National Comprehensive Cancer Network®

2026

NCCN Guidelines for Patients®

Cancer care recommendations from leading experts at the National Comprehensive Cancer Network® (NCCN®)

Marginal Zone Lymphomas



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NCCN Guidelines for Patients®

The essential guide for people facing cancer.

Based on care recommendations from leading cancer experts.

Explains high-quality cancer care provided at state-of-the-art cancer centers.

Reviewed and revised every year.

Did you know that top cancer centers across the United States work together to improve cancer care? This alliance of leading cancer centers is called the National Comprehensive Cancer Network® (NCCN®).

Because cancer care is always evolving, NCCN develops and frequently updates evidence-based cancer care recommendations used by health care providers worldwide. These recommendations are known as the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

The NCCN Guidelines for Patients plainly explain these expert recommendations, so you can talk with your care team about the best care for you.

These NCCN Guidelines for Patients are based on the NCCN Guidelines® for B-Cell Lymphomas, Version 4.2026 — May 20, 2026.

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About MZL

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Marginal zone lymphoma (MZL) develops from B lymphocytes, a type of white blood cell. It's a slow-growing lymphoma that can be found in almost any organ in the body. MZL is treatable. Read this guide to learn more about the types of MZLs and how they're treated.

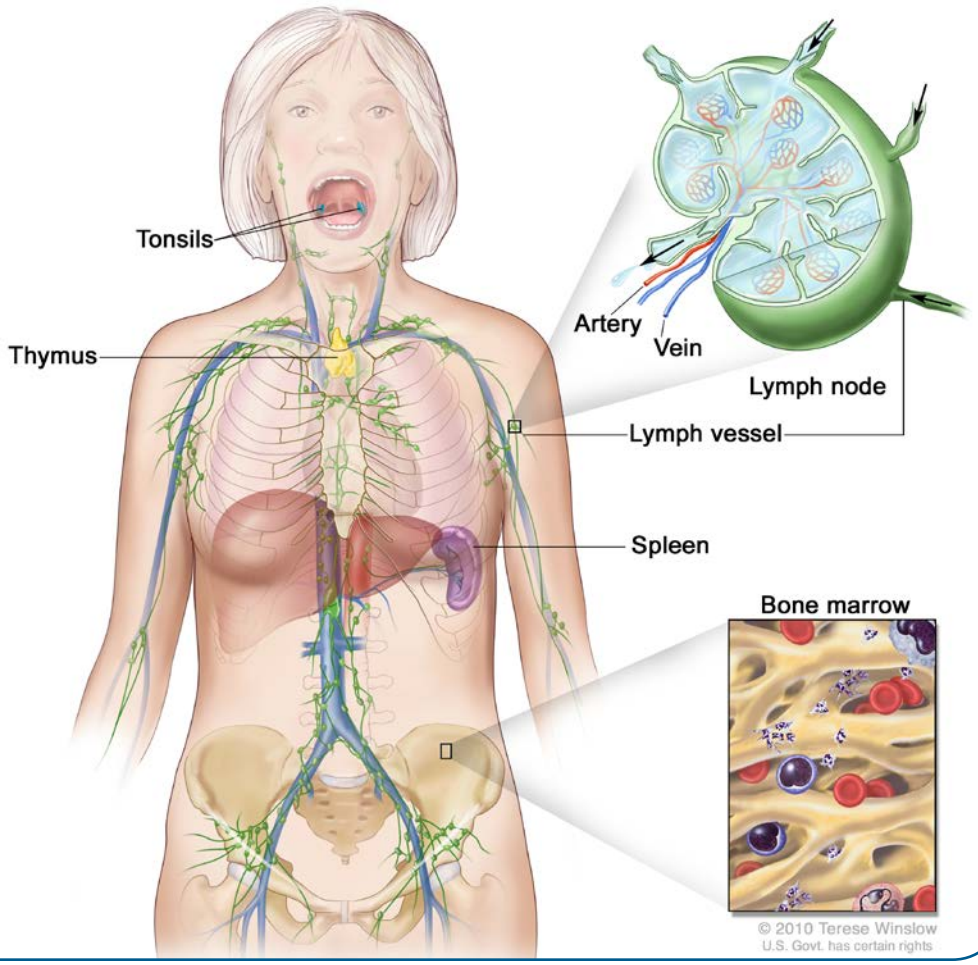
What is marginal zone lymphoma?

Marginal zone lymphoma (MZL) is a cancer of lymphocytes. Lymphocytes are a type of white blood cell that helps fight and prevent infection. They are found in blood, lymph vessels, lymph nodes, and every organ in the body. Lymphocytes normally grow in response to infection or inflammation. When they grow on their own without proper regulation, they can develop into lymphomas like MZL.

MZL is a type of B-cell lymphoma. There are many types of B-cell lymphomas.

Marginal zone lymphoma is a type of B-cell lymphoma

B-cell lymphomas start in the lymphatic system. The lymphatic, or lymph, system is part of the immune system. It includes lymph vessels, lymph nodes, tonsils, thymus, spleen, and bone marrow. Bone marrow is the main producer of blood cells. These include white blood cells, red blood cells, and platelets.



Types of lymphocytes

There are 3 main types of lymphocytes:

- **B lymphocytes, or B cells**, make antibodies and eventually mature into plasma cells. An antibody is a protein that specifically targets infections or cancer cells and recruits other parts of the immune system.
- **T lymphocytes, or T cells**, help fight infections and cancer, and control immune responses.
- **Natural killer (NK) cells** can kill tumor cells or virus-infected cells.

MZL forms in B-cell lymphocytes that live in the marginal zone part of the spleen, lymph nodes, or lymphoid tissues. Lymphoid or lymph tissues are organized structures that support immune responses. They are where lymphocytes are found. Examples include bone marrow, the thymus, and tonsils.

The marginal zone is a very active area that receives large amounts of circulating blood. Here, blood interacts with different types of white blood cells that engulf and digest cancer cells, microbes, cellular debris, and foreign substances. When abnormal marginal zone B cells grow out of control, then marginal zone lymphoma develops. Chronic infection, inflammation, or autoimmune disorders might cause some types of MZL due to increased activity in the immune system. But, in most cases, the cause of MZL is unknown.

How is marginal zone lymphoma treated?

Marginal zone lymphoma (MZL) is treatable. The goal of treatment is to cure the disease, when possible. For many people with MZL, treatment is radiation therapy, drug (systemic) therapy, or a combination of both. Radiation therapy is typically directed to the tumor. Systemic therapy travels in the bloodstream to kill lymphoma cells throughout the body.

This guide contains treatment recommendations for the following subtypes of MZL:

- Extranodal
- Nodal
- Splenic

If you've been diagnosed with MZL, consider seeking the opinion of a lymphoma specialist.



Take our survey and help make the NCCN Guidelines for Patients better for everyone!

NCCN.org/patients/comments

How can I get the best care?

Advocate for yourself. You have an important role to play in your care. Many people feel more satisfied when they actively take part in planning their cancer care.

The NCCN Guidelines for Patients will help you play a larger role in your care. Discuss the recommendations in this guide with your care team. Ask questions about your options and share your goals and concerns.

Don't know what to ask? You're not alone. That's why we include suggested questions to ask at the end of chapters.

Keep reading to find the best care for you.

How this guide can help you

Making decisions about cancer care is stressful. There's a lot to learn, and you don't know what the future holds.

Use this guide to get the information and support you need.

Patients, doctors, and other health care professionals trust the NCCN Guidelines for Patients. This guide uses clear, everyday language to explain current cancer care recommendations made by respected experts in the field. Their recommendations are based on the latest research and practices at leading cancer centers.

Your health is unique to you, so your cancer care should be, too. As you read this guide, you'll learn which treatments are likely to provide the best results for you. And you'll be better prepared to talk with your care team

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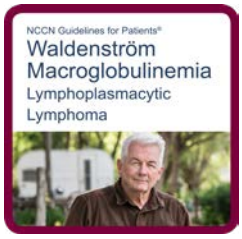
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Accurate testing is essential to diagnose and treat marginal zone lymphoma (MZL). Information on possible tests and procedures can be found in this chapter. It's okay to skip over information that doesn't interest you.

For more information, read *NCCN Guidelines for Patients: Waldenström Macroglobulinemia*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Types of marginal zone lymphomas

Marginal zone lymphomas (MZLs) can be divided into 3 distinct subtypes:

- **Extranodal MZL** found in the stomach and other organs outside the lymph nodes, and accounts for about 6 out of 10 MZL cases per year
- **Nodal MZL** found in the lymph nodes and accounts for about 3 out of 10 MZL cases per year
- **Splenic MZL** found in the spleen, bone marrow, and blood, and accounts for about 1 out of 10 MZL cases per year

MZL has some features that overlap with another type of lymphoma called Waldenström macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma. In WM, bone marrow produces too many abnormal white blood cells that crowd out healthy blood cells.

Extranodal MZL

Extranodal marginal zone lymphoma (EMZL) is the most common form of MZL. It's called extranodal because it forms outside the lymph nodes in places such as the stomach, small intestine, salivary glands, thyroid, eyes, breast, skin, or lungs. Each type is based on location. EMZL in the skin is called cutaneous MZL.

In the past, the term mucosa-associated lymphoid tissue (MALT) lymphoma was used to describe this type of MZL. Now, EMZL is the preferred term because it more accurately describes all possible EMZL disease sites.

EMZL can be caused by certain types of infection, inflammation, or autoimmune disorders of the affected organ. The most common location for EMZL is the stomach, where it's often caused by the bacteria *Helicobacter pylori (H. pylori). H. pylori* can also cause stomach ulcers.

Nodal MZL

Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. Lymph nodes make immune cells that help the body fight infection. They also filter the lymph fluid and remove foreign material, such as bacteria and cancer cells.

Splenic MZL

Splenic marginal zone lymphoma (SMZL) involves the spleen, blood, and bone marrow. The spleen makes immune cells, filters the blood, stores blood cells, and removes old blood cells. The most common sign of SMZL is an enlarged spleen. This type of MZL is sometimes associated with hepatitis C infection.

General health tests

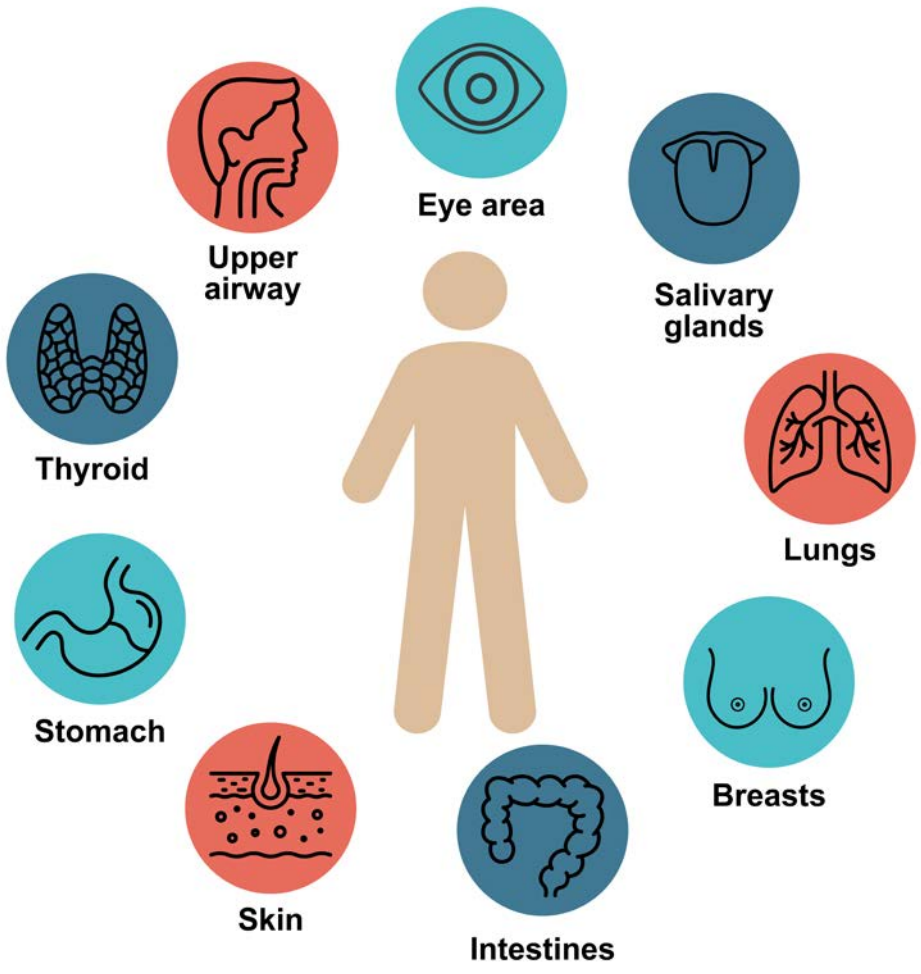
Some general health tests are described next.

Medical history

A medical history is a record of all health issues and treatments you've had in your life. It asks about past surgeries and current health conditions. Bring a list of old and new medicines and any over-the-counter medicines, herbals, or supplements you take. Some supplements interact with and affect medicines your care team may prescribe. Since there's often a lack of published

Extranodal MZL

The diagram shows the most common sites for extranodal MZL. Extranodal MZL accounts for about 6 out of every 10 cases of MZL per year.



information about how certain supplements interact with standard medicines, your care team may recommend that many of them be discontinued during treatment.

Family history

Some cancers and other diseases can run in families. Your care team will ask about the health history of family members who are blood relatives. This information is called family history. Ask members on both sides of your family about their health issues, like heart disease, cancer, and diabetes, and at what age they were diagnosed. It's important to know their specific type of cancer, where the cancer started, if it's in multiple locations, and if they had genetic testing.

