



GUIDELINES

on the Use in Oncology

PUBLIC VERSION FOR INFORMATIONAL PURPOSES

TERMS USED IN THE GUIDELINES

Guidelines	Guidelines on RIGVIR® use in oncology
RIGVIR®	Oncolytic virus Rigvir
Virotherapy	Therapy with RIGVIR
Oncotropism	Virus ability to find tumour cells
Oncolysis	Selective destruction of tumour cells
Regional principle	Intramuscular injections in one of the 4 regions adjacent to the axillary and inguinal lymph nodes (right or left <i>musculus deltoideus</i> , right or left <i>musculus gluteus maximus</i>)
Regional injection	Intramuscular administration of a RIGVIR dose (2 ml unless otherwise stated) according to the regional principle
Local therapy	Peritumoural and intratumoural administration of RIGVIR
Intranasal therapy	Intranasal administration of RIGVIR
Protocol	Mode of virotherapy specified in the guidelines
Immunisation	Induction of the body's immunity by making regional injections

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Appendix (please see separately):

- Virotherapy with RIGVIR Summary
- RIGVIR Availability
- RIGVIR Intramuscular Injection Step by Step
- Immunity Changes Along with Tumour Progression

VIROTHERAPY AND RIGVIR CHARACTERISTICS

Virotherapy is a perspective cancer treatment method using oncolytic viruses. The mechanism of action of oncolytic viruses in virotherapy may differ.

RIGVIR oncotropic and oncolytic virus was registered as the world's first virotherapy medicine in 2004. [41]

RIGVIR solution for injection, 2 ml, titre $\geq 10^6$ TCID₅₀/ml – live, nonpathogenic RNA virus **that has not been genetically modified.**

Active substance – RIGVIR (*ECHO-7* virus strain) *Picornaviridae* family, *Enterovirus* genus, *ECHO* group, type 7.

The direct **antitumoural activity** of RIGVIR is related to oncotropism and oncolysis. As a result of it, the virus changes tumour cell microenvironment and cancels the block on those immune reactions that are caused by tumour progression. In the fight against the tumour, RIGVIR involves the affected person's immune system and exposes the tumour to cytotoxic immune mechanisms; it boosts the immune system's natural defenses against foreign genetic information that has entered the body, as well as against genetically modified cells and tissue in the body, including malignant cells; therefore, immunotherapy also works as an activation method of primary immunogenesis and antigen-specific defense mechanisms of the immune system. [1; 2; 24]

The **cytolytic activity** of RIGVIR is selective – with regard to malignant cells without damaging normal tissue cells and by promoting specific immunity against itself.

The **immunomodulatory activity** of RIGVIR is related to the activation of immune cells in the lymphoid tissue, lymph nodes. RIGVIR stimulates humoral immunity – B cell activation, production of antibodies and interferon induction as well as cellular T system of immunity activation processes - increasing the cytotoxic CD8+ cells, helper – CD4+ cells, the activated CD38+ cell counts in peripheral blood and apoptosis receptor CD95+ expression on lymphocytes. This indicates of the activation of the cytotoxic immune response. Activation of non-specific immune cells also occurs: natural killer cells (NK) and monocytes/macrophages. In the process of activating immune response against the expressed tumour-associated antigens, the immunological rejection of tumour that is apoptotic occurs. With repeated and skillful use of the medicine, it is possible to achieve gradual and total regression of lymph node micro-metastases and subcutaneous metastases. [5; 9; 34–40]

RIGVIR does not appear to reproduce in tumour-free human organs and tissue and does not excrete in the surrounding environment.

Virotherapy with RIGVIR has both **systemic action** following the regional principle (see p. 9) and **local action** in case of melanoma recurrence and subcutaneous metastases (see p. 18).

Better results may be expected if RIGVIR therapy is started in early disease stages. [1; 2 (p. 162); 3] With relevant immune status, virotherapy with RIGVIR is recommended before the excision of primary melanoma and after radical surgery to limit metastasising and reduce the risk of recurrence.

