New procedure enables selective use of lymph node dissection

Intraoperative lymphatic mapping
elegant way to identify lymph node metastases in melanoma patients

Like a number of tumors, cutaneous melanomas often spread through lymph channels to regional lymph nodes. Because of this tendency, elective lymph node dissection—removal of lymph nodes before there is clinical evidence of metastasis—has long been a standard treatment for patients with early stage cutaneous melanoma. While this procedure has not been proven to prolong survival, many surgeons believe that elective lymph node dissection in a patient with micrometastases can prolong the patient’s life and in some cases cure the disease.

Until recently, however, this approach involved a catch-22: elective lymph node dissection could benefit only those patients with micrometastases, but determining whether a patient had micrometastases required a lymph node dissection. Thus, some patients underwent unnecessary surgery—a matter of concern because elective lymph node dissection is a major surgical procedure associated with a number of potential short- and long-term complications.

A cutting-edge approach being studied in clinical trials at The University of Texas M. D. Anderson Cancer Center offers a way around this dilemma. Using this new technique—intraoperative lymphatic mapping and sentinel node biopsy—surgeons can determine the disease status of an entire lymph node basin by identifying, removing, and examining a single special lymph node called the sentinel node.

The sentinel node is the first node that the dermal lymphatics around a tumor drain to. Studies have shown that the pathologic status of the sentinel node accurately predicts the status of all of the lymph nodes along that drainage pathway. In other words, if the sentinel node is free of tumor, so are all of the other nodes, and formal lymph node dissection is not necessary.

“This procedure can help identify which patients are most likely to benefit from lymph node dissection and which patients probably would not benefit,” said Merrick I. Ross, M.D., associate professor in the Department of Surgical Oncology. “It allows us to be more selective about performing lymphadenectomy.”

Lymphoscintigraphy reveals nodes at risk

Before performing intraoperative lymphatic mapping, the surgeon must know which nodal basins are at risk for micrometastases. For melanomas on the arms or legs, the lymphatic drainage patterns are fairly predictable: the arm drains to the axilla, and the leg drains to the groin. For lesions on the trunk, however, the drainage patterns are ambiguous. A melanoma on the upper trunk might drain to the groin, for example, or a melanoma near the left axilla might drain to the right axilla. And sometimes a lesion drains to more than one nodal basin. “It’s not uncommon to find two nodal basins,” said Ross, “and it’s not unheard of to find three. We will pursue these multiple nodal basins if necessary.”

When the drainage patterns are ambiguous, lymphoscintigraphy is used to identify the nodal basins at risk. This simple outpatient procedure is typically performed several days before the intraoperative lymphatic mapping and sentinel node biopsy. Lymphoscintigraphy begins with injection of a radiolabeled colloid into the skin adjacent to the tumor. Over the course of a few minutes, the colloid passes through the dermal lymphatics to one or more lymph node basins, where it is taken up by the macrophages in the lymph nodes. A continued on page 2
scintillation camera is then used to document the path of the radiolabeled colloid through the lymphatic system. This is the same path that tumor cells would follow if they broke away from the primary lesion and entered the lymphatics.

“Lymphoscintigraphy doesn’t tell us if there’s tumor in these areas,” said Ross, “but it does tell us that if tumor had traveled to a lymph node area, that’s where tumor would most likely be.” With this information in hand, the surgeon can plan the intraoperative lymphatic mapping.

**Dye, radiolabeling help locate sentinel node**

Intraoperative lymphatic mapping and sentinel node biopsy is performed at the same time as wide local excision of the primary tumor. The operation is typically performed as an outpatient procedure, with patients staying in the clinic about 23 hours.

About an hour before surgery, the patient is taken to the nuclear medicine station, where technicians inject a radiolabeled colloid into the skin adjacent to the tumor. The next stop is the operating room, where the surgeon injects a blue vegetable dye called isosulfan blue near the tumor.

While the blue dye travels through the lymphatic system, the surgeon scans the skin over the nodal basin with a hand-held, portable gamma probe, looking for areas with high levels of radioactivity. These “hot” areas signal lymph nodes that have taken up the radiolabeled colloid; the hottest area corresponds to the sentinel node.

