# Cancer Association of South Africa (CANSA)

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## Fact Sheet on Richter's Syndrome

**Introduction**

The non-Hodgkin lymphomas (NHLs) are a diverse group of blood cancers that include all kinds of lymphoma except Hodgkin's lymphomas. Types of NHL vary significantly in their severity, from slow growing to very aggressive types.


[Picture Credit: Richter's Syndrome]

Lymphomas are types of cancer derived from lymphocytes, a type of white blood cell. Lymphomas are treated by combinations of chemotherapy, monoclonal antibodies (CD20), immunotherapy, radiation, and haematopoietic stem cell transplantation.

The 2008 the World Health Organization (WHO) classification of lymphomas has five large groups, including a Hodgkin disease group. Other forms of lymphoma include over 80 different forms of lymphoma in an additional four broad groups. By comparison, the 1982 Working Formation (which is now considered obsolete, is commonly used primarily for statistical comparisons with previous decades) recognised just 16 types of non-Hodgkin lymphoma.

Richter's syndrome is a type of high grade non-Hodgkin's Lymphoma. It is a diffuse large B cell lymphoma. It is called diffuse because of the way the cells look under a microscope. 'Diffuse' means spread out.
(Wikipedia; Cancer Research UK).

**Richter's Syndrome**

Richter's syndrome is very rare. It starts as chronic lymphocytic leukaemia (CLL). Then sometimes the leukaemia cells get into the lymph nodes and start growing there. In the advanced stage CLL can change and become Richter's syndrome. Fewer than 5 out of every 100 people (5%) with CLL develop Richter's syndrome. It is a quickly developing cancer. People with Richter's Syndrome can become unwell quite suddenly.
(Cancer Research UK).

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Richter's Syndrome (RS), also known as *Richter's Transformation*, is a rare complication of Chronic Lymphocytic Leukaemia (CLL) and/or Small Lymphocytic Lymphoma (SLL) characterised by the sudden transformation of the CLL/SLL into a significantly more aggressive form of large cell lymphoma. Richter's Syndrome occurs in approximately 2-10% of all CLL/SLL patients during the course of their disease. In the most cases it is normally slow growing, or indolent - CLL transforms into a common type of non-Hodgkin lymphoma (NHL) known as Diffuse Large B-Cell Lymphoma (DLBCL). Rarer cases transform into Hodgkin lymphoma (HL)/Hodgkin Disease (HD), and some types of T-cell lymphomas also have been reported.
(Leukaemia Foundation).

**Incidence of Richter's Syndrome in South Africa**

The National Cancer Registry (2012) does not furnish any information on the incidence of Richter's Syndrome in South Africa. It groups all forms of non-Hodgkin's Lymphoma together. According to the National Cancer Registry (2013) the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2013:

| Group - Males 2013 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All males | 882 | 1:221 | 2,45% |
| Asian males | 25 | 1:241 | 2,97% |
| Black males | 516 | 1:316 | 4,79% |
| Coloured males | 88 | 1:192 | 2,12% |
| White males | 254 | 1:123 | 1,26% |

| Group - Females 2013 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All females | 802 | 1:327 | 2,19% |
| Asian females | 21 | 1:296 | 1,98% |
| Black females | 471 | 1:461 | 3,02% |
| Coloured females | 76 | 1:267 | 1,87% |
| White females | 234 | 1:163 | 1,47% |

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2013 was as follows (National Cancer Registry, 2013):

| Group - Males 2013 | 0 – 19 Years | 20 – 29 Years | 30 – 39 Years | 40 – 49 Years | 50 – 59 Years | 60 – 69 Years | 70 – 79 Years | 80+ Years |
|---|---|---|---|---|---|---|---|---|
| All males | 29 | 46 | 152 | 199 | 172 | 144 | 85 | 40 |
| Asian males | 0 | 0 | 1 | 7 | 7 | 5 | 2 | 1 |
| Black males | 25 | 30 | 126 | 142 | 105 | 40 | 18 | 5 |
| Coloured males | 2 | 4 | 7 | 14 | 18 | 27 | 8 | 4 |
| White males | 2 | 9 | 15 | 32 | 38 | 67 | 55 | 28 |

| Group - Females 2013 | 0 – 19 Years | 20 – 29 Years | 30 – 39 Years | 40 – 49 Years | 50 – 59 Years | 60 – 69 Years | 70 – 79 Years | 80+ Years |
|---|---|---|---|---|---|---|---|---|
| All females | 24 | 54 | 164 | 165 | 124 | 125 | 81 | 52 |
| Asian females | 1 | 0 | 0 | 3 | 2 | 7 | 4 | 1 |
| Black females | 16 | 47 | 140 | 122 | 61 | 39 | 16 | 10 |
| Coloured females | 2 | 3 | 10 | 12 | 18 | 13 | 11 | 4 |
| White females | 5 | 2 | 12 | 23 | 38 | 60 | 48 | 36 |

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

**Signs and Symptoms of Richter's Syndrome**
Patients may experience the following:

- Rapidly enlarging lymph nodes
- Abdominal discomfort related to enlargement of the spleen and liver (called hepatosplenomegaly)
- Symptoms of low red blood cell count (anaemia), such as feeling extra tired, pale skin, shortness of breath
- Symptoms of low platelet count (thrombocytopenia), such as easy bruising and unexplained bleeding
- Signs of extranodal involvement in unusual sites, such as brain, skin, gastrointestinal system, skin, and lungs
- Fever which is not caused by an infection
- Night Sweats
- Weight loss

(About Health; Cancer Research UK).