RIGVIR may be used in combination with chemotherapy, immunotherapy and radiotherapy thus reducing the immunity-suppressing effect (immunosuppression) caused by those therapies. [2 (p. 22 and p. 127); 4; 5 (p. 106); 6 (p. 262)]

Using RIGVIR, the cell break-down products are faster eliminated from the body than in chemotherapy and radiotherapy due to the immunosuppression caused by the latter. [2 (p. 97)]

Virotherapy with RIGVIR has to be a regular and long-term treatment (at least 3 years).

CLINICAL EXPERIENCE WITH RIGVIR

The virus Rigvir has been shown to be effective against the following types of cancer:

- **Melanoma of several locations – skin, uterine cervix, eye, brain metastasis, adrenal gland;** [1; 3; 4; 5 (p. 115); 7–13; cf. 19; 28; 30; 41; 45; 46; cf. 47; 48; 50; 51]
- **stomach;** [7; 10; 14–16; cf. 19; 26]
- **colorectal;** [7; 9; 10; 14; 16–18; 26; 42]
- **pancreatic;** [cf. 19]
- **uterine cervix;**
- **kidney;** [43]
- **urinary bladder;**
- **ovarian;**
- **lung;** [cf. 19; 28]
- **prostate;** [27]
- **breast;** [29]
- **rima glottidis;** [44]
- several types of **sarcoma:** lymphosarcoma, angiosarcoma, reticulosarcoma, rhabdomyosarcoma; [cf. 19; 28]
- **prevention of metastases** (before/after surgery).

BASIC CONDITIONS FOR USE OF VIROTHERAPY

Virotherapy is used on an outpatient treatment basis. In virotherapy, intramuscular injections are assigned, following the regional principle. Local therapy (peritumoural/intratumoural injections) or intranasal therapy (intranasal administration) may also be assigned. An individual virotherapy plan is developed for each patient, based on a specific protocol. It should be noted that not all situations can be described in protocols, and in certain cases, healthcare professionals must be able to develop an individual protocol based on their individual experience and taking into account the actual situation.

Inclusion Criteria

BEFORE THERAPY, MANDATORY EVALUATION IS THE FOLLOWING:

- complete blood count (including WBC count and ESR);
 - biochemical analysis, including ALP, LDH, ALT, AST, CRP, creatinine, and if possible – serum albumins;
 - tumour markers (according to localisation);
 - tumour spread according to the chosen method of diagnosis (CT, ultrasound, MRI, PET/CT).
-
- In case when leukocyte count is above the normal range, it is first advised to use anti-inflammatory medicines to diminish inflammatory processes as much as possible;
 - If the absolute lymphocyte count is below 1000 ($10^9/L$ – in case of lymphopenia), it is first advised to normalise the lymphocyte count as much as possible, e.g. by using medicines for thymus gland stimulation and vitamins A, C, E in therapeutic doses; and then start virotherapy.

Contraindications

VIROTHERAPY IS NOT RECOMMENDED IN THE FOLLOWING CASES:

- During the acute or chronic infection phase;
- During acute inflammation or healing of surgery wound;
- To patients with hypersensitivity of the immune system, e.g. right after vaccination;
- Simultaneously with chemotherapy or radiotherapy (see Protocol 6, p. 22); Simultaneously with antiviral therapy;
- Simultaneously with immunosuppressive medicines that are used, e.g. after organ transplantation.

RIGVIR should be used with caution in the treatment of patients with autoimmune diseases. Constant monitoring of the disease course is required.

Dynamic Observation

During virotherapy, the disease course is followed using diagnostic radiology methods (CT, ultrasound, MRI, PET/CT) as well as blood test results.

The first check-up is done 3–4 weeks after the first injection by assessment of complete blood count, biochemical analysis and (if possible) parameters of cellular immunity.

Then, check-ups are done:

- During first therapy year – every 3 months;
- During second and third therapy years – every 6 months;
- After three therapy years – once a year or as needed.

Virotherapy is a long-term treatment method (2–3 years). Virotherapy may provide faster results in the normalisation or moderate suppression phases when the patient's immune system is not yet weakened by the disease.