Physical exam

During a physical exam, your health care provider may:

- Feel and apply pressure to parts of your body to see if organs are a normal size, are soft or hard, or cause pain when touched.
- Feel for enlarged lymph nodes in your neck, armpit, and groin.

Performance status

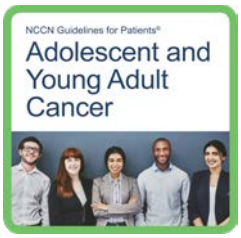
Performance status is a rating of your general level of fitness and ability to perform daily tasks. It includes whether you can walk, work, and take care of yourself. It's 1 factor taken into consideration when choosing a treatment plan.

Fertility (all genders)

Treatment with systemic therapy can affect your fertility, or the ability to have children. If you think you want children in the future, ask your care team how lymphoma treatment might affect your fertility.

Fertility preservation is all about keeping your options open, whether you know you want to have children later in life or aren't sure. Fertility and reproductive specialists can help you sort through what may be best for your situation.

More information on fertility preservation can be found in *NCCN Guidelines for Patients: Adolescent and Young Adult Cancer*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Preventing pregnancy during treatment

Preventing pregnancy during treatment is important. Lymphoma treatment can affect the ovaries, damage sperm, and hurt a developing baby. Therefore, becoming pregnant or having one's partner become pregnant during treatment should be avoided. If you're pregnant or breastfeeding at the time of your lymphoma diagnosis, treatments may need to be adjusted.

Blood tests

Blood tests check for signs of disease and how well organs are working. They require a sample of your blood, which is removed through a needle placed into your vein.

Some possible blood tests are described next.

Complete blood count and differential

A complete blood count measures the levels of red blood cells, white blood cells, and platelets in your blood. A differential counts the number of each type of white blood cell (neutrophils, lymphocytes, monocytes, eosinophils, and basophils). It also checks if the counts are in balance with each other.

Comprehensive metabolic panel

A comprehensive metabolic panel measures different substances in your blood. It provides important information about how well your liver and kidneys are working, among other things.

Creatinine

Creatinine is produced when you use your muscles. It's filtered out of the blood by the kidneys. The level of creatinine in the blood tells how well the kidneys are working. Higher levels of creatinine mean the kidneys aren't working as well as they were when someone had lower levels of creatinine.

Electrolytes

Electrolytes help move nutrients into cells and help move waste out of cells. Electrolytes are ions or particles with electrical charges that help the nerves, muscles, heart, and

"Don't let yourself stop doing the things you enjoy doing. Whatever your hobbies are, whatever things you like to do, keep doing them. It'll help you feel more like yourself and stay positive during what is an extremely exhausting, mentally straining time."



brain work as they should. Your body needs electrolytes to function properly.

Helicobacter pylori

Helicobacter pylori, or *H. pylori*, is a bacterium that causes inflammation and ulcers in the stomach or small intestine. People with *H. pylori* infections may be more likely to develop cancer in the stomach, including extranodal marginal zone lymphoma (EMZL).

Hepatitis B and hepatitis C

Hepatitis B and hepatitis C virus infections can affect the liver. A blood test shows if you had hepatitis in the past or if you have it now. Some lymphoma treatments can wake up (or reactivate) the virus. If this happens, it can harm the liver. People with hepatitis C may be more likely to develop splenic marginal zone lymphoma (SMZL).

HIV

Human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS). An HIV antibody test checks for HIV antibodies in a sample of blood, urine, or saliva. It's important to let your doctor know if you've ever had HIV infection.

Infections related to MZL

Certain infections can cause ongoing (chronic) inflammation and increased activity of the immune system. Infections, such as *Helicobacter pylori* (*H. pylori*), *Chlamydia psittaci* (*C. psittaci*), *Campylobacter jejuni* (*C. jejuni*), *Borrelia burgdorferi* (*B. burgdorferi*), and hepatitis C virus, are often found in people with MZL. These infections are different from infections that can be a result of treatment.

Lactate dehydrogenase

Lactate dehydrogenase (LDH), or lactic acid dehydrogenase, is a protein found in most cells, including red blood cells and lung cells. Dying cells release LDH into the blood. Fast-growing cells, such as lymphoma cells, also release LDH.

Pregnancy test

If planned treatment might affect pregnancy, then people who can become pregnant will be given a pregnancy test before treatment begins.

SPEP

Serum protein electrophoresis (SPEP) examines specific proteins in the blood called globulins, which may be increased in certain conditions.

Biopsy

A biopsy removes a tissue sample from your body for testing. It's an important part of an accurate diagnosis of lymphoma. Your sample should be reviewed by a pathologist who's an expert in lymphoma. The pathologist (or hematopathologist) will note the overall appearance and size, shape, and type of cells and write a report. This review is often referred to as histology, histopathology, or hematopathology review. Tests are done on the biopsied cells to accurately diagnose MZL.

Types of biopsies include the following:

- **Fine-needle aspiration** uses a very thin needle to remove a sample of tissue.
- **Core needle biopsy** uses a hollow needle to remove a larger sample of tissue.
- **Incisional biopsy** removes a small amount of tissue through a cut in the skin or body.
- **Excisional biopsy** removes the entire tumor through a cut in the skin or body.
- **Lymph node biopsy** removes tissue from a lymph node.
- **Endoscopic biopsy** uses a thin, tube-shaped tool guided through the mouth to take a sample of the stomach and intestines.

Lymph node biopsy

When MZL involves lymph nodes, they can be swollen, enlarged, hard, or don't move when pushed. A lymph node biopsy is sometimes required to diagnose MZL. It can be done using a needle biopsy procedure or as a small surgery to remove (excise) a lymph node.

Bone marrow tests

Bone marrow tests might be done in certain cases.

There are 2 types of bone marrow tests that are often done at the same time:

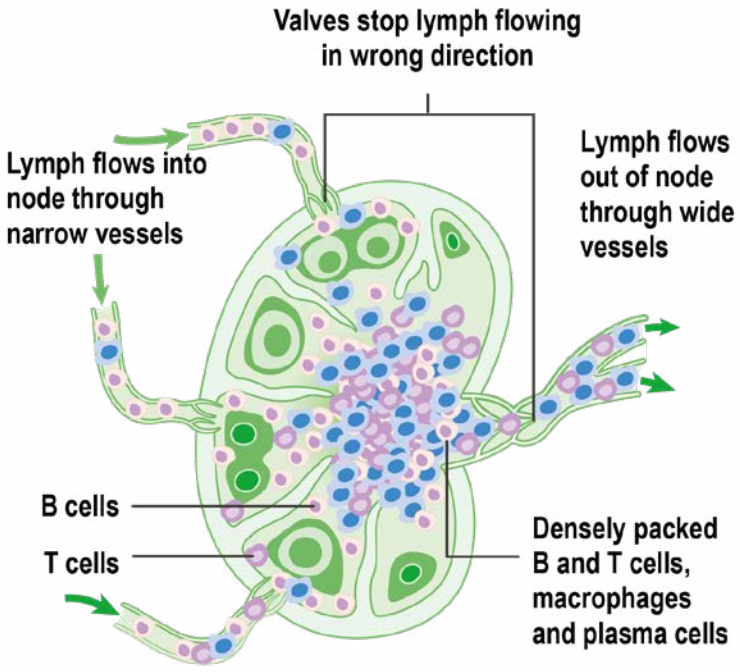
- Aspiration
- Biopsy

Your bone marrow is like a sponge holding liquid and cells. Aspiration takes some of the liquid and cells out of the sponge, and a biopsy removes a piece of the sponge.

Lymph nodes

There are hundreds of lymph nodes throughout the body. They work as filters to help fight infection and remove harmful substances from your body. A lymph node biopsy is sometimes required to diagnose marginal zone lymphoma.

https://commons.wikimedia.org/wiki/File:Diagram_of_a_lymph_node_CRUK_022.svg
Cancer Research UK / Wikimedia Commons



Bone marrow aspiration and biopsy are often bedside procedures. They aren't surgeries and don't usually require an operating room. Your care team will try to make you as comfortable as possible during the procedures.

The samples are usually taken from the back of the pelvis. You'll likely lie on your belly or side. For the aspiration, a hollow needle is pushed through your skin and into the bone marrow. Liquid bone marrow is then drawn into a syringe. For the biopsy, a wider needle is used to remove a small piece of bone marrow. You may feel pain at your hip for a few days. Your skin may bruise.

Immunophenotyping

Immunophenotyping is a process that uses antibodies to detect the presence or absence of white blood cell antigens called biomarkers. These antigens are proteins that can be found on the surface of or inside white blood cells. They help the pathologist tell what type of cells make up a tumor. Certain biomarkers help identify MZL or are targeted in MZL treatment.

Specific groupings of antigens are normal. However, some specific patterns of antigens, called the immunophenotype, are found on abnormal cells, including MZL. The immunophenotype for MZL is usually negative for the proteins CD10, CD5, cyclin D1, and BCL2 and positive for CD20.

Immunophenotyping can be done using specialized techniques, such as flow cytometry or immunohistochemistry. These techniques are used to distinguish MZL from other types of lymphoma. The immunophenotype can change as lymphoma progresses.

Immunophenotyping is used to help support a diagnosis. However, an accurate diagnosis of MZL requires a trained pathologist to review the tissue for abnormal cells seen under a microscope. More testing may be needed to establish an MZL subtype.

Flow cytometry

Flow cytometry is a laboratory method used to detect, identify, and count specific cells. It involves adding a light-sensitive dye to cells. The dyed cells are passed through a beam of light in a machine. The machine measures the number of cells, as well as things like their size and shape.

Flow cytometry may be used on cells from circulating (peripheral) blood, bone marrow, or biopsy. The most common use of flow cytometry is to identify markers on cells, particularly in the immune system (called immunophenotyping).

Immunohistochemistry

Immunohistochemistry (IHC) is a special staining process that involves adding a chemical marker to immune cells. The cells are then studied under a microscope. IHC looks for the immunophenotype of cells from a biopsy or tissue sample.

Testing takes time. It might take days or weeks for all test results to come in.

Biomarker tests and MZL genetic changes

Biomarker and genetic tests are used to learn more about your type of MZL, to guide treatment, and to determine the likely path your MZL will take (prognosis). This genetic testing is different from family history genetic testing or genetic cancer risk testing. It looks for changes only in the MZL cells that have developed over time and not changes in the rest of your body's cells.

Inside our cells are DNA molecules. These molecules are tightly packaged into what's called a chromosome. Chromosomes contain most of the genetic information in a cell. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each chromosome contains thousands of genes. Most genes contain information for making a specific protein. A mutation is when something goes wrong in the genetic code.

Proteins are written without italics, like this: BCL6. Genes are written with italics, like this: *BCL6.* When a gene or protein is found (expressed), it's shown with a plus sign (+), as in CD10+. When a gene or protein isn't found, it's written with a minus sign (-), as in CD10-.

MZL cells sometimes have changes in genes and chromosomes that can be seen under a microscope or found with other tests. These DNA changes may affect your MZL diagnosis, treatment options, and prognosis.

- Testing your MZL cells can gather specific information about your lymphoma to help guide treatment.
- Some results take days to weeks, but treatment may start before all results are in.

MZL genetic testing

Genetic testing using methods, such as fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and multigene panel testing, look for changes or abnormalities that are unique to MZL cells. A sample of your blood, bone marrow, or lymph node might be used to see if the MZL cells have any specific changes or mutations.

Some genetic changes may determine the type of treatment given. Subtle, new, drug-resistant changes may occur over time. It can happen during treatment and lead to resistance to certain therapies.

Deletions

When part of a chromosome is missing, it's called a deletion. For example, in del(7q), the q part of chromosome 7 is missing (deleted). Specific chromosomal deletions can be found in some types of marginal zone lymphomas but can also be found in other types of blood cancers and disorders.

FISH

Fluorescence in situ hybridization (FISH) is a method that involves special dyes, called probes, that attach to pieces of DNA. Since this test doesn't need growing cells, it can be performed on bone marrow, lymph node, or a blood sample.

FISH can find translocations that are too small to be seen with other methods. A translocation occurs when parts of 2 chromosomes switch with one another. However, FISH can only be used for known specific changes. It cannot detect all the possible changes found within the chromosomes or genes.

Translocations

Translocation is a switching of parts between 2 chromosomes. It's sometimes referred to as rearrangement. A translocation between chromosome 14 and 18 is written as t(14;18). It might also be referred to as *BCL2* gene rearrangement. Specific translocations can help distinguish between types of lymphomas.

Gene rearrangements

Normal B cells and T cells break their DNA in certain ways to create diversity within your immune system. In a tumor, all cancer cells originate from the same cell. In MZL, that cell is a B cell. Some tumors can have gene rearrangements—where part of a gene has broken off and attached to another gene, creating a new gene. For example, in a *BCL2* rearrangement, a gene from chromosome 14 moves to chromosome 18. A *BCL2* rearrangement might be written as t(14;18).



Marginal zone lymphoma genetic changes

Marginal zone lymphoma (MZL) cells can have changes in genes and chromosomes. Mutation testing looks for these changes or abnormalities that are unique to MZL cells.

Examples include the following:

- ✓ **Amplification** – When a part or whole chromosome or gene is increased (for example, duplicated).
- ✓ **Deletion** – When part of a chromosome or gene is missing.
- ✓ **Insertion** – When a new part of a chromosome or gene is included.
- ✓ **Inversion** – When parts within 1 chromosome are switched.
- ✓ **Point mutation** – When part of a gene is changed.
- ✓ **Chromosome translocation and gene rearrangement** – When parts between 2 chromosomes are switched. When described at the chromosome level, it's called a translocation. When described at the gene level, it's called rearrangement.

Imaging tests

Imaging tests take detailed pictures of areas inside the body to look for cancer, enlarged lymph nodes, or other abnormalities that might suggest lymphoma. A radiologist, an expert in interpreting imaging tests, will write a report and send it to your care team.