The surgeon makes a small incision directly over the sentinel node and inserts the gamma probe, which is covered with a sterile sheath. By moving the probe around, the surgeon can further pinpoint the area of high radioactivity. Within this region, the surgeon hunts for a blue-stained node—the sentinel node—and carefully dissects it.

How does the surgeon know that the blue-stained node in question is actually the sentinel node? “There’s a time element involved,” said Ross. “If you wait too long, the dye can pass through several nodes. We generally do the biopsy within 20 minutes after injecting the blue dye.” The lymphatic channels connecting the nodes are also stained blue, so “once you find the node, you can trace back the lymphatic channels leading to it to make sure it’s the first node—that there isn’t a node before that one.”

When surgeons at M. D. Anderson Cancer Center first performed intraoperative lymphatic mapping, they relied on the blue dye alone to localize the node. The gamma probe was introduced about one and a half years ago. “When we were using just the dye,” said Ross, “we were confident between 85 and 90 percent of the time that the node we found was the sentinel node, because we were limited to visual inspection. Since we’ve been using the gamma probe, we almost never have a concern about not finding the appropriate lymph node.”

With use of the gamma probe, said Ross, “we know where the sentinel node is going to be. This allows us to make a very small incision and also makes the operation much quicker.”

After the sentinel node is removed, it is examined by a pathologist. If the node looks clinically suspicious, it is examined by frozen section. The results are available in a matter of minutes, and if the node contains metastases, the surgeon can proceed with a formal lymph node dissection in the same operative setting. However, “if the node looks normal,” said Ross, “we prefer to evaluate the lymph nodes by serial sectioning with permanent sections. It is more accurate, and we are less likely to miss tumor. We are looking for a small amount of microscopic disease, and you can sometimes lose important tissue when you do a frozen section.” In this case, if the sentinel node contains micrometastases, the lymph node dissection is performed at a later date.

**New procedure offers several advantages**

This new procedure offers a number of important advantages over traditional treatment, chief among them the ability to avoid formal lymph node dissection and its attendant risks—including obvious scarring, nerve damage, or lymphedema—in patients who would not benefit from the procedure.

The new procedure may also allow better detection of micrometastatic disease. “There are patients who are thought to be lymph node negative who eventually have a recurrence,” said Ross. “We think that a number of these patients are actually lymph node positive, but we missed the micrometastases because we weren’t able to look at every lymph node carefully enough.” With a traditional lymph node dissection, detailed examination of all the nodes removed is not feasible—the time and expense involved are prohibitive. However, with only one or two nodes to focus on, said Ross, “it is more feasible to perform very careful examination by using serial sectioning and immunohistologic studies,” and thus the chances of detecting micrometastases are greater. The sentinel nodes are also thought to be the nodes

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Cooperative multicenter clinical trials a boon to lung cancer therapy

Combined chemotherapy and radiation therapy bringing hope for inoperable lung cancer

In the United States, lung cancer has been surpassed by cancers of the prostate and breast in sheer numbers of cases, but lung cancer has been and remains the number one cancer killer. About 177,000 new cases of lung cancer are expected in this country in 1996, and about 159,000 people will die of lung cancer during the same period. What these numbers suggest—that most people who have lung cancer will die of it—is true. Only about 13% of patients with lung cancer are alive five years after the cancer is diagnosed.

The primary reason for lung cancer's low survival rate is that the disease is rarely diagnosed in its early stages, when it is most successfully treated. Lung cancer is usually not betrayed by symptoms before it reaches an advanced stage. Thus, more than 70% of lung tumors are diagnosed only when they have grown very large or metastasized. For these advanced tumors, surgical resection is rarely possible. Now, multiple modality regimens being developed at The University of Texas M. D. Anderson Cancer Center may offer patients with locally advanced, inoperable lung cancer (stage III) a longer and more comfortable life.

For the past several years, clinical research in lung cancer has focused on earlier detection, but little headway has been made. Much of the emphasis is now shifting to chemoprevention and to molecular techniques for detecting premalignant conditions and predicting cancer risk. Until clinical applications of those techniques become available, however, standard treatments—chemotherapy and radiation therapy—are the best hope for patients with inoperable lung cancers. Ritsuko Komaki, M.D., F.A.C.R., radiation oncologist and professor in the Department of Radiotherapy at M. D. Anderson, related how these treatments for lung cancer have been refined continuously over the past two decades.