Virotherapy efficiency is greatly dependent on both the cancer stage and the immune system status; therefore, if possible, it is advised to test the following parameters before the therapy (as well as during the therapy):

- lymphocyte subpopulations (CD3, CD4, CD8, CD16, CD19, CD38, HLA-DR);
- serum immunoglobulins (IgA, IgG, IgM, IgE)

The assessment of immunological status is essential not only at the beginning of virotherapy but during the whole treatment process. During an oncological disease, the immunity changes. In early stages of the disease, immune system activation processes are observed at all levels, including leukopoiesis and lymphopoiesis (activation). Very important primary immunogenesis occurs in lymphoid tissue, lymph nodes. As the disease progresses, a phase is reflected in the blood test as the normalisation of all parameters, that can persist for up to 6–12 months. Under the influence of infections, stressful situations and other negative factors, as well as due to cancer aggressiveness, the immune system suppression occurs, which is seen as the hyperactivation of some parameters, that may result in complete immunosuppression.

Those interested are welcome to read the table "Immunity Changes along with Tumour Progression", developed by the main author of the guidelines, Professor, *Dr. Habil. Med.*, virologist, immunologist Aina Muceniece. The table is based on her personal observations and conclusions and published in A. Muceniece and D. Venskus book "How to Assess Immunity – Melanoma Model". [2 (p. 21)]

Virotherapy as an active therapy increases energy consumption; therefore, during virotherapy, the patient is advised nutritious nourishment, supplementing it with vitamins (C, D, A, E, etc.) and trace elements (selenium, zinc, etc.).

ATTENTION!

For prevention against metastases, if possible, virotherapy should be started before surgery.

POSSIBLE SIDE EFFECTS OF RIGVIR

Like other medicines, RIGVIR can cause side effects (not all patients experience those). The side effects are short-term, and there is no need for special treatment.*** [1; 6; 13; 14; 17; 41]

The frequency of side effects is defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1000$), and very rare ($< 1/10\ 000$).

Body system	Very common	Common	Uncommon	Rare	Very rare
General disorders and administration site conditions	—	Temperature up to 37.5°C temporary (1–3 days)	—	—	Pain in the tumour area, fatigue
Nervous system disorders	—	—	—	—	Sleepiness
Gastrointestinal disorders	—	—	—	—	Dyspepsia (diarrhea)

PROTOCOL USE

The guidelines describe 7 protocols with examples and therapy schedules. The protocol is chosen depending on the course of disease development and stage.

Protocol 1. RIGVIR Before and After Primary Melanoma Excision

Protocol 2. RIGVIR After Radical Surgery

Protocol 3. RIGVIR After Excision of Regional Metastatic Lymph Nodes

Protocol 4. RIGVIR for Local Therapy of Melanoma Subcutaneous Metastases and Recurrence

Protocol 5. RIGVIR in Case of Brain Metastases

Protocol 6. RIGVIR in Combination with Chemotherapy and/or Radiotherapy, Immunotherapy

Protocol 7. RIGVIR at Dissemination

Protocols 1, 2, 3, 5, and 7 include individual therapy schedules.

