



LYMPHOMA
CANADA

The First-Line Treatment of Follicular Lymphoma in Canada

A Patient Guide to the 2014 Canadian
Follicular Lymphoma Guidelines

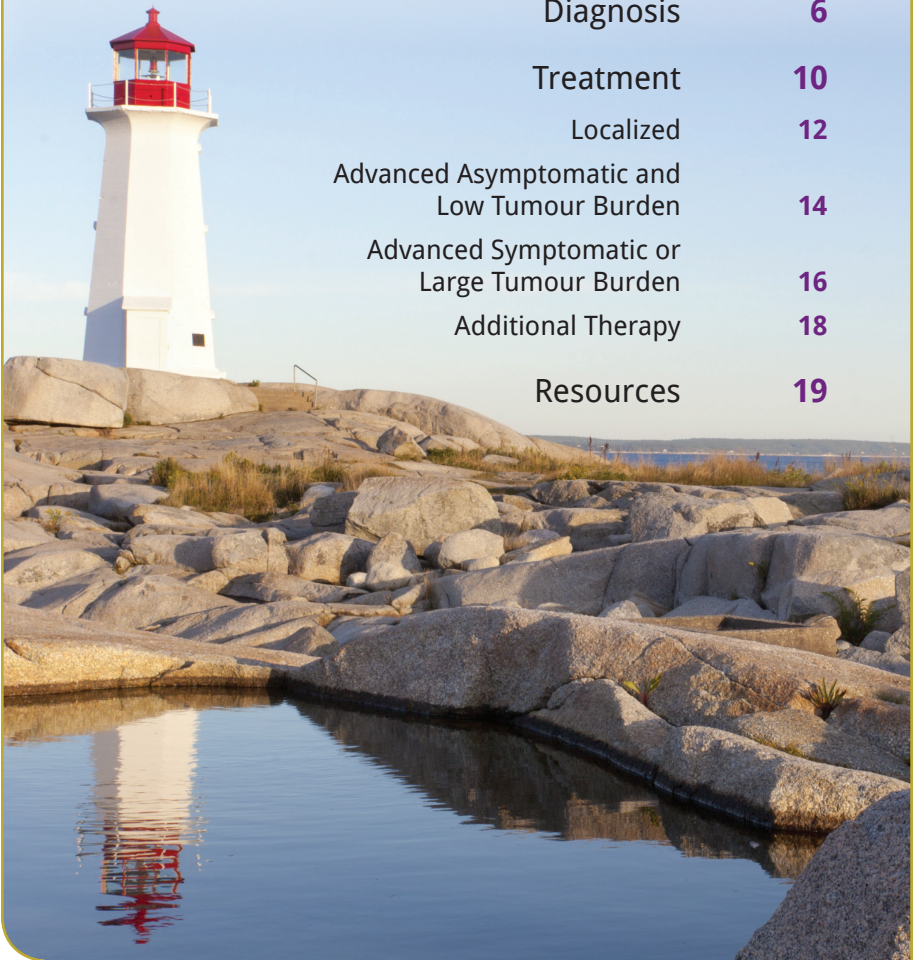




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Lymphoma Canada

About us

Lymphoma Canada is an organization that is wholly Canadian. All of our data are derived from Canadian statistics and feature only Canadian specific information. Materials used by the foundation are reviewed and approved by our Scientific Advisory Board, which consists of Canadian researchers and clinicians. All members of our Board of Directors reside in Canada and Lymphoma Canada funds only Canadian researchers.

Mission: We empower lymphoma patients and the lymphoma community through education, support, and research. Lymphoma Canada advocates for patients to be informed so that they can be participants in their treatment pathway.

How we do it: Lymphoma affects many people, from patients, their families and caregivers, to medical professionals and researchers. Lymphoma Canada connects and empowers this community. Together we are promoting early detection, finding new and better treatments, helping patients access those treatments, learning lymphoma's causes, and finding a cure.

Lymphoma Canada provides, at no cost and in both official languages: Electronic and print materials on Hodgkin lymphoma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia for patients, caregivers, and healthcare professionals. We also offer peer and family support, conduct educational forums, and advocate on behalf of patients. Lymphoma Canada also funds Canadian research.