Radiation dose escalation prolonged life

"Until the early 1970s," explained Komaki, "the standard treatment for locally advanced, inoperable lung cancer was radiation therapy. This therapy was largely palliative, helping to open the airway and relieve pain, cough, and hemoptysis. The two-year survival rate for patients who underwent this therapy was about 10%. Then, in 1973, therapy for these cancers began to change, a process still underway today. The Radiation Therapy Oncology Group (RTOG), a group of investigators from many institutions who do collaborative research on radiation therapy for cancer, began treating patients with locally advanced tumors with a higher dose of radiation than had been used before, 60 Gy over six weeks. In 1980, RTOG reported that the patients who received the higher dose had a two-year survival rate of 20%, double that of the patients who received the conventional dose (20 to 40 Gy). From that time, 60 Gy over six weeks became the standard radiation dose for inoperable lung cancer.

The patients in the RTOG trial had non-small cell lung cancer, which accounts for about three of every four lung cancers and includes squamous cell carcinoma (the most common type), adenocarcinoma, and large cell carcinoma. These cancers tend to grow and spread less rapidly than small cell lung cancer, which grows quickly, spreads aggressively, and is almost always in an advanced stage when diagnosed.

Combined chemoradiation: the rationale

Some patients with locally advanced, inoperable non–small cell lung cancer received only chemotherapy. In these patients, the tumor usually recurred very quickly, typically in the chest or brain. Although chemotherapy prevented or limited metastasis, it did not prolong life; moreover, it disrupted bone marrow function and normal tissues, putting a much greater strain on the patient than local therapies. On these grounds, chemotherapy has been rejected as the sole treatment for stage III lung cancer. But once certain chemotherapy drugs became available that increase tumor sensitivity to radiation, the combination of chemotherapy and radiation began to make sense. The rationale was that chemotherapy could not continue on page 4
only prevent the cancer from spreading to other parts of the body but also sensitize the tumor so it could be killed more effectively by radiation.

This rationale was validated when another collaborative research group called the Cancer and Leukemia Group B (CALGB) conducted a large randomized study of chemoradiation in patients with stage III lung cancer. This trial compared two regimens: one consisted of chemotherapy followed by standard daily radiation therapy (60 Gy) and the other of radiotherapy as the sole treatment. The two-year and five-year survival rates in the group that received the combination regimen were 35% and 19%, significantly higher than those in the group that received only radiation. “After that study,” said Komaki, “combined chemotherapy and radiation therapy became the standard instead of radiation therapy by itself. However, we didn’t know the best timing or sequence of these treatments, and we still don’t, although we have gotten a lot closer. All of our clinical trials are now designed to refine and improve these combinations.”

**Hyperfractionation allows higher doses**

Radiation dose is also an issue. “We know that a very high dose of radiation is best for controlling stage IIIIB lung tumors,” said Komaki, “but most patients cannot withstand these doses. We reasoned that patients with a good performance status who have lost relatively little weight (less than 5% of body weight) might tolerate high radiation doses with fewer side effects later if they were given a smaller fraction twice daily rather than a larger fraction once daily. This strategy, called hyperfractionation, has been an effective innovation in that it allows a somewhat higher dose (69.6 Gy) to be given over the same period or a slightly shorter period.”

The hyperfractionation concept was tested in a large randomized trial in which another collaborative research organization, the Eastern Collaborative Oncology Group (ECOG), worked with RTOG. This study compared three regimens: sequential chemotherapy and standard daily radiation therapy as in the CALGB study, hyperfractionated radiation therapy (69 Gy), and once-daily radiation therapy (60 Gy). The two-year survival rate in the combined modality group was 35%, just as it had been in the CALGB study. The rates for the twice-daily and once-daily radiation therapy groups were 29% and 24%, respectively.

“These studies,” noted Komaki, “showed us that sequential chemotherapy and radiation would prolong life. European investigators found that patients who received simultaneous radiosensitizing cisplatin and radiation therapy also had better survival rates than patients who received only radiation. Opinion in lung cancer treatment began to favor concurrent rather than sequential chemotherapy and radiation therapy. Here at M. D. Anderson, we planned a series of trials that would compare the two approaches.”