Imaging tests are used to look for areas of lymphoma involvement and are part of MZL staging. Possible imaging tests are described next. They're listed in alphabetical order and not in order of importance. You won't have all of these tests.

Contrast material

Contrast material is a substance used to improve the quality of CT and MRI imaging scans. It's used to make the pictures clearer. Not all imaging tests require contrast, but many do.

Contrast might be taken by mouth (oral) or given through a vein (intravenously, or IV).The types of contrast vary and are different for CT and MRI.

Tell your care team if you've had allergic reactions to contrast in the past. This is important. You might be given medicines to avoid the effects of those allergies. Contrast might not be used if you have a serious allergy or if your kidneys aren't working well.

CT scan

A CT, or CAT, scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make 1 detailed picture. You may have a CT scan of your head, neck, chest, abdomen, and pelvis to look for lymphoma. In most cases, contrast is used.

MRI scan

An MRI scan uses radio waves and powerful magnets to take pictures of the inside of the body. MRI doesn't use radiation. Because of the very strong magnets used in the MRI machine, tell the technologist if you have any metal or a pacemaker in your body. Contrast is often used.

MRI scans take longer than CT scans. A closed MRI has a capsule-like design where the magnet surrounds you. An open MRI has a magnetic top and bottom, which allows for an opening on each end. Closed MRIs are more common than open MRIs, so if you have claustrophobia (a fear of enclosed spaces), be sure to talk to your care team.

PET scan

A PET scan uses a radioactive substance called a tracer. A tracer is injected into a vein to see where lymphoma cells are in the body and how much sugar they take up, since malignant cells metabolize sugar faster than normal cells. This gives information on how fast the lymphoma cells are growing. Lymphomas often show up as bright spots on PET scans. However, not all tumors appear on a PET scan, and not all bright spots are lymphoma. It's normal for the brain, heart, kidneys, and bladder to be bright on PET. Inflammation or infection can also show up as a bright spot. When a PET scan is combined with CT, it's called a PET/CT scan.

Heart tests

Heart, or cardiac, tests are used to see how well the heart works. These tests might be used to monitor treatment side effects or to measure your heart function before you start treatment. You may be referred to a heart specialist called a cardiologist.

Key points

- Blood and imaging tests check for signs of disease, how well organs are working, and treatment results.
- A biopsy removes a sample of tissue for testing. It's an important part of an accurate marginal zone lymphoma (MZL) diagnosis.
- Immunophenotyping is used to distinguish MZL from other types of lymphoma.
- A sample from your biopsy may undergo lab tests to learn more about your MZL and to choose the best treatment for you.
- Biomarker and genetic tests are used to learn more about your type of MZL, to guide treatment, and to determine the likely path your lymphoma will take (prognosis).
- Imaging tests are used to look for areas of lymphoma involvement and are part of your staging workup.
- Certain treatments can affect heart function. Heart tests might be used to see how well your heart works.

Questions to ask

- What can you tell me about the type and location of my MZL?
- What websites about my condition do you recommend? Is there any information I can take home to read?
- Is there a cancer center or hospital nearby that specializes in treating lymphoma?
- What type of biopsy will I have?
- What types of biomarker and genetic tests will be done on the biopsy sample? How long will it take to get the results?

What's next?

The next chapter provides information on the types of treatment and what to expect from treatment.

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There's more than one treatment for marginal zone lymphomas (MZLs). This chapter presents an overview of the possible types of treatment and what to expect. Not everyone will receive the same treatment. Treatment options are based on many factors. Together, you and your care team will choose a treatment plan that's best for you.

Marginal zone lymphoma (MZL) is highly treatable and may be curable in certain circumstances. Treatment for MZL varies but can include radiation therapy, chemotherapy, immunotherapy, targeted therapy, antibiotic therapy, or combinations of these treatments. Some MZLs can be observed without any active treatment. Surgery may be an option in very select cases of localized marginal zone lymphoma. Localized means confined to one area.

It's important to have regular talks with your care team about your goals for treatment and your treatment plan.

Your care team

Treating lymphoma takes a team approach. Treatment decisions should involve a team of health care and psychosocial care professionals from different backgrounds who have knowledge and experience in your type of lymphoma. This team is united in planning and implementing your treatment.

Standard of care is the best-known way to treat a particular disease based on past clinical trials. There may be more than one treatment regimen that is considered standard of care. Ask your care team what treatment options are available and if a clinical trial might be right for you.



Treatment phases

The goal of treatment is remission, which means there's no evidence of lymphoma. You might hear the following terms used by your care team.

First-line therapy

First-line therapy is the first phase of treatment. The goal is a complete response, or complete remission. After finishing first-line therapy, you'll have tests to look for a response.

Remission

There are different types of remission. When there aren't any signs of lymphoma, it's called a complete response, or complete remission. Remission can be short-term (temporary) or long-lasting (permanent). In a partial response, lymphoma is still present, but it's reduced in size or amount.

Maintenance

Maintenance is treatment to prevent cancer from returning. It may be given for years. Not everyone receives maintenance therapy. Maintenance may be recommended depending on your type of disease, treatments received in the past for your lymphoma, and risk of relapse.

Relapse

When MZL returns after a period of remission, it's called a relapse. The goal of treatment is to achieve remission again. MZL might relapse more than once. A relapse can be serious. It's important to ask about your prognosis.

Refractory

When MZL remains and doesn't respond to treatment, it's called refractory, or resistant, disease. It may be resistant at the start of treatment or become resistant during treatment. Although not common, refractory disease is very serious. It's important to ask about your prognosis.

Transformation into an aggressive lymphoma

In some cases, MZL can change into a faster-growing type of lymphoma. Doctors call this transformation. If it happens, your doctor will look at what type of fast-growing lymphoma it has become and choose the best treatment plan. When a slow-growing lymphoma transforms into a faster-growing one, it can be harder to treat. Your care team will watch you closely and talk with you about the best options available.

Surveillance and monitoring

You'll be monitored during and after treatment. Surveillance watches for any changes in your condition. You'll have tests during surveillance to check for relapse. You might hear it called active surveillance.

Observation without treatment

Some slow-growing (indolent) lymphomas, like MZL, don't require immediate treatment. During observation, your care team will monitor for changes in your health or signs that the lymphoma has grown or progressed. Observation is sometimes called active surveillance or watch and wait.

Radiation therapy

Radiation therapy (RT) uses high-energy beams to eradicate lymphoma cells and shrink tumors. Most MZLs are extremely sensitive to radiation. Because of this, radiation therapy is widely used to treat MZL, especially as a curative treatment for early-stage disease, or for palliative treatment at any stage. The dose of radiation prescribed for MZL is typically very low. Involved-site radiation therapy treats the area surrounding the tumor.

The first step of RT is simulation (or mapping). This consists of finding the best position for treatment and then undergoing a planning CT scan in the radiation oncology department. Your radiation oncologist uses that scan and computer software to create a 3D radiation treatment plan. During treatment, radiation in the form of beams shaped to the tumor area is delivered from outside the body by a machine called a linear accelerator.

Depending on your situation, you may receive as little as 1 treatment or as many as 15. Treatment is given in small daily doses, typically Monday through Friday.

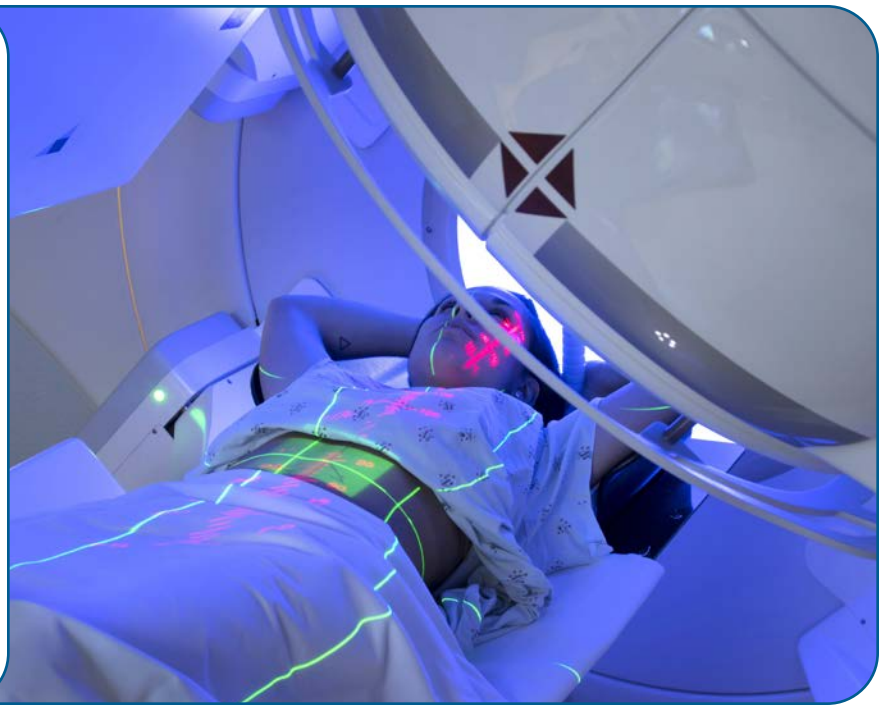
You'll see your radiation oncologist at least once a week during RT. During these visits, the doctor will examine you and ask how you're feeling.

Systemic therapy

Systemic therapy works throughout the body. Types include chemotherapy, chemoimmunotherapy, immunotherapy, and targeted therapy. Systemic therapy might be used alone or with other therapies. Goals of systemic therapy may be curative or palliative and should be discussed before starting treatment.

Radiation therapy

Most marginal zone lymphomas (MZLs) are extremely sensitive to radiation. Because of this, radiation therapy is widely used to treat MZL, especially as a curative treatment for early-stage disease, or for palliative treatment at any stage.



About NCCN recomendations for therapy

Marginal zone lymphoma (MZL) is treated with radiation therapy and systemic therapy.

All treatments listed in this guide are deemed recommended and appropriate, by our NCCN panel members for MZL. This panel often assign levels of preferrence to the treatment recommendations as described below.

- **Preferred therapies** have the most evidence they may work better and be safer than other therapies.
- **Other recommended therapies** can provide effective results but may have less evidence, more side effects, or may not work quite as well as preferred therapies.
- **Therapies used in certain cases** work best for individuals with specific cancer features or health circumstances.

The choice of therapy takes into consideration many factors, including the stage of the disease, your age and other serious health issues, and future treatment possibilities (such as a hematopoietic cell transplant or CAR T-cell therapy). Your preferences about treatment are important. If you have any religious or personal beliefs about certain kinds of treatment, now would be the time to share them with your care team.

Chemotherapy

Chemotherapy kills fast-dividing cells throughout the body, including lymphoma cells and some normal cells. More than 1 chemotherapy may be used to treat MZL. When only 1 drug is used, it's called a single-agent regimen. When 2 or more drugs are used, it's called a combination or multi-agent regimen. An example of a chemotherapy drug combination (regimen) is cyclophosphamide, vincristine, and prednisone (CVP).

Some chemotherapy drugs are liquids given through a vein or injected under the skin with a needle. Other chemotherapy drugs are given as a pill. The dose differs between people because it's based on body weight and height.

Most chemotherapy is given in cycles of days of treatment followed by days of rest. This allows the body to recover before the next cycle. Cycles vary in length depending on which drugs are used. The number of treatment days per cycle and the total number of cycles also vary. You might spend time in the hospital during treatment.

Chemoimmunotherapy

Chemoimmunotherapy, also called immunochemotherapy, includes chemotherapy and immunotherapy drugs to treat lymphoma. There are several chemoimmunotherapy regimens used to treat MZL. One example is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP).

Immunotherapy

Immunotherapy comprises many kinds of treatment that directly affect your immune system or lymphoma. This therapy helps your immune system recognize and fight cancer. For MZL, immunotherapy can be used alone or in combination with chemotherapy.

Antibody therapy

Monoclonal antibody and bispecific antibody therapies use antibodies to help the body's immune system fight lymphoma, infection, or other diseases. Antibodies are proteins made by the immune system that bind to specific markers (proteins) on cells or tissues.

CD20-targeting monoclonal antibody therapy

A monoclonal antibody (mAb) is made from a unique white blood cell, such as a B cell or plasma cell. CD20-targeting mAbs (also called anti-CD20 mAbs), such as rituximab (Rituxan) and obinutuzumab (Gazyva), target the CD20 protein found on the surface of B cells and MZL. The drug attaches to the CD20 protein, alerting the immune system to MZL. This triggers normal immune cells to kill the lymphoma cells.

Bispecific antibody therapy

Bispecific antibodies bind to 2 different proteins (CD20 and CD3 antigen) at the same time—one on the immune T cells and the other on the lymphoma cells. Bispecific antibody therapy treats lymphoma by engaging and activating T cells and redirecting them to the lymphoma site. Examples of bispecific antibody therapies include epcoritamab-bysp (Epkinly), glofitamab-gxbm (Columvi), and mosunetuzumab-axgb (Lunsumio).

CD19-targeting CAR T-cell therapy

CAR T-cell therapy is a personalized form of immunotherapy called cellular therapy. T cells from your body are removed in a process called pheresis, or apheresis. Then a CAR (chimeric antigen receptor) is added to your T cells. This programs the T cells to find and attack lymphoma cells. The programmed T cells are infused back into your body after a brief course of chemotherapy (called lymphodepleting chemotherapy). Chemotherapy is needed to get the body ready to accept the CAR T-cells. This treatment isn't for everyone.

CAR T-cell therapy is one way to target the CD19 protein found on almost all B-cell lymphomas, including MZL. CD19-directed CAR T-cell therapies used to treat MZL include axicabtagene ciloleucel (Yescarta) and lisocabtagene maraleucel (Breyanzi).