Our structure: We are Canada's only national organization focused entirely on lymphoma. A registered charity, we are led by a volunteer Board of Directors that comprises community members with diverse professional expertise and includes lymphoma patients and medical experts. Our small, dedicated team brings expertise in education and support programming, medical research and writing, marketing and communications, and fundraising. We are guided by expert members of a Scientific Advisory Board. Lymphoma patients across the country help organize, and participate in, education events, support groups, and online forums.

Lymphoma Canada is a national charitable organization that operates in both official languages.



Key Terms

Antibody: A protein made by the immune system in response to a foreign substance or cancer cells. The antibody attaches itself to the foreign substance or cancer cells so that the immune system can destroy them.

Adenopathy: Enlarged or swollen lymph glands.

Autologous stem cell transplant (ASCT): A procedure in which stem cells that produce blood cells are collected, stored, and later given back to the same person from whom they were collected.

Asymptomatic: Not experiencing symptoms.

B-cells: Cells that are responsible for producing antibodies, which help fight off infections.

Biopsy: A procedure in which cells or tissue is removed for examination by a pathologist.

Chemoimmunotherapy: A type of cancer therapy that combines chemotherapy with treatments that use the immune system to fight cancer cells.

Chemotherapy: Treatment with drugs that kill cancer cells.

Consolidation (therapy): Treatment that is given after the cancer has disappeared following the initial therapy. Consolidation

therapy is used to kill any cancer cells that may be left in the body.

Computed tomography (CT) scan/ computerized axial tomography (CAT) scan: A series of X-rays that provide detailed, three-dimensional images of the inside of the body.

First-line treatment: The initial treatment that is given to make the cancer disappear.

Follicular lymphoma: A sub-type of indolent non-Hodgkin lymphoma.

High-dose therapy (HDT): An intensive drug treatment used to kill cancer cells. This treatment also destroys the bone marrow and is usually followed by stem cell transplantation to rebuild the bone marrow.

Immunotherapy: A type of treatment that uses the immune system to fight infections or diseases like cancer.

Indolent: Slow-growing.

Lymphoma: A type of cancer that starts in the cells of the immune system. There are two basic categories of lymphomas: Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphomas may either be indolent (slow-growing) or aggressive (fast-growing). Follicular lymphoma is a type of indolent non-Hodgkin lymphoma.

Magnetic resonance imaging (MRI):

A tool that uses magnets to obtain very detailed three-dimensional images of the body.

Maintenance (therapy): Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy.

Positron emission tomography (PET) scan:

A tool used to visualize cancer in the body by using radioactive glucose. The procedure involves injecting the patient with radioactive glucose, which is then absorbed preferentially by cancer cells. A scanner is then used to visualize the cancer.

Radiation therapy: A treatment that involves giving high doses of radiation to a specific area of the body where the cancer is located.

Radioimmunotherapy: A type of radiation therapy in which a radioactive substance is attached to a monoclonal antibody and injected into the blood so that it can kill the cancer cell to which the antibody attaches.

Rituximab: A designed antibody that binds to B-cells and causes their death. It is used to treat all B-cell lymphomas, including follicular lymphoma.

Splenomegaly: An enlarged or swollen spleen.

Watchful waiting: Closely watching a patient's condition but not giving treatment unless symptoms appear or the cancer becomes dangerously bulky or invades major organs.

Background

What was the role of Lymphoma Canada in creating these guidelines?

The development of national guidelines on follicular lymphoma (FL) was an initiative of Lymphoma Canada, which funded the costs of developing the guidelines. The project was developed by Lymphoma Canada's Scientific Advisory Board, consisting of doctors who are experts on blood cancers.

Where can I get the full version of the guidelines?

The guidelines were published in an international peer-reviewed journal called Clinical Lymphoma, Myeloma & Leukemia. The full guidelines can be found at the following link:
[http://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650\(14\)00310-3/abstract](http://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(14)00310-3/abstract)

Who are the authors and how did they arrive at the recommendations?

The guidelines were developed by a Steering Committee made up of members of Lymphoma Canada's Scientific Advisory Board. See p.5 for a list of authors.

