Lymphoma action
Inform | Support | Connect

Helpline (freephone) 0808 808 5555
information@lymphoma-action.org.uk
www.lymphoma-action.org.uk

Grey zone lymphoma, double-hit lymphoma, triple-hit lymphoma, and high-grade B-cell lymphomas, not otherwise specified (NOS)

This page is about rare types of fast-growing (high-grade) B-cell lymphoma that are difficult to classify: grey zone lymphoma, double-hit and triple-hit lymphoma, and high-grade B-cell lymphoma, not otherwise specified (NOS).

On this page

What types of high-grade B-cell lymphoma are difficult to classify?

Grey zone lymphoma

Double-hit and triple-hit lymphomas

High-grade B-cell lymphoma, not otherwise specified (NOS)

Finding further information

We have separate information about the topics in **bold font**. Please get in touch if you'd like to request copies or if you would like further information about any aspect of lymphoma. Phone 0808 808 5555 or email **information@lymphoma-action.org.uk**.

What types of high-grade B-cell lymphoma are difficult to classify?

There are lots of different **types of lymphoma**. The **tests** you have when you are diagnosed help your medical team find out which type of lymphoma you have. This is called 'classifying' your lymphoma. It is important that your medical team know which type of lymphoma you have so they can give you the most appropriate treatment.

Sometimes a lymphoma doesn't fit neatly into the main categories of lymphoma. For example, it might have features of more than one type of lymphoma, or particular genetic changes (mutations) that might require a different treatment approach.

© Lymphoma Action

If your lymphoma is difficult to classify, your medical team might need to carry out more specialised tests on your **biopsy** (sample from your lymphoma). This might mean it takes longer to get the results of your tests but it helps make sure you get the most suitable treatment.

High-grade B-cell lymphomas that are difficult to classify are rare. They include:

- grey zone lymphoma
- double-hit and triple-hit lymphomas
- high-grade B-cell lymphomas, not otherwise specified (NOS).

Grey zone lymphoma

Rarely, a lymphoma has features of both **classical Hodgkin lymphoma** and **diffuse large B-cell lymphoma (DLBCL)**, particularly a type of DLBCL called '**primary mediastinal B-cell lymphoma (PMBL)**'. This is officially called 'B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.' It is usually referred to as 'grey zone lymphoma'.

Grey zone lymphoma can develop at any age but it is more common in younger people (20 to 40 years old). It affects around twice as many men as women. It is more likely to affect white people than Asian people or black people.

Grey zone lymphoma usually starts in an area called the mediastinum, which is in the centre of the chest. This is sometimes called 'mediastinal grey zone lymphoma'. Most people with mediastinal grey zone lymphoma develop a large lump of lymphoma in this area. The lump might press on your airways or lungs, causing **symptoms** such as cough or breathing problems. You might have **swollen lymph nodes** just above your collar bone, but most people do not have swollen nodes in other places. It is usually diagnosed when it is at an early **stage**.

In fewer than 1 in 3 cases, grey zone lymphoma starts outside the chest. This is sometimes called 'non-mediastinal grey zone lymphoma'. It tends to develop in older people. It might be at a more advanced stage than mediastinal grey zone lymphoma by the time it is diagnosed.

Grey zone lymphoma is rare and it can be difficult to diagnose. On lab tests, it can have features that are very like other types of lymphoma, such as PMBL or classical Hodgkin lymphoma.

© Lymphoma Action

There is no standard treatment for grey zone lymphoma. Depending on your individual circumstances and the results of your lab tests, your doctor might ask you if you would like to take part in a **clinical trial** of a new treatment. This can help find out what the best treatment is for grey zone lymphoma. You can find out more about clinical trials or search for a trial that might be suitable for you on **Lymphoma TrialsLink**.

If you don't want to take part in a clinical trial, or if there isn't one that is suitable for you, you are likely to have treatment similar to that used for people with **DLBCL** or **classical Hodgkin lymphoma**. This usually involves **chemotherapy**, often combined with **antibody therapy** (known as chemo-immunotherapy).

You might have treatment regimens commonly used for DLBCL (such as **R-CHOP** or **DA-EPOCH-R**) or treatment regimens that are used for classical Hodgkin lymphoma (such as **ABVD** or **BEACOPP**). However, your treatment depends on your exact circumstances and, in particular, how the lymphoma looks under the microscope. Your medical team might recommend a different regimen for you based on your particular symptoms and test results.

