Overall, the rates of acute toxic effects of grade 2 or higher were significantly lower among patients who received hypofractionated WBI than in patients who received conventionally fractionated WBI. Specifically, patients who received hypofractionated WBI had significantly lower rates of grade 2 or higher dermatitis, pruritus, breast pain, hyperpigmentation, and fatigue.

At baseline, patients in both arms had similar physical well-being and self-reported fatigue as assessed using the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire. However, 6 months after completing radiation therapy, the patients who received hypofractionated WBI had better physical well-being and self-reported fatigue scores on the FACT-B than did those who received conventionally fractionated WBI. Oncologic outcomes, to date, are similar in the two arms.

“These were the first real data that the 4-week regimen was not just equivalent to the longer regimen in terms of oncologic outcomes but better in terms of side effects—especially fatigue,” Dr. Smith said. “In addition to the benefits of reduced side effects and improved overall quality of life, the treatment plan is decreased by 2 weeks, which the average patient prefers.”

The results of the study were presented by Dr. Shaitelman in September at ASTRO’s annual meeting in San Francisco and will be submitted for publication later this year.

Moving forward

Even as patients in the trial continue to be monitored for long-term cosmetic outcomes, Dr. Smith and his colleagues hope to build on the results of this study to open a randomized clinical trial to assess hypofractionated WBI in patients who do not meet the current ASTRO guidelines for such treatment. ■

FOR MORE INFORMATION

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IMPACT2 Study Tests Benefits of Personalized Cancer Treatment Based on Molecular Profiling

By Bryan Tutt

Molecular profiling has the potential to revolutionize cancer medicine by helping clinicians select treatments based on the genomic characteristics of each patient’s tumor. But for most types of cancer, this potential has yet to be verified by a randomized clinical study. Such a study—in which treatment selection based on tumor molecular profiling is compared with treatment selection not based on tumor molecular profiling—is now enrolling patients with metastatic solid tumors at The University of Texas MD Anderson Cancer Center.

The study, IMPACT2, is based on early results from the ongoing first IMPACT study, in which researchers are examining the molecular profiles of tumors from patients enrolled in phase I clinical trials at MD Anderson. In a preliminary analysis of 1,144 cases, genomic alterations have been identified in 40% of the tumors. The analysis also showed that patients treated with targeted therapies known

to work against at least one of their tumors’ molecular alterations have had significantly higher overall response rates and longer median overall survival and time to treatment failure than patients whose treatments did not match their tumors’ alterations.

The preliminary results of the first IMPACT study were presented at the 2011 American Society of Clinical



“Access to clinical trials of targeted therapies is extremely limited. ... These should be available to all patients with cancer.”

– Dr. Apostolia Tsimberidou

IMPACT2 Tests Personalized Cancer Treatment

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Oncology Annual Meeting by Apostolia Tsimberidou, M.D., Ph.D., an associate professor in the Department of Investigational Cancer Therapeutics and the principal investigator of that study and the IMPACT2 study. Dr. Tsimberidou said, “These results are very encouraging, but they need to be confirmed by a randomized study before precision medicine can be widely implemented.”

Precision medicine, also known as personalized medicine, is the integration of tumor molecular data into medical practice decisions. Previous studies of precision medicine, such as the BATTLE trials in lung cancer, have focused on single tumor types, but Dr. Tsimberidou envisions a day when all cancer treatment will be guided by molecular profiling. “We wanted to develop a randomized trial to test precision medicine across multiple tumor types,” she said.

IMPACT2

The IMPACT2 study is enrolling patients with solid tumors who have metastatic disease and have received 0–3 prior therapies. Patients must have tumors that are accessible by biopsy or have tumor tissue available that was removed within the previous year, with no therapeutic intervention in the interim.