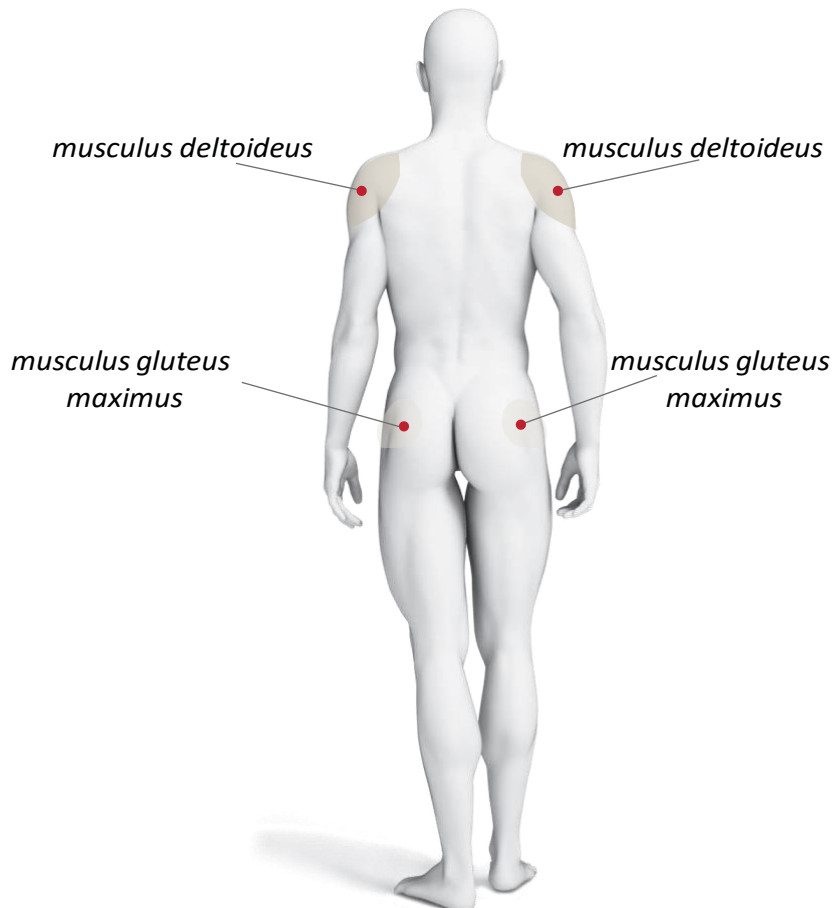
Based on knowledge and experience, the healthcare professionals may adapt the chosen protocol to the particular patient case. It is advised to contact a specialist in case of any doubt (see p. 29).

REGIONAL PRINCIPLE

The protocols are based on the regional principle, according to which the intramuscular injections are made in different sites (regions) adjacent to the axillary and inguinal lymph nodes (see example), i.e. in:

- right or left *musculus deltoideus*;
- right or left *musculus gluteus maximus*.

Example



The aim of the regional principle is to stimulate the immune cells in the regional lymph nodes and to induce immunity activation. [3]

LOCAL THERAPY

RIGVIR may be administered locally, i.e. peritumourally and intratumourally in case of locally advanced or recurrent melanoma and melanoma subcutaneous metastases (see Protocol 4, p. 18).

INTRANASAL THERAPY

RIGVIR may be administered intranasally in case of brain metastases (see Protocol 5, p. 19).

PROTOCOL 1

RIGVIR BEFORE AND AFTER PRIMARY MELANOMA EXCISION

To limit tumour metastasising, it is important to start virotherapy before the excision of the melanoma primary tumour (and other RIGVIR sensitive tumours as well). In this case, the RIGVIR oncotropic and oncolytic properties are used along with the virus-caused primary immunogenesis and antitumour antigen-specific and nonspecific immunity activation. [1; 8; 14; 20–23; 28; 31; 51]

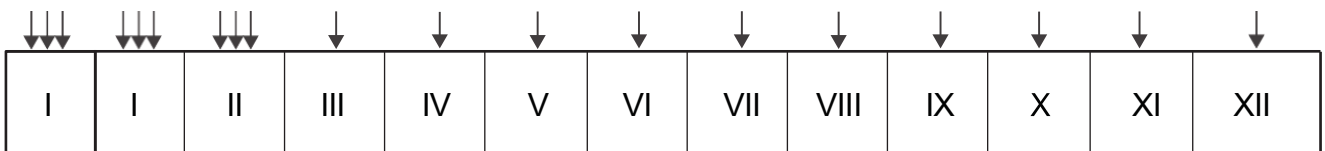
1st YEAR

5–7 days prior to surgery, make 3 regional injections (1 per day for 3 consecutive days) **closer to the primary tumour** to activate the regional lymph nodes (see Example 1). On the 3rd day, if possible, additionally make **peritumoural** injections around the primary tumour (0.3–2.0 ml depending on the tumour size and localisation).