The first was a phase I trial of concurrent chemotherapy and hyperfractionated radiation therapy. Patients received twice-daily radiation (69.6 Gy) with cisplatin or etoposide. When the patients in this trial had a higher two-year survival rate than historical control patients who received only radiation, Komaki and her colleagues planned a phase II trial to determine the efficacy of concurrent chemotherapy and hyperfractionation.

**Balancing therapeutic and side effects**

In both the phase I and II trials, many patients developed esophagitis, sometimes severe. The lining of the esophagus is very sensitive to radiation, and the damage it sustained was exacerbated by the chemotherapy. The esophagitis made swallowing difficult, and about one third of the patients in the trial were affected severely enough that they lost 10% or more of their body weight.

“As uncomfortable as this esophagitis was,” recalled Komaki, “it disappeared in most of the patients within three weeks of completing the therapy. Most began to regain the lost weight within a month of completing therapy. And, the two-year survival rate for the 76 patients in this trial was almost 40%. Despite the side effects, RTOG agreed to conduct a multicenter phase III trial that included concurrent chemotherapy and hyperfractionated radiation therapy as one of the three arms. The purpose of this study is to look for regimens that are as effective as standard therapy and more tolerable to patients.”

This phase III trial, which has recruited about one third of its target 600 patients at 25 RTOG institutions, is comparing three regimens: standard sequential chemotherapy (weekly for five weeks) plus once-daily radiation therapy, concurrent chemotherapy (weekly for five weeks) plus once-daily radiation therapy, and concurrent weekly chemotherapy plus hyperfractionated radiation therapy. Patient enrollment in the trial should be completed by 1997. Komaki said the RTOG investigators have had no problem recruiting patients into the study, despite the side effects of the combined modality regimens.
One recently completed randomized phase II trial compared sequential chemotherapy and once-daily radiation therapy with concurrent chemotherapy and hyperfractionated radiation therapy. The two-year survival rates were the same, about 35%. The concurrent therapy group received a somewhat lower dose of etoposide than in the earlier trial, which reduced the severity of esophagitis.

Small cell tumors respond to combination therapy

Combined chemotherapy and radiation therapy have also helped patients with the less common locally advanced and inoperable form of small cell (or oat cell) lung cancer, which is referred to as limited disease rather than locally advanced. These cancers have always presented a particular treatment challenge. “Fifty years ago,” said Komaki, “small cell lung cancer was not curable at all, not even limited disease. Almost everybody who had it died. Investigators began using radiation therapy on these patients, and maybe 5% of them survived. Chemotherapy regimens were somewhat effective, but again the side effects—neurotoxicity and bone marrow suppression—were severe, and local recurrence was common. In the face of the same challenges, the development of combination therapies for limited small cell lung cancers paralleled that for locally advanced non–small cell lung cancers.

“Twenty years ago,” Komaki went on, “about 10% of patients with limited small cell lung cancer could be cured with combination chemotherapy and radiation therapy. Through a series of trials begun at the National Cancer Institute and continued by RTOG and ECOG, we have tested doses, timing, and duration of treatments, looking for the combination that will stop cancer and prevent recurrences. Because of its aggressiveness, however, limited small cell lung cancer requires higher doses and more intensive treatments than non–small cell lung cancer. More and more, clinical trial results are supporting concurrent chemotherapy and hyperfractionated radiation therapy.”

A trial that originated at M. D. Anderson and is now in phase II at several RTOG centers is comparing two more intensive regimens of concurrent chemotherapy and hyperfractionated radiation therapy. The radiation is given in a shortened three-week schedule; this might allow patients to take a bone marrow–stimulating drug to support the more aggressive chemotherapy needed to limit metastasis of small cell lung cancer.

Concurrent therapies enhance local control

There is evidence that concurrent therapy reduces the rate of local cancer recurrence in both small cell and non–small cell lung cancers. Explained Komaki, “If lung cancer comes back, or spreads to other places, such as the brain or liver or bone, it usually happens within 15 months after treatment. This is the why the two-year survival rate is a landmark in this disease. However, patients who have had one lung cancer are at risk of having a second cancer, and second lung malignancies may not develop until three or even five or more years after the treatment. Once patients have survived two or three years after treatment for their initial cancer, they are eligible for chemoprevention studies to help prevent these second cancers from developing. But the first thing we have to do is help patients survive the first two years.”