Targeted therapy

Targeted therapy focuses on specific or unique features of lymphoma cells. Targeted therapies seek out how lymphoma cells grow, divide, and move in the body. They stop or inhibit the action of molecules that help lymphoma cells grow and/or survive.

Bruton tyrosine kinase inhibitors (BTKi), such as acalabrutinib (Calquence), pirtobrutinib (Jaypirca), and zanubrutinib (Brukinsa), block the BTK protein, which the lymphoma relies on for survival. Since the main signal for MZL growth is blocked, the lymphoma cells eventually die off.

Surgery

Surgery is an operation or procedure to remove cancer from the body. Surgery isn't a routine part of treatment for MZL. However, If it's needed, seek a surgeon who's an expert in performing your type of surgery in people with MZL. Hospitals that perform many surgeries often have better results. You can ask for a referral to a hospital or cancer center that has experience in treating your type of cancer.

Hematopoietic cell transplant

A hematopoietic cell transplant (HCT), or stem cell transplant, is a cellular therapy that replaces a person's bone marrow and immune system with their own healthy cells or donor cells. More specifically, an HCT replaces hematopoietic stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy as part of the transplant process. A hematopoietic stem cell is an immature cell that can develop into any type of blood cell. HCTs are performed in specialized centers. An HCT for MZL is very rare. Sometimes, MZL can transform into a type of lymphoma that requires a more aggressive therapy, like an HCT.

There are 2 types of HCTs:

- **Autologous** – Stem cells come from you.
- **Allogeneic** – Stem cells come from a matched donor. An allogeneic HCT is preferred over an autologous HCT in MZL.



Warnings about supplements and drug interactions

Some supplements and foods can affect the ability of a drug used to treat marginal zone lymphoma to do its job. This is called a drug interaction. Since there's often a lack of published information about how certain supplements interact with standard medicines, your care team may recommend that many of them be discontinued during treatment

Also, certain medicines can affect the ability of a drug to do its job. Antacids, heart or blood pressure medicine, and antidepressants are just some of the medicines that might interact with systemic therapy or supportive care medicines given during systemic drug therapy.

Therefore, it's very important to tell your care team about all medicines, vitamins, over-the-counter drugs, herbals, or supplements you're taking.

Bring a list with you to every visit.



Finding a clinical trial

In the United States

NCCN Cancer Centers
NCCN.org/cancercenters

The National Cancer Institute (NCI)
cancer.gov/about-cancer/treatment/clinical-trials/search

Worldwide

The U.S. National Library of Medicine (NLM)
clinicaltrials.gov

Need help finding a clinical trial?

NCI's Cancer Information Service (CIS)
1.800.4.CANCER (1.800.422.6237)
cancer.gov/contact

Clinical trials

You may also be able to receive treatment through a clinical trial. A clinical trial is a type of medical research study. After being developed and tested in a lab, potential new ways of treating cancer need to be studied in people.

If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. FDA.

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

Phases

Most cancer clinical trials focus on treatment and are done in phases.

- **Phase 1** trials study the safety and side effects of an investigational drug or treatment approach.
- **Phase 2** trials study how well the drug or approach works against a specific type of cancer.
- **Phase 3** trials test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase 4** trials study the safety and benefit of an FDA-approved treatment.

Who can enroll?

It depends on the clinical trial's rules, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. They ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Informed consent

Clinical trials are managed by a research team. This group of experts will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss it with people you trust. Keep in mind

that you can leave and seek treatment outside of the clinical trial at any time.

Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in lymphoma clinical trials. It's common to receive either a placebo added to a standard treatment, or a new drug with a standard treatment.

Are clinical trials free?

There's no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. But you may need to pay for other services, like transportation or childcare, due to extra appointments. Most clinical trials do not cover routine CT scans or other imaging tests. Unless they were being done specifically for the trial. During the trial, you'll continue to receive standard cancer care. This care is usually covered by insurance.

Key points

- Marginal zone lymphoma (MZL) is highly treatable and may be curable in certain circumstances.
- The choice of therapy takes into consideration many factors, including the stage of the disease, your age and other serious health issues, and future treatment possibilities.
- MZL is treated with radiation therapy, systemic therapy, or a combination of both. The goal of treatment is to achieve a complete response, or remission.
- Radiation therapy uses high-energy beams to eradicate lymphoma cells and shrink tumors.
- Systemic therapy works throughout the body. It includes chemotherapy, targeted therapy, and immunotherapy.
- A clinical trial is a type of research that studies a treatment to see how safe it is and how well it works.

Questions to ask

- What type of MZL do I have, and what can you tell me about the stage or other features?
- What experience do you have treating MZL or other lymphomas?
- How long will treatment take, and in what order will it be given?
- Are there resources to help pay for treatment or other care I may need?
- Is a hematopoietic cell transplant (HCT), CAR T-cell therapy, or a clinical trial an option for me?

What's next?

Now that you've read about the different types of treatment and what to expect, the next chapter talks about some general side effects of treatment and what might be done to manage those effects.

4
Supportive care

30 What is supportive care?

31 Side effects

35 Key points

35 Questions to ask

Supportive care helps manage the symptoms of marginal zone lymphoma (MZL) and the side effects of treatment. This chapter discusses supportive care for possible treatment side effects.

What is supportive care?

Supportive care is an important part of cancer care. The goal is to improve your quality of life during and after cancer treatment. Supportive care is for everyone with cancer and their families, not just for those at the end of life.

Supportive care includes a wide range of services. Supportive care prevents or manages the symptoms of cancer and the side effects of cancer treatment, like pain and cancer-related fatigue. It also addresses the mental, social, emotional, and spiritual concerns faced by people with cancer.

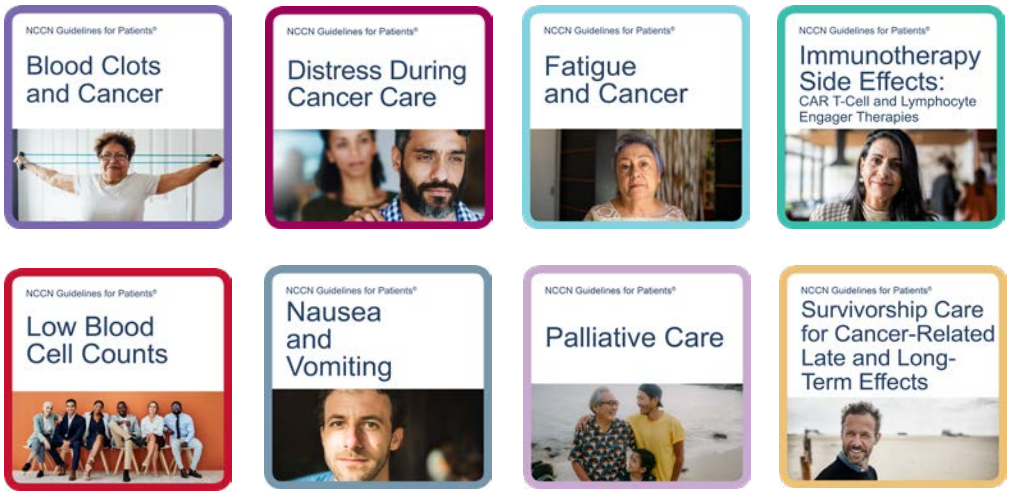
Supportive care provides help with additional needs, such as:

- Making treatment decisions
- Coordinating your care
- Paying for care
- Planning for advance care and end of life

Some health care professionals refer to palliative care as supportive care. They think these types of care are alike or overlap. Others think there are important differences, but both help people with cancer to live as well as they can. Your cancer center may have palliative care specialists, who can give you additional support and help coordinate your supportive care needs.

Supportive care resources

More information on supportive care is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Read more about the types of support you may receive in *NCCN Guidelines for Patients: Palliative Care*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Tell your care team about any new or worsening symptoms so they can be managed.

Side effects

All lymphoma treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person. Some side effects are very serious. Tell your care team about any new or worsening symptoms.

Some potential side effects are described next. They are not listed in order of importance.

Blood clots

Cancer can cause blood clots to form. This can block blood flow and oxygen delivery to parts of the body. Blood clots can break loose and travel to other parts of the body, causing breathing problems, stroke, or other health issues.

Cytokine release syndrome

Cytokine release syndrome only happens during treatment with CAR T-cell therapy or bispecific antibody therapy. It's caused by a large, rapid release of cytokines from immune cells. Cytokines are proteins made and released by the body in response to infection, inflammation, or some treatments. Signs and symptoms include fever, muscle aches, nausea, headache, rash, fast heartbeat, low blood pressure, and trouble breathing.

Diarrhea or constipation

Diarrhea, frequent and watery bowel movements, is a common side effect. Your care team will tell you how to manage diarrhea. When it occurs, it's important to drink lots of fluids.

Constipation means having less frequent and more difficult bowel movements. Constipation is also common, especially if you're taking certain pain medicines and some anti-nausea medicines. Drinking fluids, staying active, and taking medicines for constipation are often recommended.

Emotional distress

Depression, anxiety, and sleeping issues are common during a lymphoma diagnosis. Talk to your care team and those with whom you feel most comfortable about how you're feeling. There are services, people, and medicine that may help relieve your distress.

Fatigue

Fatigue is a state of physical or mental tiredness that can feel like a lack of energy, motivation, or stamina. Fatigue is complex. It may be caused by lymphoma or be a side effect of treatment. Let your care team know how you're feeling and if fatigue is getting in the way of doing the things you enjoy. Eating

a balanced diet, exercise, yoga, acupuncture, and massage therapy can help. You might be referred to a nutritionist or a dietitian to help with fatigue. It's important to try to stay active.

Hair loss

Chemotherapy may cause hair loss (alopecia) all over your body—not just on your scalp. Some chemotherapy drugs are more likely than others to cause hair loss. Dosage might also affect the amount of hair loss. Most of the time, hair loss from chemotherapy is temporary. Hair often regrows 3 to 6 months after treatment ends. Your hair may be a different shade or texture at first. Scalp cooling (or scalp hypothermia) might help lessen hair loss in people receiving certain types of chemotherapy. However, scalp cooling isn't recommended for marginal zone lymphoma (MZL).

Hand-foot syndrome

Hand-foot syndrome is a common side effect of chemotherapy. Small amounts of chemotherapy leak out of very small blood vessels, called capillaries, in the palms of the hands and soles of the feet. It causes redness, swelling, and pain. Sometimes blisters appear. You'll want to protect your hands and feet by applying moisturizer or lotion.

Hypersensitivity, allergy, and anaphylaxis

Hypersensitivity is an exaggerated response by the immune system to a drug or other substance. This response can include hives, skin welts, and trouble breathing. An allergy is an immune reaction to a substance that normally is harmless or would not cause an immune response in most people. An allergic response may cause symptoms, such as itching or inflammation (swelling). Anaphylaxis or anaphylactic shock is a severe and possibly life-threatening allergic reaction.

Infections

Infections are more common and more severe in people with a weakened immune system. Drug treatment for lymphoma can reduce the body's natural defense against infections. If not treated early, infections can be fatal.

Neutropenia, a low number of white blood cells, can lead to frequent or severe infections. When someone with neutropenia also develops a fever, it's called febrile neutropenia (FN). With FN, your risk of infection may be higher than normal. This is because a low number of white blood cells reduces your ability to fight infections. FN is a side effect of some types of systemic therapy. **Notify your care team immediately of any fevers while you may be neutropenic.**

Loss of appetite

The side effects from lymphoma treatment and the stress of having MZL might cause you to feel not hungry or sick to your stomach (nauseated). You might have a sore mouth or difficulty swallowing.

Healthy eating is important during treatment. It includes eating a balanced diet, eating the right amount of food, and drinking enough fluids. A registered dietitian who's an expert in nutrition and food can help.

Low blood cell counts

Some lymphoma treatments can cause low blood cell counts.

- **Anemia** is a condition where your body doesn't have enough healthy red blood cells, resulting in less oxygen being carried to your organs. You might tire easily if you're anemic.
- **Neutropenia** is a decrease in neutrophils, a type of white blood cell. This puts you at risk of infection.
- **Thrombocytopenia** is a condition where there aren't enough platelets. This puts you at risk of bleeding.

Lymphedema

Lymphedema is a condition in which lymph fluid builds up in tissues and causes swelling. It may occur when part of the lymph system is damaged or blocked. Lymphomas that block lymph vessels can also cause lymphedema in the arms or legs. Swelling usually develops slowly over time. If you have lymphedema, you may be referred to an expert in lymphedema management. The swelling may be reduced by exercise, massage, compression devices, and other means.

Nausea and vomiting

Nausea and vomiting are common side effects of treatment. You may be given medicine to prevent nausea and vomiting.

Neuropathy and neurotoxicity

Some treatments can damage the nervous system (neurotoxicity), causing neuropathy and problems with concentration, memory, and thinking (brain fog). Neuropathy is a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse with additional cycles

"My doctor reminded me that stress cannot help me, but it can hurt me! It helped me remember to control those things I could control and relax in front of those that I could not control."



of treatment. Most of the time, neuropathy improves gradually and may eventually go away after treatment.

Organ issues

Treatment might cause your kidneys, liver, and heart not to work as well as they should.

Pain

Tell your care team about any pain or discomfort. You might meet with a palliative care specialist or a pain specialist to manage pain.

Palliative care

Palliative care is appropriate for anyone, regardless of age, cancer stage, or the need for other therapies. It focuses on the physical, emotional, social, and spiritual needs that affect quality of life.

Radiation dermatitis

Radiation dermatitis can develop after radiation therapy for MZL, but it's typically very mild since only low doses are used. Radiation dermatitis can cause the skin to change color or cause dry and itchy skin, pain, peeling, blistering, or swelling. Your health care provider can help you find the best treatment for radiation dermatitis.