Continue virotherapy 2–3 weeks after the surgery (after the wound has healed).

In the first 2 months after the surgery, make 3 regional injections (1 per day for 3 consecutive days) **closer to the primary tumour**. Continue with **immunisation** once a month – a regional injection, activating also the more distant lymph nodes (see Example 1).

Injection (↓) schedule in the 1st year (in months)



Before
surgery

2nd YEAR

Make a regional injection **closer to the primary tumour**:

- every 6 weeks in the first half of the year;
- every 2 months in the second half of the year.

3rd YEAR

Make a regional injection **closer to the primary tumour** every 3 months.

Example 1

Injection sites in the 1st therapy year if the primary tumour is on the right leg

Before surgery – Region 1 (1 injection per day for 3 consecutive days)

After surgery

Months I, II – Region 1 (1 injection per day for 3 consecutive days)

Month III – Region 2 (1 injection)

Month IV – Region 3 (1 injection)

Month V – Region 4 (1 injection)

Month VI – Region 1 (1 injection)

Month VII – Region 2 (1 injection)

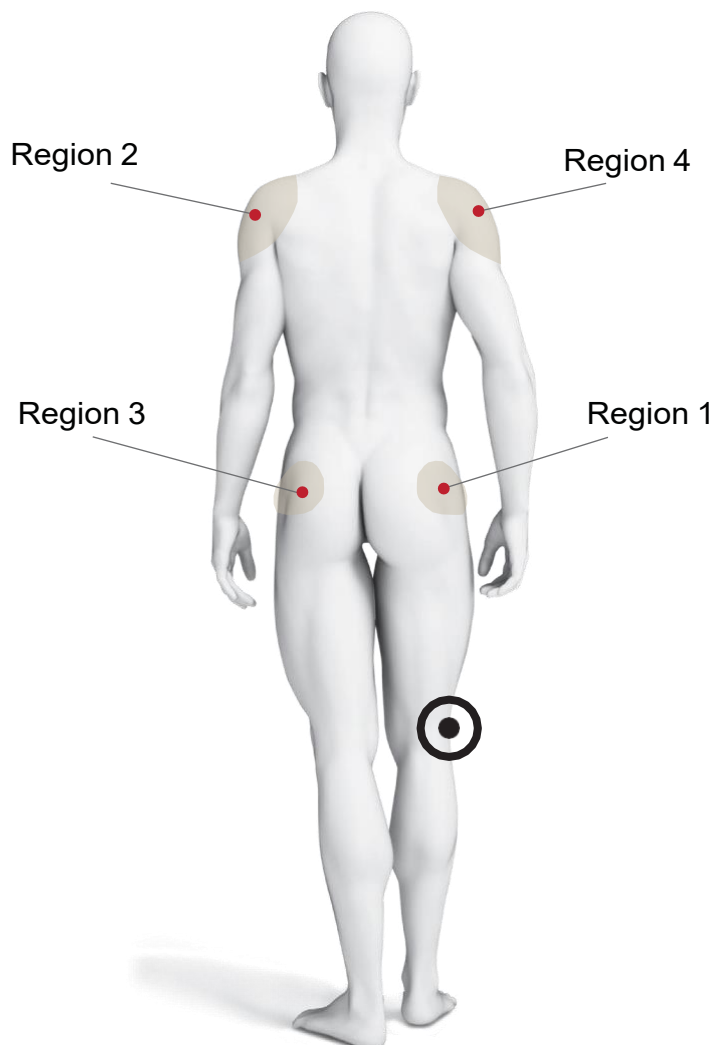
Month VIII – Region 3 (1 injection)

Month IX – Region 4 (1 injection)

Month X – Region 1 (1 injection)

Month XI – Region 2 (1 injection)

Month XII – Region 3 (1 injection)