Their recommendations were based on extensive research and careful review of all sources of evidence.

What is the purpose of creating these follicular lymphoma (FL) guidelines?

In Canada, there are no unified national guidelines for the treatment of newly diagnosed patients with FL. While some provinces have their own guidelines, these vary from province to province and often base treatment choices on funding issues. Therefore, there was a need for evidence-based national treatment guidelines that are developed and supported by Canadian experts to ensure that patients with FL have equal access to the best available care.

What is the reason for creating this patient guide to the guidelines?

This patient guide is part of a communication plan to inform patients, caregivers, and healthcare practitioners about the guidelines.

Steering Committee

The guidelines steering committee consisted of key members of Lymphoma Canada's Scientific Advisory Board:

- Dr. John Kuruville, MD, FRCPC; CHAIR – Hematologist in the Division of Medical Oncology and Hematology, Princess Margaret Hospital;
- Dr. David MacDonald, MD, FRCPC – Assistant Professor in the Division of Hematology, Dalhousie University;
- Dr. Douglas Stewart, MD, FRCPC – Professor in the Departments of Medicine and Oncology, Divisions of Medical Oncology, Hematology, and Hematological Malignancies, University of Calgary;
- Dr. Sarit Assouline, MD – Physician, Division of Hematology, Sir Mortimer B. Davis-Jewish General Hospital; Assistant Professor, Department of Oncology, McGill University;
- Dr. David Hodgson, MD, MPH, FRCPC – Associate Professor, Department of Radiation Oncology, University of Toronto Staff Radiation Oncologist, Princess Margaret Hospital/ University Health Network;
- Dr. Joseph Connors, MD; PAST CHAIR – Clinical Professor, University of British Columbia; Chair, Lymphoma Tumour Group, British Columbia Cancer Agency.

Diagnosis

Overview

What is follicular lymphoma (FL)?

FL is a type of blood cancer that starts from a type of blood cell called a **B-cell**. In healthy immune systems, B-cells are responsible for producing **antibodies** that help fight off infections. However, in lymphomas, B-cells grow uncontrollably and spread to different organs, including the spleen, lymph nodes, and bone marrow. FL is characterised by a slow follicle-like growth pattern in affected tissues.

The two main types of lymphomas are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). FL is the most common type of **indolent** (slow growing) NHL. More than 1500 patients are diagnosed with FL every year in Canada.

How is FL diagnosed?

A complete diagnosis of FL takes into account the following:

- Health history
- Physical examination
- Imaging techniques: X-ray, **CT/CAT** scans, **MRI**, **PET** scans
- Lab tests
- **Biopsies**



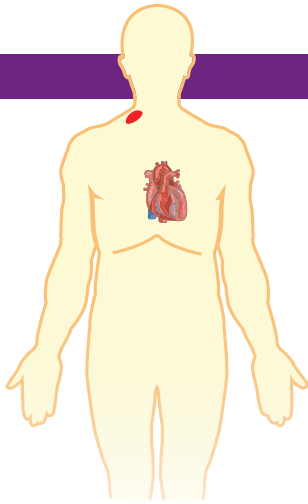
Definitions of words in **yellow** can be found on pages 2–3

How is follicular lymphoma (FL) classified?

FL is staged using the **Ann Arbor staging system**, in which stages I and II are considered limited or localized disease, and stages III and IV are considered advanced disease. The classification is based on where the lymphoma is located in the body and how far it has spread.

The Ann Arbor staging system:

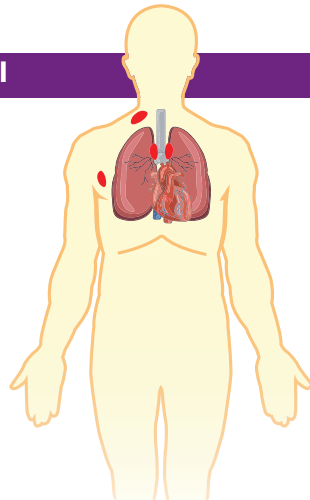
STAGE I



The lymphoma is in only one group of lymph nodes or in one organ only

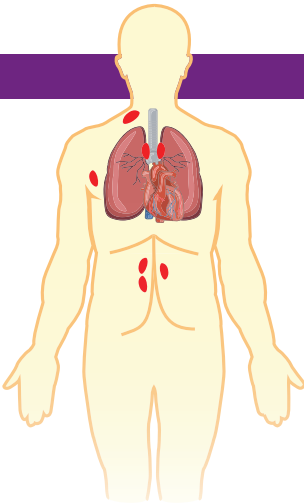
STAGE II

Two or more groups of lymph nodes, or an organ and one or more groups of lymph nodes, are affected. In both cases they are all either above or below the diaphragm