Second cancers

Chemotherapy, immunotherapy, radiation therapy, CAR T-cell therapy, and hematopoietic cell transplant can increase your risk of a future, different cancer. Therefore, it's very important to continue follow-up visits with your doctors.

What's the difference between a sign and symptom?

A sign can be seen by someone else like a doctor or nurse. A symptom is something only you can feel.

Therapy-related toxicity

Many of the drug therapies used to treat lymphomas can be harmful to the body. You'll be closely monitored for therapy-related toxicity.

Tumor lysis syndrome

Lymphoma treatment causes cell death. In tumor lysis syndrome (TLS), waste released by dead cells builds up in the body, causing kidney damage and severe blood electrolyte disturbances. Changes in creatinine, lactic acid, uric acid, phosphorus, potassium, and calcium levels can be a sign of TLS. TLS can be life-threatening.

Weight gain

Weight gain is a side effect of steroids. This can be uncomfortable and cause distress. It's important to maintain muscle mass. Find a physical activity you enjoy. Ask your care team what can be done to help manage weight gain.

Key points

- Supportive care is health care that relieves symptoms caused by treatment and improves quality of life.
- All lymphoma treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person.
- Some side effects are very rare. Ask your care team what to expect.
- Tell your care team about any new or worsening symptoms.
- During and after treatment, your health will be monitored for side effects and the return of marginal zone lymphoma (MZL).

Questions to ask

- Who will coordinate my care?
- Who should I call when I have questions or notice changes in my condition?
- How long should I wait if I notice changes in my condition?
- What should I do on weekends and other non-office hours?
- Will my care team be able to communicate with the emergency department or urgent care team?

What's next?

The next chapter explains how MZL found in the stomach is tested and treated.

5
Extranodal MZL (stomach only)

37 Overview

39 Testing

39 EMZL confined to the stomach

41 EMZL that’s spread outside the stomach

43 Recurrence

43 Key points

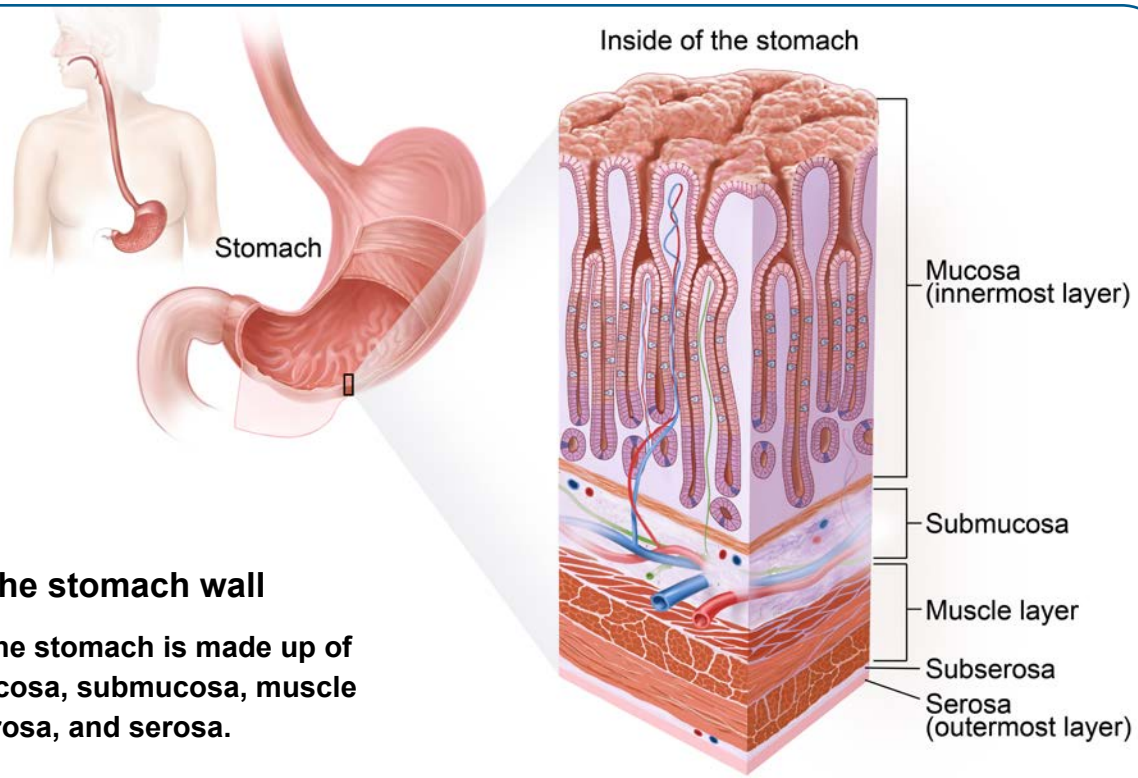
43 Questions to ask

Extranodal marginal zone lymphoma (EMZL) can be found in almost any part of the body. The stomach is the most common site. This chapter focuses on EMZL of the stomach. Depending on the cancer stage, EMZL might be treated with antibiotic therapy, radiation therapy, or chemoimmunotherapy.

Overview

Extranodal marginal zone lymphomas (EMZLs) are found outside the lymph nodes (extranodal) in almost any site in the body. EMZL of the stomach starts in the wall of the stomach. EMZL of the stomach is also called gastric EMZL. Most EMZLs grow slowly and tend not to spread to other places in the body.

The stomach is part of the digestive, or gastrointestinal (GI), tract. The GI tract also includes the esophagus, small intestine, colon, and rectum. The innermost layer of the GI tract is called the mucosa. Extranodal marginal zone lymphoma (EMZL) of the stomach forms in the cells in the mucosa that help make antibodies. Antibodies are proteins that protect you when an unwanted substance or



Layers of the stomach wall

The wall of the stomach is made up of 5 layers: mucosa, submucosa, muscle layer, subserosa, and serosa.

infection enters your body. People with EMZL of the stomach may also have infection in the stomach caused by *Helicobacter pylori (H. pylori)*.

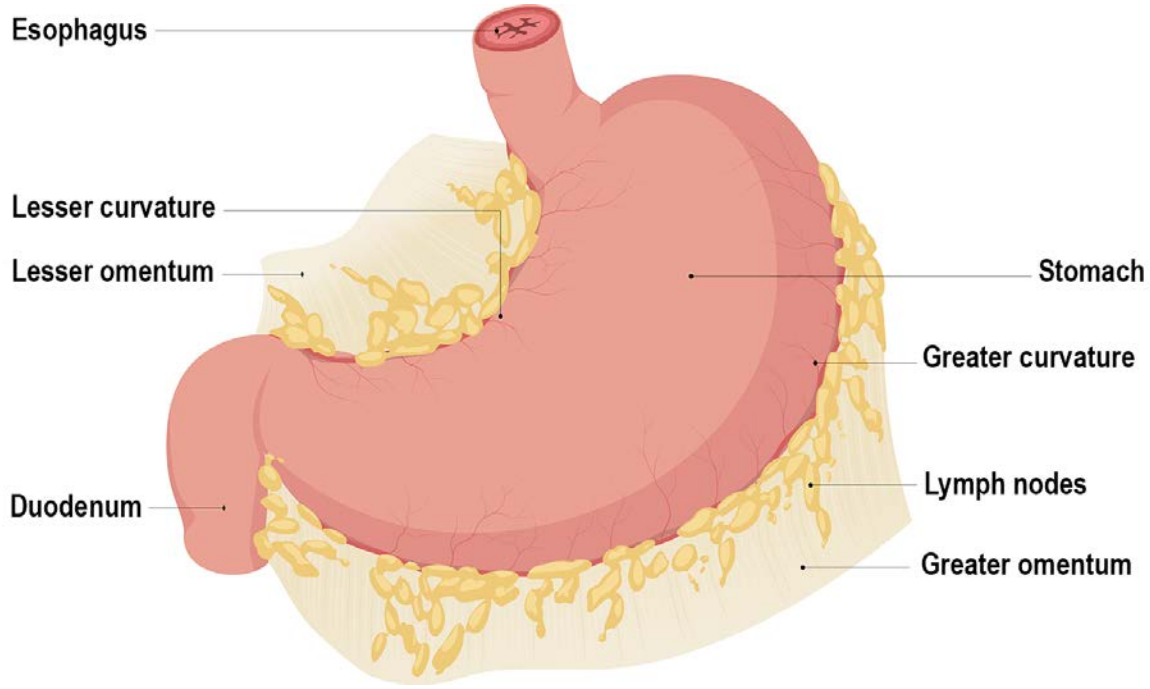
H. pylori

Helicobacter pylori (H. pylori) is a type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with *H. pylori* infections may be more likely to develop cancer in the stomach, including EMZL. You'll be tested for *H. pylori* before starting treatment.

Lymph nodes

EMZL of the stomach can sometimes spread to nearby lymph nodes. Lymph nodes work as filters to help fight infection and remove harmful substances from your body. Lymphatic fluid moves through lymphatic vessels in the mucosa and submucosa. From there, it drains into lymph nodes outside the stomach.

Extranodal marginal zone lymphoma of the stomach can sometimes spread to nearby lymph nodes, tissues, and organs outside the stomach.



Testing

To diagnose EMZL of the stomach, a biopsy sample is taken during an endoscopy. In an endoscopy, a device is guided down the throat into the stomach. Biopsy tests are done to confirm you have EMZL of the stomach, to learn more about the cancer, and to plan treatment. The immunophenotype for EMZL of the stomach is usually CD10-, CD5-, CD20+, cyclin D1-, and BCL2-. This means that the abnormal B cells express CD20, but not CD10, CD5, cyclin D1, or BCL2.

Translocation is when 2 chromosomes switch parts. A translocation between chromosome 11 and 18 is written as t(11;18) or as *MALT1* rearrangement. It occurs in some cases of EMZL of the stomach and is the most frequent genetic abnormality found. If this translocation is found, the tumor tends not to respond to antibiotic treatment in EMZL caused by *H. pylori* infection. Therefore, radiation therapy and/or rituximab may be given in addition to antibiotics.

Tests used to diagnose EMZL of the stomach are found in **Guide 1**.

Tests used to plan treatment are found in **Guide 2**.

EMZL confined to the stomach

EMZL of the stomach is often the result of an *H. pylori* infection. For *H. pylori*-positive EMZL, the initial treatment is antibiotic therapy, usually combined with proton pump inhibitors (PPIs). PPIs reduce the production of stomach acid to help prevent or heal ulcers. Many of these lymphomas go away following antibiotic and PPI treatment, although it may take several months.

Guide 1
Biomarker and genetic tests to diagnose EMZL of the stomach

Needed	• Endoscopic biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, and BLC6 • Test for *H. pylori* • If positive for *H. pylori*, then test for *MALT1* rearrangements
In some cases	• Flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, and CD10 • Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements and *MYD88* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL) • FISH: t(1;14), t(3;14), t(11;14), t(14;18)

For *H. pylori*-negative EMZL, treatment might include radiation therapy or rituximab. Involved-site radiation therapy (ISRT) treats the stomach, or lymphoma found in or near lymph nodes (nodal disease).

Treatment takes time. In some people, lymphoma regresses very slowly, and it can take up to 18 months to achieve a complete response after antibiotics or ISRT.

After treatment with antibiotics (*H. pylori* positive)

After completing treatment, you'll have an endoscopic biopsy to see if *H. pylori* or lymphoma remains. It's also done to rule out the development of a more aggressive lymphoma, such as diffuse large B-cell lymphoma. Treatment might include more antibiotics if *H. pylori* remains. ISRT might be considered.

After treatment with ISRT or rituximab (*H. pylori* negative)

After completing treatment, you'll have an endoscopic biopsy to see if lymphoma remains and to rule out the development of a more aggressive lymphoma, such as diffuse large B-cell lymphoma.

- If lymphoma remains after rituximab, then ISRT or first-line systemic therapy are options.
- If there's no sign of lymphoma, then you'll have regular follow-up appointments every 3 to 6 months for 5 years and then every year as needed.

Guide 2
Tests to plan treatment: EMZL of the stomach

Endoscopic biopsy and hematopathology review
Immunophenotyping with immunohistochemistry and flow cytometry, and biomarker tests, such as fluorescence in situ hybridization (FISH)
Physical exam with performance status
Complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, *H. pylori* testing, hepatitis B and C testing, and serum protein electrophoresis (SPEP) blood test
CT with contrast of chest, abdomen, and pelvis or PET/CT scan
Pregnancy test for people of childbearing age
Possible: • Bone marrow biopsy with or without aspirate • Heart tests • Endoscopy with ultrasound (if available) with multiple biopsies of sites • Discussion of fertility preservation

For systemic therapy options, see **Guide 3**.

EMZL that's spread outside the stomach

EMZL can spread outside the stomach into the surrounding organs or tissues. It can also spread to distant areas of the body.

Treatment will likely start if you have any of these:

- Symptoms
- Gastrointestinal (GI) bleeding
- Threatened end-organ function (damage to major organs fed by the circulatory system, such as the heart, kidneys, brain, and eyes)
- Significant bulky disease
- Steady or rapid disease progression

Treatment includes ISRT or first-line systemic therapy. A clinical trial is always an option even in people without signs or symptoms. First-line systemic therapy is the first set of drug treatment given. For a list of first-line therapy options, see **Guide 3**.

Guide 3
First-line sytemic therapy options: EMZL

Preferred therapies	• Bendamustine plus Rituximab • CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (RCHOP) • CVP (Cyclophosphamide, Vincristine, Prednisone) plus Rituximab • Rituximab
	For people who are older or unwell: • Rituximab • ISRT
Other recommended therapies	• Lenalidomide plus Rituximab • Rituximab
	For people who are older or unwell: • Cyclophosphamide with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

Second-line therapy is the next set of drug treatment given if the cancer doesn't respond to the current treatment or relapses (comes back) during or after systemic therapy. After 2 or more lines of systemic therapy, CAR T-cell therapy (lisocabtagene maraleucel or axicabtagene ciloleucel) might be given. For a list of second-line therapy options, see **Guide 4**.