How close are they to that goal? “We look very closely at the results of these trials,” said Komaki. “We look for what works and what does not, and from that we plan the next trial. From these trials, we have learned that twice-daily radiation reduces the risk of local recurrence, and that chemotherapy helps prevent or stop metastasis and enhances the effectiveness of local radiation. We need to put them together to cure lung cancer, but for how long? In what order? Then, we have the problem of patient tolerance. Finding just the right combination of therapies is a delicate business. But we are finding new ways. We are making progress.”

Komaki and her colleagues at M. D. Anderson will soon begin using three-dimensional radiation therapy in lung cancer patients, which allows greater precision and thus better protection of normal tissues and sensitive structures such as the esophagus.

Komaki and her fellow RTOG investigators are ambitious. “With our current trial,” commented Komaki, “we are aiming for a two-year survival rate of 50%. But even if we improve the survival rate by only 1%, that means a lot of lives.”

—KATHRYN L. HALE

REFERRALS. Physicians who have questions may write Dr. Komaki, Department of Radiotherapy, Box 97, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-3420. Those who would like to refer a patient may call the New Patient Referral Office at (800) 392-1611 or (713) 792-6161.
Referrals
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"Since the policy change to self-referral," continued von Eschenbach, "the New Patient Referral Office is supporting the institution's transition to a multidisciplinary, disease site approach to cancer care." The office created four teams of referral specialists, each of which concentrates on certain types of cancer or cancer sites. Each team is headed by a registered nurse with experience in the care of patients with those types of cancer. After extensive retraining, each team has an understanding of the medical criteria for accepting patients to M. D. Anderson. The referral specialists have checklists of specific questions that need to be answered when screening patients with each type of cancer. The lists of questions were developed by the cancer center's medical services.

Referral specialist first contact

"The person calling with the referral, whether patient or physician, will first talk to a referral specialist," said von Eschenbach. "Referring physicians who wish to speak to an M. D. Anderson staff physician about a case will, of course, be patched through to the physician on call for that service, just as they always were. But because our referral specialists are so knowledgeable, it may not be necessary." The new referral process is designed to offer maximum convenience to referring physicians. "Doing more screening up front is helping save time for referring physicians; it facilitates the process of getting two busy physicians together on the telephone."

To simplify and hasten the referral process, von Eschenbach recommends that physicians making referrals to M. D. Anderson have all of the relevant information about the patient handy when they make the call. M. D. Anderson's Clinical Staff Directory includes instructions to help referring physicians prepare for the questions they will be asked. The referral specialists will ask many questions about the patient's medical status and the treatment the patient has received. If the patient clearly falls within the parameters set out by the medical service, the referral specialist will also ask for demographic and financial information about the patient. The answers to all of these questions will determine whether the patient is admitted to the appropriate outpatient clinic at M. D. Anderson.

If the referring physician is able to supply all of the needed information, the referral specialist may be able to immediately accept the referral pending verification of the patient's insurance coverage. If, however, the patient does not clearly fall within the medical parameters, the case will be reviewed by the nurse team leader and, if necessary, a staff physician. If the referring physician does not have demographic or financial information about the patient, the referral specialist will contact the patient for that information. If all acceptance criteria are satisfied and the financial information is verified, an appointment will be set for the patient.

Complex cases handled by staff physicians

von Eschenbach emphasized that the referral specialists cannot refuse referrals. "If a patient falls outside of the established medical criteria for acceptance, all that means is that the patient's case is complex enough that the referral specialist can't make the decision whether to give an appointment. That decision will be made by a staff physician. The referral specialist is there to collect information and, in some cases, accept the referral without further medical review. The referral specialist will also relegate a referring physician's questions about specific treatment protocols or clinical trials to the medical staff."