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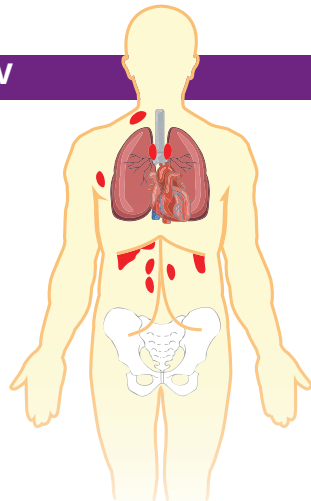
STAGE III



Two or more lymph nodes are affected on both sides of the diaphragm

STAGE IV

Lymphoma is in at least one organ (e.g., bone marrow, liver, or lungs) as well as the lymph nodes on both sides of the diaphragm



What are the symptoms of patients with FL?

Patients with follicular lymphoma, including those with advanced stages of the disease, may or may not have symptoms. Patients presenting with the following symptoms are considered symptomatic:

- Fever
- Night sweats
- Weight loss
- Painful **adenopathy/splenomegaly**
- Symptoms caused by blockages



Definitions of words in **yellow** can be found on pages 2–3

Treatment

How is follicular lymphoma (FL) treated?

- **Watchful waiting (also called watch and wait):**

This approach is typically used for patients who have no symptoms or other risk factors that require them to have immediate treatment. Patients are closely monitored with regular visits to the doctor and with diagnostic tests, including laboratory tests and imaging. Treatment is not started until the cancer progresses or symptoms appear.



- **Radiation therapy:** Radiation therapy involves giving high doses of radiation to a specific area of the body where the cancer is located. Radiation kills cancer cells by damaging their genetic material (i.e., DNA) so they are unable to survive. Normal cells are also affected and killed. However, unlike cancer cells, normal cells are able to heal

more easily. Radiation treatment is delivered over a fixed area called a radiation field. The size of this field depends on many factors, including the health of the patient and the stage of the disease. In general, the wider the field of radiation, the greater the area that can be affected and vice versa. Another factor that determines the damage caused by radiation is the dose, which is measured in Gray units. A Gray unit is the amount of energy absorbed from radiation by a specific amount of tissue. A high dose means that more energy will be absorbed by the tissues, with potentially more healthy cells being affected.



- **Immunotherapy:** Immunotherapy is a type of treatment that uses the immune system to fight diseases like cancer. It is also called biologic therapy. The most widely used immunotherapy in FL is an **antibody** treatment called **rituximab**. Rituximab binds a protein on the surface of **B-cells** and causes the activation of the immune system to kill the B-cells.

Definitions of words in **yellow** can be found on pages 2–3

• **Chemoimmunotherapy:** Unlike **radiation therapy**, which targets specific areas of the body, chemoimmunotherapy affects the whole body. The main advantage of this approach is that it combines **chemotherapy** with **immunotherapy** to increase the damage to cancer cells. On its own, chemotherapy works by killing rapidly dividing cells in the body. Because cancer cells divide at a more rapid rate than normal cells, chemotherapy has a greater effect on cancer cells. **Antibodies** are special proteins that bind tightly to special receptors on bacteria or viruses to help the immune system find and kill them. These antibodies can also be engineered to bind to cancer cells so that they can be killed by the immune system. Thus, chemoimmunotherapy brings together two powerful tools to make treatments work better.