The tumor biopsy specimens are screened with a profiling assay that detects alterations in 315 cancer-related genes. Patients are eligible for trial randomization if their tumors have genomic alterations for which a treatment is available commercially or is being studied in a clinical trial at MD Anderson. However, patients whose tumors can be treated with a targeted drug that is approved by the U.S. Food and Drug Administration (FDA) for their cancer type are not eligible for randomization; such patients would instead receive the FDA-approved drug from their treating physician.

For example, *BRAF* gene mutations are seen in about half of patients with

In the first IMPACT study, cancer patients whose treatments were selected on the basis of their tumors' molecular profiles had a longer median progression-free survival than did patients whose treatments were not based on molecular profiling ($P < .0001$). A randomized study is now under way to confirm these results. Adapted from slides presented by Dr. Tsimberidou at the 2011 American Society of Clinical Oncology Annual Meeting.

melanoma. Two drugs that target the *BRAF* protein, vemurafenib and dabrafenib, are approved by the FDA for the treatment of melanoma; therefore, a patient with *BRAF*-mutant melanoma would not be a candidate for randomization in IMPACT2. However, *BRAF* mutations also occur, although less frequently, in patients with other tumor types, such as lung cancer or head and neck carcinoma. Such patients would be eligible for IMPACT2 because *BRAF* inhibitors are available but not approved for their cancer types.

Eligible patients are randomly assigned to receive targeted therapy or treatment not selected on the basis of the tumor's molecular alterations; the latter is determined by the treating

physician. Treatments for patients assigned to receive targeted therapies are determined by a tumor board that uses a standardized treatment algorithm. This algorithm is updated weekly based on the available clinical trials that are actively recruiting patients.

The tumor board, which consists of investigators from each participating department, establishes the ordered lists of molecular alterations to be targeted and of available clinical trials and targeted drugs. Each individual department determines the trial priority for each tumor type and provides updated lists of clinical trials.

“This study would not be possible without the active participation of several departments in the Division of

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Telling Your Child About Your Cancer

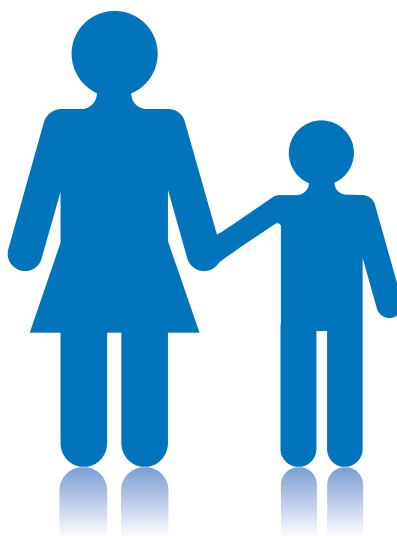
Open, honest communication helps children cope

Learning that you have cancer is extremely challenging; however, telling your child about it may be even more difficult. Many people diagnosed with cancer face this issue: more than one-fifth of cancer patients and survivors have a son or daughter under 18 years old. Here are some tips about when, where, and how to explain your cancer diagnosis to your child.

Tell your child about your cancer as soon as possible. Even though some parents feel the urge to protect their children, delaying this conversation is never a good idea. “It’s not a matter of if they’ll find out; it’s a matter of when,” said Martha Aschenbrenner, LPC, a counselor in the Acute Palliative Care Unit at The University of Texas MD Anderson Cancer Center. Being open with your child sooner rather than later fosters trust and lets your child understand that he or she can openly talk to you about your cancer.

Choose a familiar location for the conversation. If this isn’t possible, choose a quiet place where you won’t be interrupted by others. Your primary goal should be making your child feel safe and secure. Ms. Aschenbrenner suggested having a minimal number of adults there so that your child can be comfortable and react naturally to your news. If you have multiple children, you can tell them at the same time as long as you allow them to individually express questions or concerns with you in private after your conversation.

Be honest but as encouraging as possible. Ms. Aschenbrenner said, “It is important to present cancer in the context of an illness for which treatment can be provided.” Although you might be anxious about the obstacles ahead of you, it will help your child if you focus on the treatments available and your hope for remission. Let your child know that you are ready to fight cancer and that you have a team of doctors helping you.