PROTOCOL 1 THERAPY SCHEDULE

Year, month, day	Date	Injection site
1 st year		
5–7 days before surgery		
Day 1		
Day 2		
Day 3		
Month I (2–3 weeks after surgery)		
Day 1		
Day 2		
Day 3		
Month II		
Day 1		
Day 2		
Day 3		
Month III		
Month IV		
Month V		
Month VI		
Month VII		
Month VIII		
Month IX		
Month X		
Month XI		
Month XII		
2 nd year, first half		
6-week interval		
6-week interval		
6-week interval		
6-week interval		
2 nd year, second half		
2-month interval		
2-month interval		
2-month interval		
3 rd year		
3-month interval		
3-month interval		
3-month interval		
3-month interval		

PROTOCOL 2

RIGVIR AFTER RADICAL SURGERY

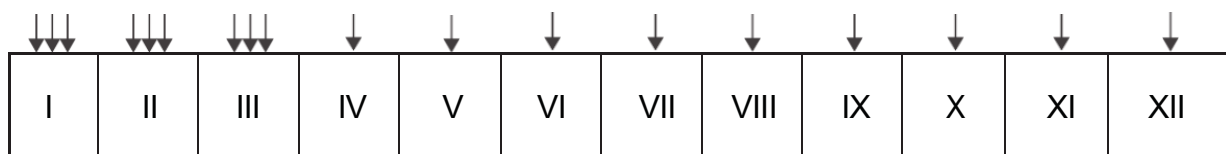
1st YEAR

Start adjuvant virotherapy 2–3 weeks after the surgery (after the wound has healed).

In the first 3 therapy months, make 3 regional injections (1 per day for 3 consecutive days) **closer to the primary tumour** (see Example 2).

Continue with **immunisation** once a month – a regional injection, activating also the more distant lymph nodes (see Example 2). [1; 14; 20; 21; 28; 30; 31; 46; 49; 50]

Injection (↓) schedule in the 1st year (in months)



2nd YEAR

Make a regional injection **closer to the primary tumour**:

- every 6 weeks in the first half of the year;
- every 2 months in the second half of the year.

3rd YEAR

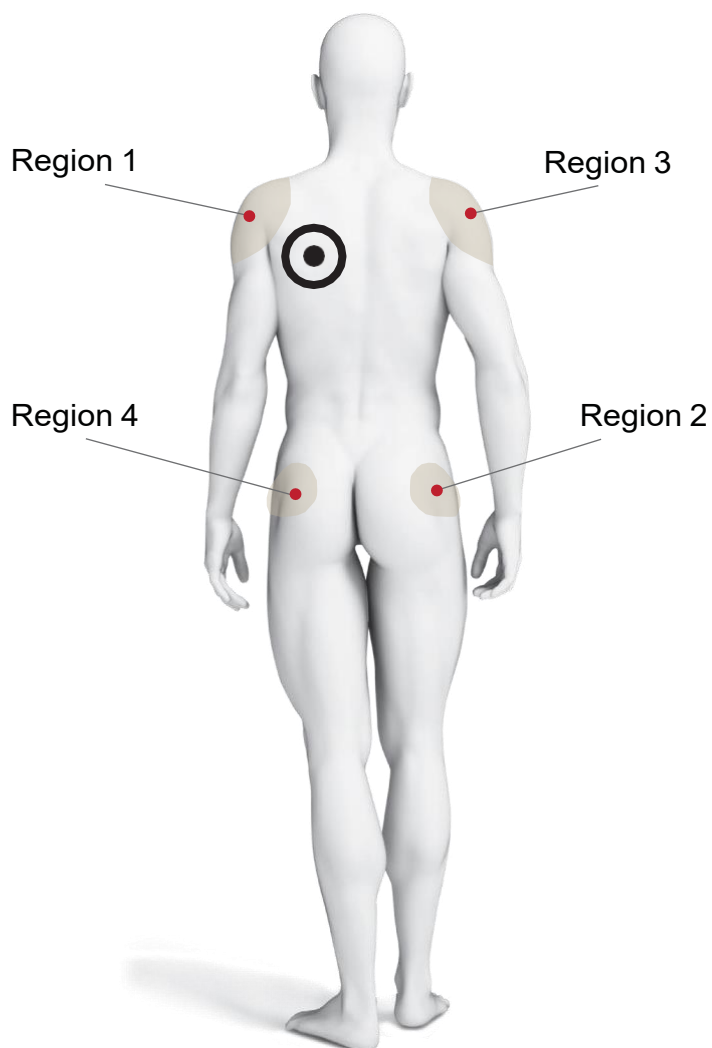
Make a regional injection **closer to the primary tumour** every 3 months.