**Diagnosis of Richter's Syndrome**
Most patients contact their doctor because they have developed new symptoms. The doctor will do a clinical examination and arrange for the patient to have tests similar to those CLL.

These may include:

- Lymph node biopsy - to make a diagnosis of Richter's syndrome your doctor will need to take some cells from one of your enlarged lymph nodes. A pathologist will then look at the cells under a microscope. For this test you'll usually need to have one of the enlarged lymph nodes removed during a small operation, usually under general anaesthetic.

- Blood tests – the patient may have various blood tests. These include a full blood count and a test to check the patient's levels of an enzyme called lactate dehydrogenase (LDH). LDH is a normal substance in the blood, but it is at higher than normal levels in some types of cancer.

LDH levels in the blood can go up if someone has Richter's syndrome.

Other tests may include a:

- Bone marrow biopsy
- CT scan.

(Cancer Research UK).

**Treatment of Richter's Syndrome**
Treatment options for these patients are limited and include combination chemotherapy with or without the addition of monoclonal antibodies and stem cell transplantation. Response to therapy is variable and generally short-lived. Median survival is usually in the order of 5-8 mo. More effective management for RS is needed as well as prognostic models that will identify CLL patients at risk of transformation.
(Swords, *et al*.).

Chemotherapy - this is the most common treatment for Richter's syndrome. Because Richter's syndrome is similar to both acute leukaemia and lymphoma, the chemotherapy treatment may be the same as the treatment for:

- Non-Hodgkin's lymphoma (NHL)
- Acute lymphoblastic leukaemia (ALL).

Monoclonal antibodies - monoclonal antibodies (MABs) are a type of biological therapy. They are artificially made proteins that target specific proteins on cancer cells. Monoclonal antibodies are a fairly new treatment for cancer. Doctors often use the MAB drug rituximab with chemotherapy and steroids to treat Richter's syndrome. Researchers in a trial called the CHOP-OR study are looking at whether a biological therapy similar to rituximab can make CHOP chemotherapy work better. The new drug is called ofatumumab (Arzerra). The study is for people who have just been diagnosed with Richter's syndrome.

People taking part in the CHOP-OR trial have ofatumumab with CHOP chemotherapy to get rid of the lymphoma (called induction treatment). They then have more ofatumumab on its own to try to stop the lymphoma coming back (called maintenance treatment). This trial has now closed and results are awaited.

Stem cell transplant - stem cells are very early blood cells. Having a stem cell transplant means the patient receives stem cells from a donor. The person who donates the stem cells is usually a brother or sister.

First, the patient has very high doses of chemotherapy, sometimes with radiotherapy. This destroys both the cancerous and healthy cells in the bone marrow. After the chemotherapy treatment, the doctors give the patient the donor's stem cells to replace the destroyed cells.

Stem cell transplant is an experimental way of treating Richter's syndrome. While only a few people have had this treatment, for those people it appeared to work quite well. The disease was controlled for longer than for people having normal dose chemotherapy. But stem cell transplants have serious side effects and complications, so are only suitable for a few people. More research is needed as it is too early to say how well this treatment works for Richter's syndrome.

Radiotherapy - radiotherapy is the use of radiation to treat cancer. The patient may have radiotherapy in combination with chemotherapy. The patient will only have radiotherapy:

- If Richter's syndrome is affecting the brain or spinal cord
- To control pain from enlarged lymph nodes

(Cancer Research UK).

**About Clinical Trials**

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the

development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including
other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their

individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.
In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

## Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

## Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.

- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

**Medical Disclaimer**

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## Sources and References

**About Health**
http://lymphoma.about.com/od/nonhodgkinlymphoma/qt/What-Is-Richters-Syndrome.htm

**Cancer Research UK**
http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/what-is-richters-syndrome

**Leukaemia Foundation**
http://www.leukaemia.org.au/blood-cancers/leukaemias/chronic-lymphocytic-leukaemia-cll/richter-s-syndrome

**Richter's Syndrome**
https://www.youtube.com/watch?v=5FVmAVfkzEo

**Swords, R., Bruzzi, J. & Giles, F.** 2007. Recent advances in the diagnosis and therapy of Richter's syndrome. *Med Oncol.*, 24(1):17-32.

**Wikipedia**
https://en.wikipedia.org/wiki/Non-Hodgkin_lymphoma