It is important to name cancer, isolating it from other, possibly contagious diseases. Your child may be confused if you simply say that you’re sick, so try to avoid being vague when speaking about cancer. Also, be sure to tell your child that the cancer isn’t anybody’s fault and that he or she isn’t in any way responsible for your disease; although this is obvious to adults, it may not be to a child.

Describe the treatment plan in terms your child can understand. When telling your child about your treatment, also let him or her know about possible side effects. Communicating ahead of time that you might experience hair loss or weight change makes these events less alarming if they occur later.

As you continue treatment, keep your child updated with any new information, whether it’s good or bad. Ms. Aschenbrenner stressed the importance of continued honesty and said, “Keeping your child updated is respectful. Children have a right to know what’s going on with their parents.”

Let your child know about any changes in his or her schedule. Tell your child that it’s important to continue attending school and taking part in

other activities. Although consistency in schedule is important to your child, it’s alright to ask him or her to become slightly more independent. In the weeks following your conversation, you can ask if your child would be willing to make his or her own lunch every once in a while or help with dinner if the need arises.

Monitor your child’s reaction to your cancer. “If your child responds to your illness or treatment like he or she would respond to any other difficulty, then you know you’re doing alright,” Ms. Aschenbrenner said. If your child is responding abnormally to the stresses your cancer presents, consider putting him or her in contact with a counselor, which may be available through your child’s school, or with a local support group. Most cancer hospitals, including MD Anderson, offer counseling services for patients and their families. MD Anderson also has two programs, CLIMB and Teen CLIMB, designed to help children cope with their parent’s cancer.

Keep the conversation going. Over the next weeks and months, tell your child when you do or don’t have new information, and never try to answer your child’s questions by guessing; it’s okay to admit that you don’t know. Above all, remain open to your child’s questions and concerns, and remember the importance of honesty when you respond. ■

— N. Danckers

FOR MORE INFORMATION

- Talk to your physician
- Call MD Anderson’s Department of Social Work at 713-792-6195
- To learn about CLIMB or Teen CLIMB, call 713-792-6826
- Call MD Anderson’s Supportive Care Center at 713-792-6072

IMPACT2 Tests Personalized Cancer Treatment

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Cancer Medicine and other divisions in our institution,” Dr. Tsimberidou said.

The study’s primary objective is to determine whether patients whose treatment is selected based on molecular profiling have longer progression-free survival than do patients whose treatment is not based on molecular profiling.

Increasing access to targeted therapy

Dr. Tsimberidou said that the IMPACT2 study is designed to address some of the barriers to the implementation of precision medicine. These barriers include the absence of routine biopsies (required for molecular profiling) for many types of cancer, the subjective nature of targeted therapy selection, and the long waits (weeks or months) for the results of molecular profiling. The study’s standardized treatment algorithms address the subjective use of targeted agents, and the turnaround time for results of the profiling assays is 14 days.

Another barrier that the study aims to help overcome is the limited access to targeted agents. By providing molecular profiling to patients who typically would not receive it because of their cancer type, IMPACT2 enables these patients to receive targeted therapy in clinical trials that they otherwise would not have been considered for.

“Access to clinical trials of targeted

**“[H]opefully
molecular
profiling will
become the standard
of care for all patients
with cancer.”**

– Dr. Apostolia Tsimberidou

therapies is extremely limited,” Dr. Tsimberidou said. “In a best-case scenario, at an academic institution such as ours, perhaps 10%–30% of patients have access to targeted therapies. These should be available to all cancer patients.”

Several initiatives are under way to improve access to targeted drugs, including one by the American Society of Clinical Oncology. Dr. Tsimberidou hopes that her results will increase support for these initiatives.

Dr. Tsimberidou said, “If our results from the first IMPACT study are confirmed by IMPACT2, hopefully molecular profiling will become the standard of care for all patients with cancer.” ■

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