In Canada, the most common first-line chemoimmunotherapy treatments for patients with FL are:

- **BR:** Bendamustine (chemotherapy), **Rituximab** (antibody)
- **R-CVP:** Rituximab (antibody), Cyclophosphamide (chemotherapy)
Vincristine (chemotherapy), Prednisone (steroid medication)
- **R-CHOP:** Rituximab (antibody), Cyclophosphamide (chemotherapy), Hydroxydaunorubicin, (chemotherapy), Vincristine (chemotherapy), Prednisone (steroid medication)

Who are these guidelines intended for?

These guidelines are for the treatment of adult patients with follicular lymphoma (FL) who have not been treated before for the same disease.

What questions do these guidelines address?

The guidelines address four key questions about the treatment of FL:

1. What treatment options should be considered for localized FL?
2. How should **asymptomatic**, advanced-stage FL be managed?
3. What treatment options should be considered for symptomatic, advanced-stage FL?
4. Which additional treatments should be considered (i.e., **maintenance**, **consolidation** therapies)?

Definitions of words in **yellow** can be found on pages 2–3

Recommendations

Question 1: *What treatment options should be considered for localized follicular lymphoma (FL)?*

To come up with a recommendation for this patient group, the panel considered a number of questions:

- Should **radiation therapy** be given?
- What dose should be given?
- How big an area should be treated?
- Should other treatments be given?

✔ **Recommendation 1:** Radiation is the preferred treatment for most patients who have stage I or adjacent stage II disease involving peripheral lymph node sites. Stage I or II disease affecting the chest or abdomen might be treated with radiation or possibly other options, and requires discussion with your doctor.

✔ **Recommendation 2:** Radiation therapy should be given in lower doses and over smaller areas since higher doses over larger areas increase the risk for long-term toxicity.

✘ **Recommendation 3:** Combining treatment such as **immunotherapy** or **chemotherapy** with radiation therapy is **NOT** recommended for patients with stage I or stage II FL. This was based on the fact that there is no strong evidence from any study that shows combined therapies are better than radiation therapy for these patients.

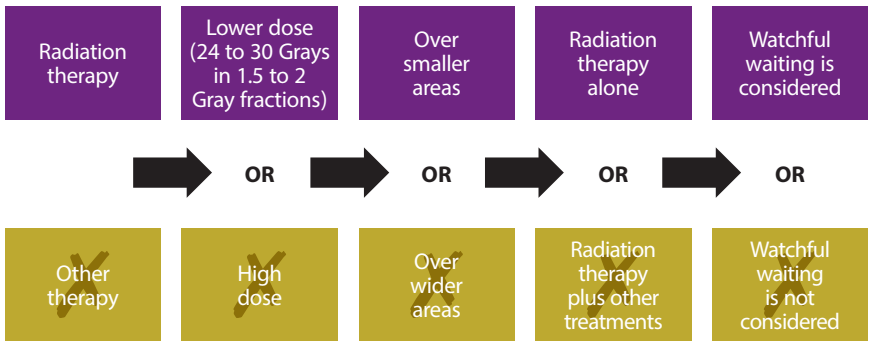
✔ **Recommendation 4:** Watchful waiting may be considered as a reasonable option for some patients who are unable to tolerate radiation therapy.



Definitions of words in **yellow** can be found on pages 2–3



Summary of recommendations for localized follicular lymphoma



Definitions of words in **yellow** can be found on pages 2-3

Advanced Asymptomatic and Low Tumour Burden

Question 2: How should patients with advanced follicular lymphoma (FL) who have no symptoms or large tumour masses or organ involvement be managed?

The decision to treat patients with advanced FL depends on whether patients are showing signs and symptoms of advanced disease. Some typical signs and symptoms include:

- Fever
- Night sweats
- Weight loss
- Malaise
- Pain
- Nausea
- Progression of the tumour in lymph nodes and in the spleen
- Large masses or organ involvement



Together, these signs and symptoms are called treatment indications. In addition to treating patients with these symptoms, physicians may also give treatment to some patients who have a lot of anxiety or feel that their disease is affecting their quality of life.

For patients who have shown signs and symptoms of advanced disease, the panel considered whether **chemoimmunotherapy** is appropriate. For patients showing no signs or symptoms, treatment options considered were chemoimmunotherapy, **chemotherapy**, and **watchful waiting**.