If you have a large lump of lymphoma, you might also have **radiotherapy** after chemotherapy to help shrink it.

Grey zone lymphoma often comes back (**relapses**) after initial treatment. If this happens, you are likely to have more intensive chemo-immunotherapy. This is often successful. If you respond well to treatment and you are fit enough, your medical team might recommend that you have a **stem cell transplant**.

Clinical trials are also looking at the possibility of using **targeted drugs** to treat relapsed grey zone lymphoma.

Double-hit and triple-hit lymphomas

Double-hit and triple-hit lymphomas are high-grade B-cell lymphomas that have major genetic changes (mutations) affecting particular genes. The genes that are affected are called *MYC*, *BCL2* and *BCL6*. These genes usually help control the growth of B cells.

- Double-hit lymphomas have mutations in two of these genes.
- Triple-hit lymphomas have mutations in all three of these genes.

© Lymphoma Action

Double-hit and triple-hit lymphomas are officially known as 'high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements'.

Double-hit lymphoma with mutations in *MYC* and *BCL2* is more common than double-hit lymphoma with mutations in *MYC* and *BCL6* or triple-hit lymphoma (mutations in all three). However, all of these types of lymphoma are rare.

Most double-hit or triple-hit lymphomas are similar to a type of lymphoma called **diffuse large B-cell lymphoma (DLBCL)**, although some are more like **Burkitt lymphoma**. Occasionally, they develop from **follicular lymphoma** (a low-grade non-Hodgkin lymphoma that can sometimes change, or **transform**, into a faster-growing lymphoma).

Double-hit and triple-hit lymphomas tend to develop in older people (over 60). They often start in extranodal sites (outside the **lymph nodes**). **Symptoms** vary depending on exactly where the lymphoma starts but most people develop **swollen lymph nodes** spread throughout their body. Many people also experience 'B symptoms' (**unexplained weight loss**, **night sweats** and **fever**). About half of all people with double-hit or triple-hit lymphoma have lymphoma in the **bone marrow**. Around 1 in 10 people with double-hit or triple-hit lymphoma have **symptoms caused by lymphoma in their central nervous system** (brain and spinal cord).

Most people have **advanced stage lymphoma** when they are diagnosed.

There is no standard treatment for double-hit or triple-hit lymphoma. These types of lymphoma can be difficult to treat. They have a higher risk of coming back (relapsing) than more common types of high-grade B-cell lymphoma.

Your doctor might ask you if you would like to take part in a **clinical trial** to access treatments that are not otherwise available. You can find out more about clinical trials or search for a trial that might be suitable for you on **Lymphoma TrialsLink**.

If you don't want to take part in a clinical trial, or if there isn't one that is suitable for you, you might have treatment with **R-CHOP** chemotherapy, or your doctor might discuss using more intensive chemo-immunotherapy (**chemotherapy** combined with **antibody therapy**). Chemo-immunotherapy regimens (combinations of drugs) your medical team might recommend include:

- **DA-EPOCH**-R
- R-**CODOX-M**/R-**IVAC**
- R-**Hyper-CVAD**.

© Lymphoma Action

If you have had R-CHOP in the past for follicular lymphoma, your medical team might suggest a different regimen, such as R-**ICE** or R-**DHAP**.

You are also likely to have treatment to help prevent the lymphoma spreading to your brain and spinal cord (your central nervous system, or CNS). This is called **CNS prophylaxis**. It either involves:

- having **particular, additional chemotherapy drugs** that are able to cross from your bloodstream into your CNS given intravenously, or
- having injections of chemotherapy into the fluid around your spinal cord through a lumbar puncture (**intrathecal chemotherapy**).

Treatments used for double-hit and triple-hit lymphoma are usually very intensive. You might have stay in hospital for long periods while you have your treatment. In some hospitals, you might be able to have DA-EPOCH-R through a portable infusion pump, reducing the time you need to spend in hospital.

If you are not able to tolerate intensive treatment, your medical team will suggest an alternative treatment option. They will recommend the most appropriate treatment for you based on your individual circumstances.

If you respond well to treatment and you are fit enough, you might be offered a stem cell transplant using your own stem cells (an **autologous stem cell transplant**). This is more likely if you had a less intensive chemotherapy regimen. If you responded well to intensive chemotherapy, a stem cell transplant is less likely to benefit you.