Guide 4
Second-line and next-line systemic therapy options: EMZL

Systemic therapies not used before are options.

Preferred therapies	• Bendamustine plus Rituximab (not recommended if you had Bendamustine before) • Zanubrutinib • CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (RCHOP) • CVP (Cyclophosphamide, Vincristine, Prednisone) plus Rituximab • Lenalidomide plus Rituximab
	For people who are older or unwell: • Zanubrutinib • Lenalidomide plus Rituximab • Rituximab
Other recommended therapies	• Bendamustine plus Obinutuzumab (not recommended if you had Bendamustine before) • Acalabrutinib • Pirtobrutinib • Lenalidomide plus Obinutuzumab • Rituximab
	For people who are older or unwell: • Acalabrutinib • Pirtobrutinib • Cyclophosphamide with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

Recurrence

If lymphoma returns after treatment (called recurrence or relapse) or doesn't respond to current treatment (refractory), then treatment options include antibiotics, radiation therapy, second-line systemic therapy, and/or a clinical trial. Second-line therapy is the next treatment given if cancer progresses during or after systemic therapy. After 2 or more lines of systemic therapy, CAR T-cell therapy (lisocabtagene maraleucel or axicabtagene ciloleucel) might be given. Sometimes, a hematopoietic cell transplant (HCT) is an option.

Second-line and next-line therapy options can be found in **Guide 4**.

Key points

- The stomach is the most common site for extranodal marginal zone lymphoma (EMZL).
- EMZL of the stomach forms in cells in the innermost layer of the digestive tract called the mucosa.
- EMZL of the stomach can be the result of an infection with *Helicobacter pylori* (*H. pylori*).
- If EMZL of the stomach tests positive for *H. pylori*, then the initial treatment is antibiotic therapy.
- If EMZL of the stomach is negative for *H. pylori*, the preferred treatment is involved-site radiation therapy (ISRT).
- For disease that has spread to distant areas of the body or is causing symptoms, treatment might include systemic therapy.
- After 2 or more lines of systemic therapy, CAR T-cell therapy might be given. Sometimes, a hematopoietic cell transplant (HCT) is an option.

Questions to ask

- Do I have *H. pylori* or does the lymphoma have the t(11;18) translocation (*MALT1* rearrangement)? How does this affect treatment options?
- How often will I have an endoscopy and how should I prepare?
- Which treatment do you recommend and why? How long will treatment take?
- Do you recommend waiting until I have symptoms?
- What side effects can I expect from this treatment?

What's next?

The next chapter explains treatment options for MZL not found in the stomach. Treatment is based on the location.

6
Extranodal MZL (other sites)

45 Overview

45 Testing

45 Treatment

47 Recurrence

48 Key points

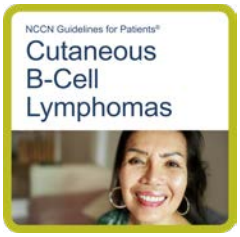
48 Questions to ask

Extranodal marginal zone lymphoma (EMZL) can develop in almost any part of the body. This chapter is for EMZL not found in the stomach (non-gastric). Treatment is usually radiation therapy but may include surgery or chemoimmunotherapy, depending on the location of the lymphoma and if it's early or advanced disease.

Overview

Extranodal marginal zone lymphoma (EMZL) can be found in almost any part of the body. Each type is based on location. Typical sites include the eyes, parotid gland, thyroid gland, lung, breast, head, and neck. EMZL may return many years after treatment.

EMZL of the skin (cutaneous) isn't covered in this guide. For primary cutaneous marginal zone lymphoma (PCMZL), read *NCCN Guidelines for Patients: Cutaneous B-Cell Lymphomas*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Testing

To diagnose EMZL, a biopsy sample is taken and tested. The immunophenotype for EMZL is usually CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, and BCL2-. This means that the abnormal B cells express CD20 but not CD10, CD5, cyclin D1, or BCL2. CD23 or CD43 may be present.

Translocation is when 2 chromosomes switch parts. A translocation between chromosome 11 and 18 is written as t(11;18). t(11;18) occurs specifically in EMZL and is the most frequent genetic abnormality found in this tumor.

Tests used to diagnose EMZL of non-stomach sites can be found in **Guide 5**.

Treatment

EMZL can appear in a variety of areas throughout the body. Therefore, treatment is based on location and the extent of spread. In cases where the primary site is thought to be the head, neck, or lungs, an upper GI endoscopy should be considered. In an upper gastrointestinal (GI) endoscopy, or esophagogastroduodenoscopy (EGD), a device is guided down the throat into the esophagus, stomach, and upper part of the small intestine (duodenum). An EGD is used to inspect the lining of these organs and to look for any signs of cancer or other abnormalities, such as enlarged blood vessels or ulcers. An EGD can also be referred to as a duodenoscopy.

Tests used to plan treatment are found in **Guide 6**.

Guide 5 Biomarker and genetic tests to diagnose EMZL (not in stomach)	
Needed	• Biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, and cyclin D1 with or without flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, and CD10
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements, *MYD88* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL), FISH for *MALT1* rearrangements • FISH: t(11;18), t(1;14), t(3;14), t(14;18)

Guide 6 Tests to plan treatment: EMZL (not in stomach)
Biopsy and hematopathology review
Immunophenotyping with immunohistochemistry and flow cytometry, and biomarker tests, such as fluorescence in situ hybridization (FISH)
Physical exam with performance status
Complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, hepatitis B and C testing, and serum protein electrophoresis (SPEP) blood test
PET/CT scan or CT with contrast of chest, abdomen, and pelvis
Pregnancy test for people of childbearing age
Possible: • Heart tests • Bone marrow biopsy with or without aspirate • Endoscopy with multiple biopsies of sites • Other imaging tests • Evaluation for autoimmune disease • Discussion of fertility preservation

Stage 1E and contiguous 2E

Stage 1E is 1 lesion not in the lymph nodes. In contiguous stage 2E, disease has extended into a surrounding organ or tissue or nearby lymph nodes on the same side of the diaphragm. Involved-site radiation therapy (ISRT) is the preferred treatment for these EMZL stages. Surgery might be an option for sites such as the skin, lung, breast (lumpectomy), thyroid, colon, and small bowel. ISRT might follow surgery. In some cases, rituximab or observation may also be options.

EMZL that's spread to distant sites

EMZL that's spread to distant sites is treated with ISRT. Observation is an option in some cases. For systemic therapy options, see "Stages 3 and 4 (advanced)" in *Chapter 7: Nodal MZL*.

Follow-up care

After treatment, you'll be monitored for signs or symptoms that lymphoma has returned. During this time, you'll have a physical exam with lab tests every 3 to 6 months for 5 years and then every year afterward. Imaging tests may be offered during this surveillance period depending on if you have new or worsening symptoms.

Recurrence

A local recurrence is the return of lymphoma near the same place as before. It's often treated with involved-site radiation therapy (ISRT) if you didn't have it before. For systemic options, see "Stages 3 and 4 (advanced)" in *Chapter 7: Nodal MZL*.

In systemic recurrence, lymphoma is found in the blood, bone marrow, or multiple different areas.

Treatment for systemic recurrence will likely start if you have any of the following:

- Symptoms
- Gastrointestinal (GI) bleeding
- Threatened end-organ function (damage to major organs fed by the circulatory system, such as the heart, kidneys, brain, and eyes)
- Significant bulky disease
- Steady or rapid disease progression

If you didn't have systemic therapy before, then you'll be treated with first-line therapy. See **Guide 3** on page 41.

If you were previously treated with rituximab, then you'll be treated with second-line therapy. See **Guide 4** on page 42.

Key points

- Extranodal marginal zone lymphoma (EMZL) may be found in almost any part of the body. It can sometimes spread to lymph nodes.
- Typical non-gastric sites include the eyes, parotid gland, thyroid gland, lung, breast, head, and neck.
- Treatment is based on the exact location and extent of spread.
- Radiation therapy is often the preferred treatment, especially if the disease is localized to one site.
- Systemic therapy is often used in addition to radiation therapy.
- Surgery may be an option depending on the location of the lymphoma.
- Observation and clinical trials may also be considered.

Questions to ask

- How large are the areas of lymphoma and where are they found?
- Which treatment do you recommend and why?
- Do you recommend waiting until I have symptoms?
- Why are some treatment options preferred over others?
- Does this treatment offer a cure? If not, how well can treatment stop the lymphoma from growing?

What's next?

The next chapter explains treatment for MZL found in the lymph nodes, called nodal marginal zone lymphoma.



Let us know what you think!

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.
NCCN.org/patients/response

7
Nodal MZL

50 Overview

50 Testing

51 Treatment

51 Stages 1 and 2 (limited)

52 Stages 3 and 4 (advanced)

55 Follow-up care

55 Key points

55 Questions to ask

Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. However, NMZL can be found outside the lymph nodes in the bone marrow or blood. Sometimes treatment can wait until you have symptoms. Treatment is usually radiation therapy and systemic therapy.

Overview

Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. However, NMZL can be found outside the lymph nodes in the bone marrow or blood. Lymph nodes make immune cells that help the body fight infection. They also filter the lymph fluid and remove foreign material, such as bacteria and cancer cells.

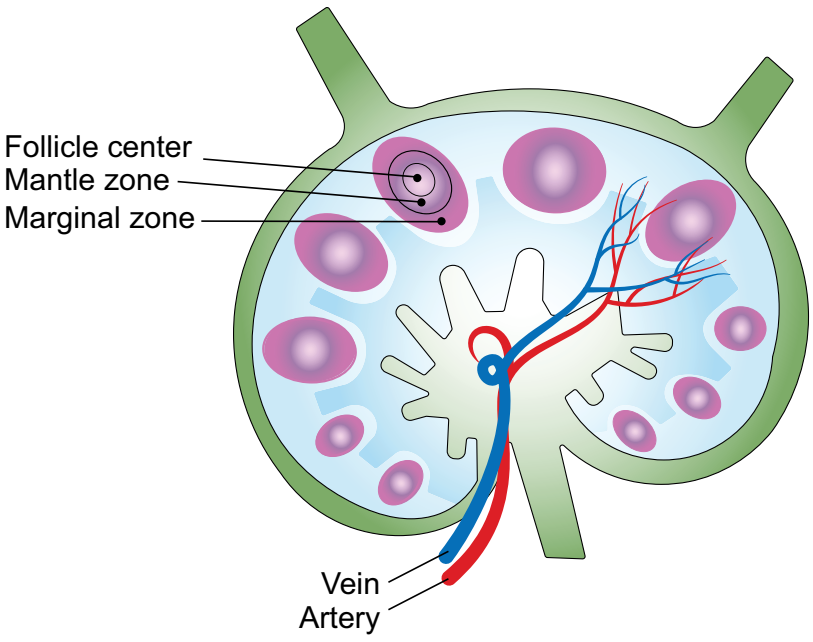
Most people with NMZL are diagnosed with advanced-stage disease (stage 3 or 4). This is cancer found in lymph nodes on both sides of the diaphragm, spleen, or any other organs besides the lymph nodes. At diagnosis, almost everyone with NMZL has lymph nodes that are abnormal in size or consistency. This is called lymphadenopathy. Many people with lymphadenopathy don't have symptoms (asymptomatic).

Testing

Testing is used to distinguish NMZL from nodal follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, and chronic lymphocytic leukemia, all of which are more

The lymph node

Nodal marginal zone lymphoma (NMZL) is found in the marginal zone area of the lymph node.



common. The immunophenotype for NMZL is usually CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, and BCL2-.

Tests used to diagnose NMZL are found in **Guide 7.**

Treatment

Since nodal MZL is most often a slow-growing (indolent) disease, your care team might wait until symptoms appear before starting treatment. This is called active surveillance, observation, or watch and wait. During active surveillance, you'll be monitored for symptoms. When specific signs or symptoms appear, you'll start treatment. Treatment options include radiation therapy and systemic therapy. Involved-site radiation therapy (ISRT) treats lymphoma located in a small area of your body.

Tests used to plan treatment are found in **Guide 8**.

Stages 1 and 2 (limited)

Stage 1 or contiguous stage 2

In stage 1 MZL, disease is found in 1 lymph node. In contiguous stage 2, disease is found in lymph node groups next to one another.

For stage 1 or contiguous stage 2 disease, treatment options include:

- ISRT (preferred).
- ISRT with CD20-targeting monoclonal antibody (mAb) therapy. Chemotherapy might be added.
- CD20-targeting monoclonal antibody therapy (rituximab or obinutuzumab) with or without chemotherapy. Obinutuzumab isn't used by itself as a single agent.

Guide 7
Biomarker and genetic tests to diagnose NMZL

Needed	• Biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, and cyclin D1 with or without flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, and CD10
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements, *MYD88* and *CXCR4* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL), FISH for *MALT1* rearrangements • FISH: t(11;18), t(1;14), del(13q), del(7q), t(14;18)

Non-contiguous stage 2

In stage 2 MZL, disease is found in 2 or more lymph node groups on the same side of the diaphragm, but the involved lymph nodes are not near each other. Treatment options include mAb therapy that targets CD20 with or without chemotherapy. Radiation might be used. Observation might be an option in some cases.

Treatment response

For a complete response or partial response, observation and follow-up care are recommended. You may have ISRT if you didn't have it before.

For no response or disease progression, see treatment for "Stages 3 and 4 (advanced)" in the next section. Information on treatment for MZL that has transformed into diffuse large B-cell lymphoma can be found in *Chapter 9: Transformed MZL*.

Stages 3 and 4 (advanced)

In stage 3, disease is found in lymph nodes on both sides of the diaphragm or in lymph nodes above the diaphragm and in the spleen.