Definitions of words in **yellow** can be found on pages 2–3

✔ **Recommendation 1:** The panel recommended that patients with advanced follicular lymphoma (FL) who are showing signs and symptoms listed on the previous page, should be treated with **chemoimmunotherapy**.

✘ **Recommendation 2:** For patients with advanced FL who are not showing symptoms, **watchful waiting** should be employed. The panel could not recommend chemoimmunotherapy or **chemotherapy** because studies have **NOT** proved that treating these patients early is better than waiting to treat them until after symptoms start.

Recommendation 3: The panel could **NOT** recommend the use of **rituximab** early on in ✘ patients with advanced FL showing no signs and symptoms because there are no data to support this.



Symptoms



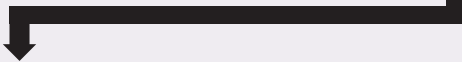
Treat



No
Symptoms



Watchful
waiting



Symptoms



Treat

Definitions of words in **yellow** can be found on pages 2-3

Advanced Symptomatic or Large Tumour Burden

Question 3: *What treatment options should be considered for symptomatic, advanced-stage follicular lymphoma (FL)?*

The panel considered three treatment options for symptomatic patients with advanced FL:

- 1) **Immunotherapy** (rituximab alone)
- 2) **Chemotherapy**, or
- 3) **Chemoimmunotherapy** (combination of the two)



The chemoimmunotherapy treatment options the panel considered were R-CVP, R-CHOP, and BR.

- ✔ **Recommendation 1:** For patients with advanced-stage FL who are showing symptoms, or have rapidly progressive or large burden of lymphoma, chemoimmunotherapy should be given instead of rituximab alone. Rituximab should be given alone only when patients have conditions that do not allow them to take chemotherapy.
- ✔ **Recommendation 2:** Many studies have shown that adding rituximab to chemotherapy is a more effective treatment than chemotherapy alone. The panel concluded that rituximab should always be added to chemotherapy for the treatment of symptomatic, advanced-stage FL **in patients who have not received** any previous treatment for FL.
- ✔ **Recommendation 3:** The panel also compared the two main treatment options for this group of patients: BR and R-CHOP. They concluded that BR is preferred because it has been shown to be more effective and more tolerable to patients receiving treatment.

Definitions of words in **yellow** can be found on pages 2–3



Additional Therapy

Question 4: *Should patients receive additional therapy after their first-line follicular lymphoma (FL) treatment?*

In addition to the first treatment a patient is given for their cancer, physicians may add more treatments to help make the first treatment work better, or to help prevent the cancer from returning.

Several additional treatments were considered by the panel after a patient is first treated for FL. These include **maintenance** therapy and **consolidation** with **radioimmunotherapy** or high-dose therapy (**HDT**) with autologous stem cell transplant (**ASCT**).

✓ Recommendation 1: The panel recommended that patients be given **rituximab** for maintenance because studies showed it worked better than observation alone. Many different rituximab maintenance schedules have been used in studies. However, rituximab maintenance is usually given every three months for two years in Canada. It is not known which treatment schedule or duration results in the best outcomes.

✗ Recommendation 2: The panel did **NOT** recommend HDT followed by ASCT as part of **first-line** treatment for FL. In addition to having the potential for long-term toxicity, this treatment has not been shown to increase lifespan. The panel did **NOT** recommend using radioimmunotherapy after first-line treatment of FL.

Recommended	Not recommended
Maintenance	Consolidation <ul style="list-style-type: none">• High-dose therapy with autologous stem cell transplant• Radioimmunotherapy

Definitions of words in **yellow** can be found on pages 2–3

Resources

American Society of Hematology (ASH)

www.hematology.org

Health Canada Drug Product Database

<http://hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>

Life Beyond Lymphoma

www.lifebeyon.lymphoma.ca

Lymphoma Canada

www.lymphoma.ca

NHL Cyber Family

www.nhlcyberfamily.org

Reference: Kuruville J, Assouline S, Hodgson D, et al. A Canadian Evidence-Based Guideline for the First-Line Treatment of Follicular Lymphoma: Joint Consensus of the Lymphoma Canada Scientific Advisory Board. *Clin Lymphoma Myeloma Leuk* 2015; 15(2):59–74.

Notes

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