Example 2

Injection sites in the 1st therapy year if the tumour is on the left side of the *thorax*

After surgery

Months I, II, III –	Region 1 (1 injection per day for 3 consecutive days)
Month IV –	Region 2 (1 injection)
Month V –	Region 3 (1 injection)
Month VI –	Region 4 (1 injection)
Month VII –	Region 1 (1 injection)
Month VIII –	Region 2 (1 injection)
Month IX –	Region 3 (1 injection)
Month X –	Region 4 (1 injection)
Month XI –	Region 1 (1 injection)
Month XII –	Region 2 (1 injection)



PROTOCOL 2 THERAPY SCHEDULE

Year, month, day	Date	Injection site
1 st year		
Month I (2–3 weeks after surgery)		
Day 1		
Day 2		
Day 3		
Month II		
Day 1		
Day 2		
Day 3		
Month III		
Day 1		
Day 2		
Day 3		
Month IV		
Month V		
Month VI		
Month VII		
Month VIII		
Month IX		
Month X		
Month XI		
Month XII		
2 nd year, first half		
6-week interval		
6-week interval		
6-week interval		
6-week interval		
2 nd year, second half		
2-month interval		
2-month interval		
2-month interval		
3 rd year		
3-month interval		
3-month interval		
3-month interval		
3-month interval		

PROTOCOL 3

RIGVIR AFTER EXCISION OF REGIONAL METASTATIC LYMPH NODES

1st YEAR

Start virotherapy after lymphadenectomy when the wound has healed. [31]

Month I

Make 3 regional injections (1 per day for 3 consecutive days) **diagonally opposite to the lymphadenectomy site** to activate distant lymph nodes (see Example 3).

Month II

Make 3 regional injections (1 per day for 3 consecutive days) to activate other distant lymph nodes (see Example 3).

Month III

Make 3 regional injections (1 per day for 3 consecutive days) to activate other distant lymph nodes (see Example 3).

Month IV

Make 3 regional injections (1 per day for 3 consecutive days) **in the region where lymphadenectomy was performed** (see Example 3).

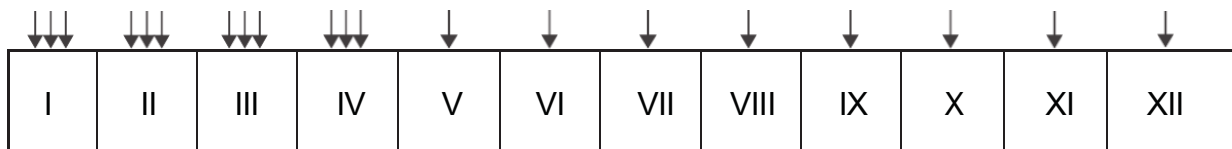
Months V, VI, VII

Make a regional injection once a month **in the region where lymphadenectomy was performed** (see Example 3).

Months VIII, IX, X, XI, XII

Continue with **immunisation** once a month – a regional injection, activating also the more distant lymph nodes (see Example 3).

Injection (↓) schedule in the 1st year (in months)



2nd YEAR

Continue with **immunisation** – a regional injection, activating also the more distant lymph nodes:

- every 6 weeks in the first half of the year;
- every 2 months in the second half of the year.