In stage 4, disease is found in various areas outside the lymph nodes.

Guide 8
Tests to plan treatment: NMZL

Biopsy and hematopathology review
Immunophenotyping with immunohistochemistry and flow cytometry, and biomarker tests, such as fluorescence in situ hybridization (FISH)
Physical exam with performance status
Complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, hepatitis B and C testing, and serum protein electrophoresis (SPEP) blood test
PET/CT scan or CT with contrast of chest, abdomen, and pelvis (C/A/P)
Pregnancy test for people of childbearing age
Possible: • Bone marrow biopsy with aspirate • Heart tests • Other imaging tests (In NMZL, disease outside lymph nodes is common) • SPEP blood test • Discussion of fertility preservation

Surveillance

Your care team might wait until certain signs or symptoms appear before starting treatment. This is called active surveillance or observation. Visits with your doctor can range between 3 to 12 months. These visits usually involve blood tests, a physical exam, and an assessment of your symptoms. During surveillance, imaging, such as CT or PET/CT scans, are only done if you have symptoms.

When to begin treatment

Treatment will likely start if you have any of the following:

- Symptoms
- Threatened end-organ function (damage to major organs fed by the circulatory system, such as the heart, kidneys, brain, and eyes)
- Low red blood cell counts not related to NMZL
- Significant bulky disease
- Steady or rapid disease progression

Treatment may include systemic therapy, radiation therapy, or a clinical trial.

First-line systemic therapy is the first set of drug treatment given. For a list of first-line therapy options, see **Guide 9**.

Guide 9
First-line sytemic therapy options: NMZL

Preferred therapies	• Bendamustine plus Rituximab • CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (RCHOP) • CVP (Cyclophosphamide, Vincristine, Prednisone) plus Rituximab • Rituximab
	For people who are older or unwell: • Rituximab • ISRT
Other recommended therapies	• Lenalidomide plus Rituximab • Rituximab
	For people who are older or unwell: • Cyclophosphamide with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

Second-line therapy is the next set of drug treatment given if cancer progresses during or after systemic therapy. See **Guide 10**.

After 2 or more lines of systemic therapy, CAR T-cell therapy (lisocabtagene maraleucel or axicabtagene ciloleucel) might be given.

Treatment response

For a complete response, observation and follow-up care are recommended. If you were treated with rituximab alone, then you might have maintenance therapy with rituximab.

Guide 10
Second-line and next-line systemic therapy options: NMZL

Systemic therapies not used before are options.

Preferred therapies	• Bendamustine plus Rituximab (not recommended if you had Bendamustine before) • Zanubrutinib • CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (RCHOP) • CVP (Cyclophosphamide, Vincristine, Prednisone) plus Rituximab • Lenalidomide plus Rituximab
	For people who are older or unwell: • Zanubrutinib • Lenalidomide plus Rituximab • Rituximab
Other recommended therapies	• Bendamustine plus Obinutuzumab (not recommended if you had Bendamustine before) • Acalabrutinib • Pirtobrutinib • Lenalidomide plus Obinutuzumab • Rituximab
	For people who are older or unwell: • Acalabrutinib • Pirtobrutinib • Cyclophosphamide with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

For a partial response, the following are recommended:

- Maintenance therapy (rituximab) for people treated with rituximab alone
- Observation
- Systemic therapy you didn't have before
- If you've had 2 or more lines systemic therapy, CAR T-cell therapy is an option

For no response or disease progression, you may have another biopsy and another round of systemic therapy with different agents (drugs), or a clinical trial could be considered. If you've had 2 or more lines of systemic therapy, then CAR T-cell therapy might be given.

For CAR T-cell therapy, lisocabtagene maraleucel is preferred, and axicabtagene ciloleucel is also an option.

Follow-up care

After treatment, you'll have physical exams and lab tests every 3 to 6 months for 5 years, and then every year afterward or as needed.

Surveillance imaging may be considered to monitor people without symptoms (asymptomatic). It includes CT scans with contrast every 6 months for 2 years, then once a year.

Key points

- Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. However, it can be found outside the lymph nodes in the bone marrow or blood.
- Treatment options include radiation therapy, chemotherapy, immunotherapy, or a clinical trial.
- Since NMZL is most often a slow-growing disease, your care team might wait until symptoms appear before starting treatment. This is called active surveillance, observation, or watch and wait.

Questions to ask

- Which lymph nodes have lymphoma? Do any other areas have lymphoma?
- Which treatment do you recommend and why?
- Can treatment wait until I have symptoms?
- Does this treatment offer a cure? If not, how well can treatment stop the lymphoma from growing?
- Is a hematopoietic cell transplant (HCT), CAR T-cell therapy, or a clinical trial an option for me?

What's next?

The next chapter explains treatment for MZL found in the blood, bone marrow, and spleen.

8
Splenic MZL

57 The spleen

58 Testing

59 Treatment

60 Recurrence

62 Key points

62 Questions to ask

The spleen makes immune cells, filters the blood, stores blood cells, and removes old blood cells. Splenic marginal zone lymphoma (SMZL) is found in the blood, bone marrow, and spleen. The most common sign of SMZL is an enlarged spleen.

The spleen

The spleen is a fist-sized organ located on the left side of the body near the stomach and pancreas, just under the diaphragm. It filters your blood of antigens (proteins) and microorganisms and removes old, damaged, or worn-out red blood cells. The spleen also contains infection-fighting white blood cells and controls the level of blood cells (white blood cells, red blood cells, and platelets) in the body.

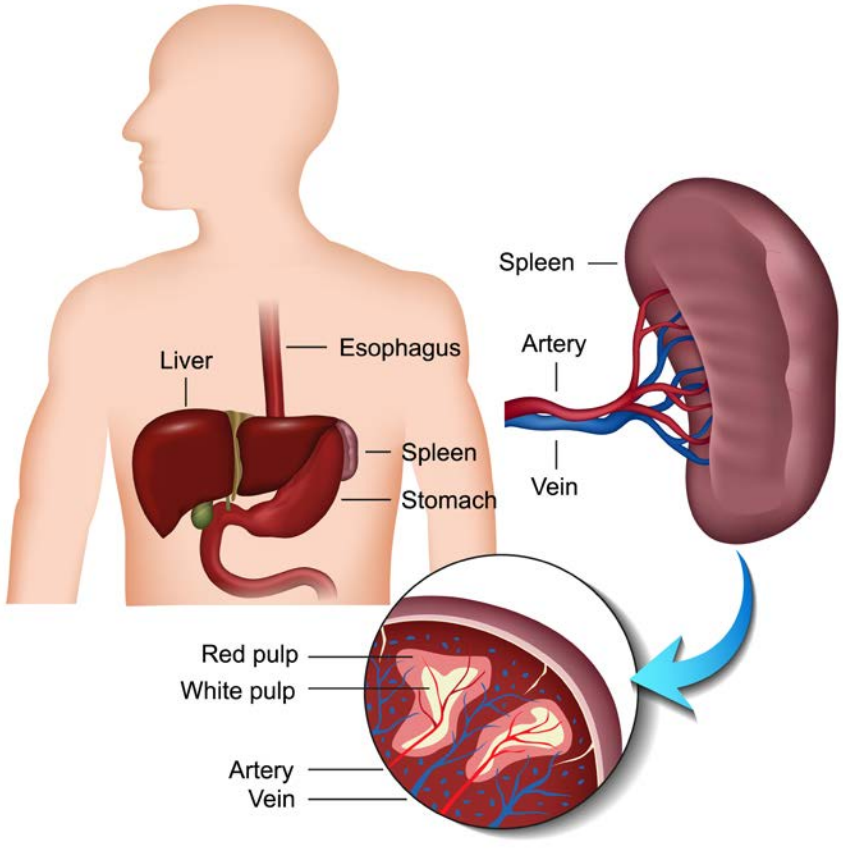
The spleen is made up of 2 types of tissues: red pulp, which filters the blood, and white pulp, which contains white blood cells that regulate inflammation and the body's response to infection.

Red pulp

Red pulp gives the spleen its red color. Red pulp is a loose, spongy tissue that contains white blood cells, such as lymphocytes,

The spleen

The spleen is made up of red and white pulp. Red pulp is a loose, spongy tissue that contains lymphocytes, macrophages, granulocytes, and plasma cells. White pulp is all lymphatic (lymphoid) tissue. It contains white blood cells.



macrophages, granulocytes, and plasma cells. The red pulp removes red blood cells—which carry oxygen—when they are old, damaged, or infected. It harvests the iron from old red blood cells for recycling into new blood cells.

White pulp

White pulp is all lymphatic (lymphoid) tissue. It's called white because it looks whiter than the surrounding red pulp. White pulp of the spleen has 3 sections: the periarteriolar lymphatic sheath (PALS), the follicles, and the marginal zone. The marginal zone is where the distribution of blood flow between slow and fast transit pathways is controlled.

Marginal zone

The marginal zone is the region at the intersection of the red pulp and white pulp. Marginal zone lymphoma in this area affects the movement of blood through the spleen.

Testing

Splenic marginal zone lymphoma (SMZL) is the rarest type of marginal zone lymphoma. SMZL may be diagnosed by removal of the spleen (splenectomy), biopsy of the bone marrow, blood testing, imaging, and other findings. The immunophenotype for SMZL is usually CD10-, CD5-, CD20+, CD23-/+, CD43-/+, and cyclin D1-, BCL2-, annexin A1, and CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD. *NOTCH2* and *KLF2* mutation status may be helpful to differentiate SMZL from other subtypes of B-cell lymphoma.

Tests used to diagnose SMZL are found in **Guide 11**.

Guide 11
Biomarker and genetic tests to diagnose SMZL

Needed	• Biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, IgD, CD43, and annexin A1 with or without flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD43, and CD103
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements, *MYD88* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL), *BRAF* mutation status to differentiate MZL from hairy cell leukemia (HCL), FISH for *MALT1* rearrangements • FISH: chronic lymphocytic leukemia (CLL) panel, t(11;18), t(11;14), del(7q), t(14;18)

Treatment

Tests to plan treatment are found in **Guide 12**.

Observation

Treatment can sometimes wait if:

- You don't have pain, discomfort, or other symptoms (asymptomatic),
- Your spleen isn't enlarged (splenomegaly), and
- Your low red blood cell or platelet counts aren't getting worse.

Enlarged spleen

If you have an enlarged spleen (splenomegaly), your blood will be tested for hepatitis C. If you have hepatitis C, then it may be causing your SMZL. Anti-viral medicines used to treat hepatitis C can also treat SMZL. If you continue to have symptoms and low blood cell counts, then treatment with rituximab is preferred. Surgery to remove the spleen (splenectomy) is an option, but it's rarely done.

You can live a normal, healthy life without a spleen. If your spleen is removed, other organs, such as the liver, can take over many of the spleen's functions. However, your care team will try other treatments before removing your spleen.

Guide 12
Tests to plan treatment: SMZL

Biopsy and hematopathology review
Immunophenotyping with immunohistochemistry and flow cytometry, and biomarker tests, such as fluorescence in situ hybridization (FISH)
Physical exam with performance status
Complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, hepatitis B and C testing, and serum protein electrophoresis (SPEP) blood test
PET/CT scan or CT with contrast of chest, abdomen, and pelvis (C/A/P)
Pregnancy test for people of childbearing age
Possible: • Bone marrow biopsy with or without aspirate • Other imaging tests • Other blood tests • Discussion of fertility preservation

Follow-up care

After treatment, you'll be monitored for the return of cancer. During this time, expect to have a physical exam with lab and imaging tests every 3 to 6 months for 5 years, and then every year afterward or as needed.

Recurrence

Recurrence is the return of cancer.

Treatment will likely start if you have any of the following:

- Symptoms, such as belly (abdominal) discomfort, pain, low blood cell counts, or difficulty breathing
- Threatened end-organ function (refers to damage occurring in major organs fed by the circulatory system, such as the heart, kidneys, brain, and eyes)
- Significant bulky disease
- Steady or rapid progression

Treatment for recurrence may include systemic therapy, surgery to remove the spleen (splenectomy), or radiation therapy.

If you didn't have systemic therapy before, then you'll be treated with first-line therapy. See **Guide 13**.

Guide 13
First-line sytemic therapy options: SMZL

Preferred therapies	• Bendamustine plus Rituximab • CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (RCHOP) • CVP (Cyclophosphamide, Vincristine, Prednisone) plus Rituximab • Rituximab
	For people who are older or unwell: • Rituximab • ISRT
Other recommended therapies	• Lenalidomide plus Rituximab • Rituximab
	For people who are older or unwell: • Cyclophosphamide with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

If you were previously treated with rituximab, then you may be treated with second-line therapy. See **Guide 14**.

Guide 14
Second-line and next-line systemic therapy options: SMZL

Systemic therapies not used before are options.

Preferred therapies	• Bendamustine plus Rituximab (not recommended if you had Bendamustine before) • Zanubrutinib • CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (RCHOP) • CVP (Cyclophosphamide, Vincristine, Prednisone) plus Rituximab • Lenalidomide plus Rituximab
	For people who are older or unwell: • Zanubrutinib • Lenalidomide plus Rituximab • Rituximab
Other recommended therapies	• Bendamustine plus Obinutuzumab (not recommended if you had Bendamustine before) • Acalabrutinib • Pirtobrutinib • Lenalidomide plus Obinutuzumab • Rituximab
	For people who are older or unwell: • Acalabrutinib • Pirtobrutinib • Cyclophosphamide with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

Key points

- The spleen is the largest lymphatic organ. It makes immune cells, filters the blood, stores blood cells, and removes old blood cells.
- Splenic marginal zone lymphoma (SMZL) is found in the blood, bone marrow, and marginal zone of the spleen.
- Treatment can sometimes wait until you have symptoms, an enlarged spleen, and a worsening low red blood cell, white blood cell, or platelet count.
- If you test positive for hepatitis C, then it will be treated. Anti-viral medicines used to treat hepatitis C virus can also treat SMZL.
- Rituximab is often the preferred treatment for people with persistent symptoms and low blood cell counts.
- After treatment, you'll be monitored for the return of cancer. Recurrence is treated with systemic therapy, surgery to remove the spleen (splenectomy), or involved-site radiation therapy (ISRT).