Patient self-referrals are assessed by exactly the same medical and financial questions as physician referrals. "However," explained von Eschenbach, "self-referrals are more complicated because we cannot, unfortunately, always take a patient's word about his or her cancer. We accept referrals only from patients who have already been diagnosed with cancer, and we need copies of medical reports documenting the cancer. The first questions we always ask patients when they call the New Patient Referral Office are when and how the cancer was diagnosed. We ask them the name of their physician and whether we can contact the physician; we also ask them to send a copy of their pathology or radiology report. The requirements vary by the medical service. In most cases these reports can be sent to us by fax to keep the process moving."

New procedures speed patient check-in

New Patient Referral Office services don't stop when the referral is accepted. The referral specialist will call the patient to let him or her know about the referral and to set up an appointment. This can often be done as part of the call in which the patient gives demographic and financial information. "This way," said von Eschenbach, "when the patient comes in for his or her first visit, much of the paperwork is done. Patients
Lymphatic mapping

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most likely to harbor micrometastatic disease, so focusing on those nodes is the best strategy for detecting micrometastases.

Early detection of disease spread to lymph nodes is especially important now that alpha-interferon has been identified as an effective adjuvant therapy for patients with lymph node spread of melanoma. The earlier micrometastases in regional lymph nodes are identified, the earlier patients can receive this therapy.

Procedure also useful for other types of cancer

Encouraged by the success of intraoperative lymphatic mapping and sentinel node biopsy for the treatment of cutaneous lymphoma, surgeons are investigating the role of this procedure in treating breast and other types of cancer. "Right now, the standard of care for patients who undergo surgery for breast cancer is to include an axillary lymph node dissection, but now that we're seeing breast cancer earlier, a lot of these patients don't have lymph node involvement," said Ross.

In a preliminary trial of sentinel node biopsy in breast cancer patients, M. D. Anderson surgeons found only one false-negative result in a series of 35 patients. According to Ross, some areas of the breast drain exclusively to the internal mammary chain—not the axilla, the traditional site of lymph node dissection in breast cancer patients. "For patients with tumors in those areas of the breast," he said, "sampling the axilla may be misleading. Using intraoperative lymphatic mapping with a gamma probe, it is possible to access the internal mammary nodes. That has been out of vogue for some period of time, but now that we're understanding lymphatic drainage better, it may be coming back into our staging evaluations of patients with breast cancer."

Intraoperative lymphatic mapping can also be used for melanomas of the vulva and for other skin cancers that spread to lymph nodes—some of the adnexal tumors of the skin, Merkel cell tumors of the skin, and some of the more aggressive squamous cell cancers. "This technique," said Ross, "is applicable to essentially any solid tumor that has a predilection for lymph node metastasis."

—STEFANIE P. DEMING

REFERRALS. Physicians who have questions or would like to refer a patient may call the New Patient Referral Office at (713) 792-6161 or (800) 392-1611. The Clinical Staff Directory is available by calling the Office of Referral Relations at (800) 252-0502. It is also available on M. D. Anderson's home page on the World Wide Web (http://utmdacc.uth.tmc.edu).
Streamlined procedures save referring physicians time

New Patient Referral Office changes with M. D. Anderson's referral policy

When The University of Texas M. D. Anderson Cancer Center was officially established by the 47th Texas Legislature in 1941, House Bill No. 268, Chapter 548, specified that “Every application shall be accompanied by a written request from the attending physician of the patient requesting the admission of such patient...” That policy remained in place for 54 years. On March 28, 1995, Texas Governor George W. Bush signed new legislation that, for the first time in M. D. Anderson’s history, allows patients to refer themselves to the center for cancer care.

Although the new policy gives patients greater flexibility and choice in seeking cancer care, M. D. Anderson encourages all patients to seek referral through their physicians. Physician referral not only simplifies the referral and transfer process for patients, said Drew von Eschenbach, operations manager of the New Patient Referral Office, but helps optimize patient care and outcomes through the continued involvement of patients’ hometown physicians. Patients have embraced the new policy, however, and in one year patient self-referrals have grown to about 25% of all new patient referrals to M. D. Anderson.

New referral procedures in place

The New Patient Referral Office used the policy change as an opportunity to change its procedures. “When there was only physician referral to M. D. Anderson, the staff in our office served primarily as operators,” said von Eschenbach. “We connected an outside physician who wanted to refer a patient to the center with a staff physician from the appropriate service. If the physicians concurred that a referral to M. D. Anderson was appropriate, we would take over, setting up the appointment.

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