If your lymphoma comes back (**relapses**) or doesn't respond (refractory) to your first treatment, you might be offered additional chemotherapy followed by a stem cell transplant using your own or donor stem cells (an **allogeneic stem cell transplant**). Some people with relapsed or refractory double-hit or triple-hit lymphoma might be eligible for **CAR T-cell therapy**. Other treatment options might be available through **clinical trials**, such as new **targeted drugs** that are currently being investigated.

© Lymphoma Action

The doctors arranged a PET scan to check that my lymphoma was completely under control. Unfortunately, it showed instead that my lymphoma had returned – my remission had only lasted 6 weeks. The doctors therefore decided that an autologous transplant wasn't going to work for me and that I should have a donor stem cell transplant.

Kat, diagnosed with double-hit lymphoma at 32

High-grade B-cell lymphoma, not otherwise specified (NOS)

If you have a high-grade B-cell lymphoma that doesn't fit any of the other categories, it is known as 'high-grade B-cell lymphoma, not otherwise specified (NOS)'. These types of lymphoma might have features of more than one type of lymphoma, such as DLBCL and Burkitt lymphoma. They do not have the genetic mutations found in double-hit or triple-hit lymphoma.

Lymphomas in this group can behave very differently to each other.

There is no standard treatment for high-grade B-cell lymphoma, NOS. Depending on your individual circumstances and the results of your lab tests, you might be offered treatments usually used for other types of lymphoma, such as **diffuse large B-cell lymphoma (DLBCL)** or **Burkitt lymphoma**. Your medical team might suggest more intensive treatment if your lymphoma has features that suggest it may be difficult to treat.

© Lymphoma Action

Your doctor might ask you if you would like to take part in a **clinical trial**. You can find out more about clinical trials or search for a trial that might be suitable for you on **Lymphoma TrialsLink**.

Finding further information

It can be difficult to find reliable information about rarer types of lymphoma. If you can't find anything about your particular type, you might find it helpful to read about the type of lymphoma it most closely resembles.

Ask your medical team for advice on what information is most relevant for you. They can advise you based on your individual circumstances.

If you prefer to find information yourself, it's important to make sure it is accurate and up-to-date. Try to find out:

- Where is the information from? Is it a reputable publication or organisation?
- Who has written the information? Has it been checked by a lymphoma expert?
- Is there a list of evidence sources (for example, a reference list)?
- When was the information last updated? Remember that research is being carried out all the time and older information might not be relevant any more.
- Is the information relevant to where you live? Different treatments might be available in different countries.
- How is the information funded? Be wary of information from sources that are selling something.

> **I had Googled my type of lymphoma and had lots of questions for the doctors. My consultant explained that there had not been many studies done in this type of lymphoma yet, and that information on the internet might well just be discouraging and unhelpful. The conversation with him was reassuring – he explained my condition and filled me with a lot more confidence.**
>
> Kat, diagnosed with double-hit lymphoma at 32

© Lymphoma Action

References

The full list of references for this page is available on our website. Alternatively, email **publications@lymphoma-action.org.uk** or call 01296 619409 if you would like a copy.

Acknowledgements

- With thanks to Dr Eve Gallop-Evans, Consultant Clinical Oncologist, Velindre Hospital, Cardiff, and Professor Andrew Davies, Consultant in Medical Oncology, University Hospital Southampton, for reviewing this information.
- We would like to thank the members of our Reader Panel who gave their time to review this information.

Content last reviewed: April 2020
Next planned review: April 2023
LYMweb0233GreyZone2020v2

✓	Evidence-based
✓	Approved by experts
✓	Reviewed by users

© Lymphoma Action

Tell us what you think and help us to improve our resources for people affected by lymphoma. If you have any feedback, please visit **lymphoma-action.org.uk/Feedback** or email **publications@lymphoma-action.org.uk**.

All our information is available without charge. If you have found it useful and would like to make a donation to support our work you can do so on our website **lymphoma-action.org.uk/Donate**. Our information could not be produced without support from people like you. Thank you.

Disclaimer

We make every effort to make sure that the information we provide is accurate at time of publication, but medical research is constantly changing. Our information is not a substitute for individual medical advice from a trained clinician. If you are concerned about your health, consult your doctor.

Lymphoma Action cannot accept liability for any loss or damage resulting from any inaccuracy in this information or third party information we refer to, including that on third party websites.