Questions to ask

- Which treatment do you recommend and why?
- Will I have surgery to remove my spleen?
- Do I have hepatitis C? And if so, how will it be treated?
- Does this treatment offer a cure? If not, how well can treatment stop the lymphoma from growing?
- Does the order of treatments matter?

What's next?

The next chapter provides treatment options for MZL that transforms into diffuse large B-cell lymphoma. This can happen before, during, or after treatment.

9
Transformed MZL

64 Overview

64 After little or no therapy

65 After multiple lines of therapy

66 Key points

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Marginal zone lymphoma (MZL) can transform into diffuse large B-cell lymphoma (DLBCL). This means the slow-growing MZL has turned into an aggressive, fast-growing lymphoma.

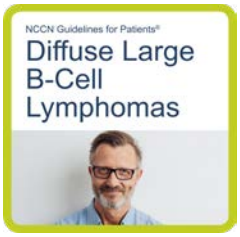
Overview

Marginal zone lymphoma (MZL) can transform into diffuse large B-cell lymphoma (DLBCL). This can occur before, during, or after treatment. In DLBCL, large-cell, fast-dividing tumors are commonly found in the lymph nodes, spleen, liver, bone marrow, or other tissues and organs. The risk of transformation into DLBCL is very low. However, transformed MZL is very serious.

Certain gene rearrangements or chromosome changes can be found in DLBCL. In gene rearrangements, part of a gene on a chromosome has broken off and attached itself to a gene on a different chromosome. Fluorescence in situ hybridization (FISH) is done to look for gene rearrangements.

- *MYC*, *BCL2*, and *BCL6* gene rearrangements are found in DLBCL.
- High-grade B-cell lymphomas (HGBLs) have mutations, gene rearrangements like *MYC*, or other high-risk features.

For more information on treatment for DLCBL and HGBLs, read *NCCN Guidelines for Patients: Diffuse Large B-Cell Lymphomas*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



After little or no therapy

If MZL changed into DLBCL after little or no therapy, then it's treated with chemoimmunotherapy. Radiation therapy might be given. The goal of treatment is remission.

Preferred chemoimmunotherapy for people who can tolerate intense chemoimmunotherapy:

- RCHOP consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
- Pola-R-CHP consists of polatuzumab vedotin-piiq, rituximab, cyclophosphamide,

Other possible chemoimmunotherapy options include:

- DA-EPOCH-R is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab.
- RCDOP is rituximab, cyclophosphamide, liposomal doxorubicin (Doxil), vincristine, and prednisone.

- RCEOP is rituximab, cyclophosphamide, etoposide, vincristine, and prednisone.
- RGCVP is rituximab, gemcitabine (Gemzar or Infugem), cyclophosphamide, vincristine, and prednisone.
- R-mini-CHOP and its variations for people who can't have intense chemoimmunotherapy.

Treatment response

After treatment, you'll have imaging (PET/CT) and lab tests to see if any lymphoma remains.

- In a complete response, no lymphoma remains. Observation or a clinical trial are options. If disease relapses, you'll have a biopsy before treatment.
- If there's a partial response, then you'll be given CD19-targeting CAR T-cell therapy. Other systemic therapies are possible.
- If your disease doesn't respond to treatment or has progressed, then you'll be given CD19-targeting CAR T-cell therapy. Other systemic therapies are possible.

After multiple lines of therapy

If MZL changed into DLBCL after multiple lines of therapy, then the treatment options include:

- Clinical trial.
- Systemic therapy. Options are based on what you were treated with before, your situation, and other factors. A type of radiation therapy called involved-site radiation therapy (ISRT) might be added to treat lymphoma located in a small region or 1 area of your body.
- ISRT.
- Best supportive care (improves quality of life and relieves discomfort).

"Bring someone with you to appointments. It doesn't have to be the same person each time. But, they can help take notes and keep a list of questions. More importantly, they'll be there to provide comfort and support."



Treatment response

After treatment, you'll have imaging (PET/CT scan) and lab tests to see if any lymphoma remains.

Complete response

In a complete response, or remission, no lymphoma remains. You might enter observation. An autologous (self) or allogeneic (donor) hemopoietic cell transplant (HCT) may be an option. After treatment, you'll enter surveillance and be monitored for relapse.

Partial response

In a partial response, treatment options are based on the types of treatment you had before. Options listed below depend on your individual situation:

- CD19-targeting CAR T-cell therapy (preferred, if not given before).
- Allogeneic HCT in some cases. ISRT might be added if not given before.
- ISRT (if not given before, and disease is in a small region or 1 area of your body).
- Observation with follow-up tests.

Relapse

If disease relapses, you'll have a biopsy before treatment. Treatment might include a clinical trial, a systemic therapy not used before, ISRT, CD19-targeting CAR T-cell therapy, bispecific antibody therapy, or best supportive care. In best supportive care, the focus is improving quality of life and relieving discomfort.

No response or disease progresses

When disease progresses during treatment or doesn't respond to multiple lines of therapy, the focus is on best supportive care.

Key points

- Marginal zone lymphoma (MZL) can transform into diffuse large B-cell lymphoma (DLBCL). This means the slow-growing MZL has turned into a fast-growing, aggressive lymphoma.
- The goal of treatment for transformed MZL is remission.
- If MZL changes into DLBCL after little or no treatment, then it's treated with chemoimmunotherapy, such as RCHOP or Pola-R-CHP. You may have radiation therapy after completing systemic therapy.
- If MZL changes into DLBCL after multiple lines of therapy, then treatment recommendations include a clinical trial, systemic therapy, radiation therapy, or best supportive care. In best supportive care, the focus is improving quality of life and relieving discomfort.
- A hematopoietic cell transplant (HCT) might be an option in some cases after multiple lines of systemic therapy. If an HCT is being considered, it's usually decided early in treatment planning.
- The order of treatment matters.
- Bispecific antibody therapy is an option before or after HCT or CD19-targeting CAR T-cell therapy.

Questions to ask

- Where do you think we should start with treatment?
- What order of treatments are you considering and why?
- How many rounds of systemic therapy do you think I'll need?
- Are you planning for a hematopoietic cell transplant (HCT) or CAR T-cell therapy in the future?
- Am I a candidate for a clinical trial?

What's next?

The next chapter provides information about resources and where you can get support.



We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer. Take our survey to let us know what we got right and what we could do better.
NCCN.org/patients/feedback

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Want to learn more? Here's how you can get additional help.

What else to know

This guide helps you know your options so you can make informed decisions and improve your cancer care. But it's not the only resource that you have.

Ask for as much information and help as you need. Many people are interested in learning more about:

- Finding an oncologist who's an expert in treating lymphoma
- Making treatment decisions, including participating in a clinical trial
- The details of treatment and possible side effects
- Getting financial help
- Coping with the stress of having lymphoma

What else to do

Your health care center can help you with next steps. It often has on-site resources to help meet your needs and find answers to your questions. Health care centers can also inform you of resources in your community.

In addition to help from your providers, the resources listed in the next section provide support for many people like yourself.

Where to get help

Look through the list below and visit the provided websites to learn more about these organizations.

AnCan Foundation
ancan.org

Blood & Marrow Transplant Information Network
bmtinfonet.org

Blood Cancer United
bloodcancerunited.org

Cancer*Care*
cancercare.org

Imerman Angels
imermanangels.org

Lymphoma Research Foundation
lymphoma.org

National Bone Marrow Transplant Link (nbmtLINK)
nbmtlink.org

NMDP
nmdp.org

Stupid Cancer
stupidcancer.org

Triage Cancer
triagecancer.org

Questions to ask

- Who can I talk to about help with housing, food, and other basic needs?
- What help is available for transportation, childcare, and home care?
- What other services are available to me and my caregivers?
- How can I connect with others and build a support system?
- Who can I talk to if I don't feel safe at home, at work, or in my neighborhood?

"If I've learned anything, it's that no one will advocate for you the way you can advocate for yourself. You deserve time and attention from your care team. You deserve to be heard. I've also learned that people will surprise you. When I felt my loneliest, when I was at my lowest, people came out of the woodwork to support me. Some of them weren't the ones I expected. Some I barely knew. But they showed up, and that meant everything."





Words to know

allogeneic hematopoietic cell transplant (allogeneic HCT)
Treatment that replaces a person's bone marrow and immune system with donor cells to fight the lymphoma.

autologous hematopoietic cell transplant (autologous HCT)
Treatment that destroys a person's bone marrow then rebuilds it with their own healthy stem cells. Also called high-dose therapy with autologous stem cell rescue (HDT/ASCR).

best supportive care
Treatment to improve quality of life and relieve discomfort.

biomarker testing
A lab test of any molecule in your body that can be measured to assess your health. Also called molecular testing.

biopsy
A procedure that removes fluid or tissue samples to be tested for a disease.

biosimilar
A drug that's almost identical to a drug made by another company. It has been approved by the U.S. FDA and must be used in the same way and at the same dose as the other drug.

bone marrow
The sponge-like tissue in the center of most bones.

bone marrow aspiration
A procedure that removes a liquid bone marrow sample to test for a disease.

bone marrow biopsy
A procedure that removes bone and solid bone marrow samples to test for a disease.

chromosome
Structures within cells that contain coded instructions for cell behavior.

clinical trial
Research that assesses health tests or treatments.

complete response (CR)
When no signs of lymphoma are found. Also called complete remission.

computed tomography (CT)
A test that uses x-rays from many angles to take pictures of areas inside the body.

contrast
A substance put into your body to make clearer pictures during imaging tests.

deoxyribonucleic acid (DNA)
A chain of chemicals in cells that contains coded instructions for making and controlling cells.

endoscope
A thin, long tube fitted with tools that's guided down the mouth.

flow cytometry
A lab test of substances on the surface of cells to identify the type of cells present.

fluorescence in situ hybridization (FISH)
A lab test that uses special dyes to look for abnormal chromosomes and genes.

gastrointestinal (GI) tract
The group of organs through which food passes after being eaten. Also called the digestive tract. It includes the esophagus, stomach, small intestine, colon, and rectum.

gene
A set of coded instructions in cells for making new cells and controlling how cells behave.

Helicobacter pylori (***H. pylori***)
A type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with *H. pylori* infections may be more likely to develop cancer in the stomach, including extranodal marginal zone lymphoma (EMZL).

hematopathologist
A doctor who specializes in the study of blood diseases and cancers using a microscope.

hematopoietic cell transplant (HCT)
Treatment that replaces a person's bone marrow and immune system with healthy cells to fight the lymphoma.

histology
The study of tissues and cells under a microscope.

imaging test
A test that takes pictures (images) of areas inside the body.

immune system
The body's natural defense against infection and disease.

immunohistochemistry (IHC)
A lab test of cancer cells to find specific cell traits involved in abnormal cell growth.

immunophenotyping
A lab test that detects the type of cells present based on the cells' surface proteins.

involved-site radiation therapy (ISRT)
Radiation therapy that treats cancer found in a small region or 1 area of the body.

lactate dehydrogenase (LDH)
A protein in blood that helps to make energy in cells.

lymph
A clear fluid containing white blood cells.

lymph node
A small, bean-shaped, disease-fighting structure.

lymphadenopathy
Lymph nodes that are abnormal in size or consistency.

lymphatic system
A germ-fighting network of tissues and organs that includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels. Part of the immune system.

lymphedema
Swelling in the body due to a buildup of fluid called lymph.

lymphocyte
A type of white blood cell that's part of the immune system.

magnetic resonance imaging (MRI)
A test that uses radio waves and powerful magnets to take pictures of areas inside the body.

monitoring
A period of testing for changes in lymphoma status.

mutation
An abnormal change in the instructions within cells for making and controlling cells.

partial response (PR)
Lymphoma is still present but has reduced in size.

pathologist
A doctor who's an expert in testing cells and tissue to find disease.

peripheral blood (PB)
Blood that circulates throughout the body.

platelet
A type of blood cell that helps control bleeding. Also called a thrombocyte.

polymerase chain reaction (PCR)
A lab process that makes copies of parts of DNA.

positron emission tomography (PET)
A test that uses radioactive material to see the shape and function of body parts.

prognosis
The likely course a disease will take.

radiation therapy (RT)
A treatment that uses high-energy rays.

recovery
A period of time without treatment to allow blood cell counts to return to normal.

recurrence
Return of lymphoma after a cancer-free period.

red blood cell (RBC)
A type of blood cell that carries oxygen from the lungs to the rest of the body. Also called an erythrocyte.

refractory cancer
Lymphoma that doesn't improve with treatment.

relapse
Return or worsening of lymphoma after a period of improvement.

remission
Minor or no signs of disease.

side effect
An unhealthy or unpleasant physical or emotional response to treatment.

spleen
An organ of the lymphatic system. The spleen makes lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It's located on the left side of the abdomen near the stomach.

splenectomy
Surgery to remove the spleen.

supportive care
Treatment for the symptoms or health conditions caused by lymphoma or its treatment. Also sometimes called palliative care or best supportive care.

translocation
A switching of parts between 2 chromosomes.

tumor lysis syndrome (TLS)
A rare condition caused when waste released by dead cells isn't quickly cleared out of your body.

white blood cell (WBC)
A type of blood cell that helps fight infections in the body. Also called a leukocyte.

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This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas, Version 4.2026. It was adapted, reviewed, and published with help from the following people:

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PAT-N-1991-1126