3rd YEAR

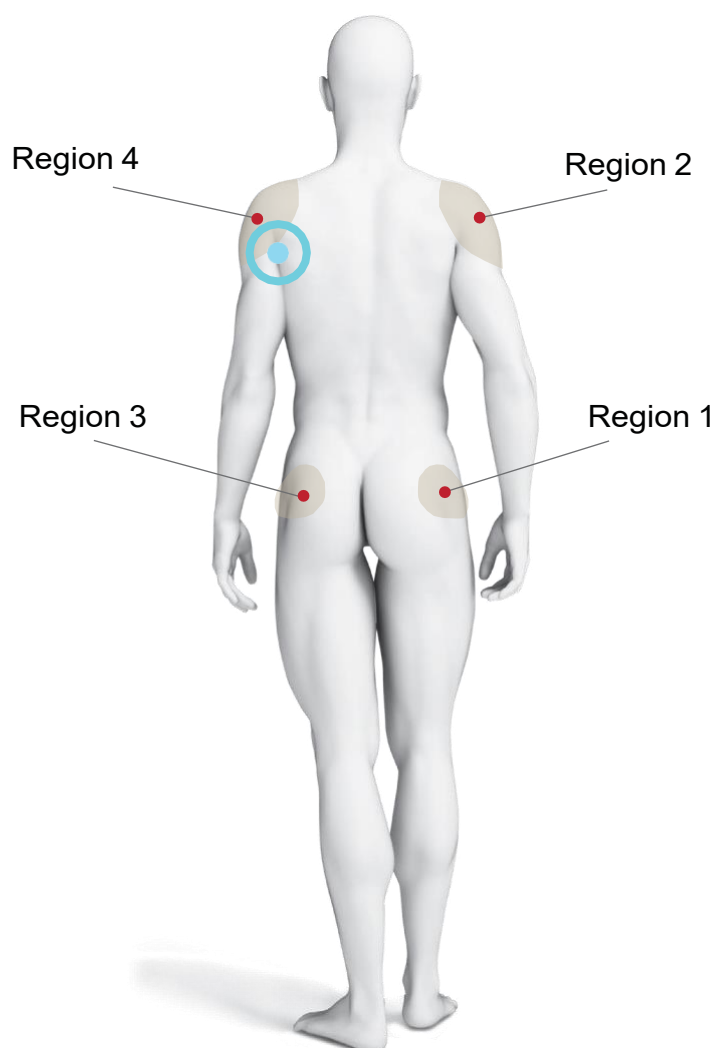
Administer RIGVIR in the same way as in the 2nd year, but with 3-month intervals.

Example 3

Injection sites in the 1st therapy year in case of left axillary lymphadenectomy

After lymphadenectomy

Month I –	Region 1 (1 injection per day for 3 consecutive days)
Month II –	Region 2 (1 injection per day for 3 consecutive days)
Month III –	Region 3 (1 injection per day for 3 consecutive days)
Month IV –	Region 4 (1 injection per day for 3 consecutive days)
Months V, VI, VII –	Region 4 (1 injection)
Month VIII –	Region 1 (1 injection)
Month IX –	Region 2 (1 injection)
Month X –	Region 3 (1 injection)
Month XI –	Region 4 (1 injection)
Month XII –	Region 1 (1 injection)



PROTOCOL 3 THERAPY SCHEDULE

Year, month, day	Date	Injection site
1 st year		
Month I (2–3 weeks after lymphadenectomy)		
Day 1		
Day 2		
Day 3		
Month II		
Day 1		
Day 2		
Day 3		
Month III		
Day 1		
Day 2		
Day 3		
Month IV		
Day 1		
Day 2		
Day 3		
Month V		
Month VI		
Month VII		
Month VIII		
Month IX		
Month X		
Month XI		
Month XII		
2 nd year, first half		
6-week interval		
6-week interval		
6-week interval		
6-week interval		
2 nd year, second half		
2-month interval		
2-month interval		
2-month interval		
3 rd year		
3-month interval		
3-month interval		
3-month interval		
3-month interval		

PROTOCOL 4

RIGVIR FOR LOCAL THERAPY OF MELANOMA SUBCUTANEOUS METASTASES AND RECURRENCE

1st YEAR

Start virotherapy with 3 regional injections (1 per day for 3 consecutive days) **diagonally opposite to the subcutaneous metastases or the recurrence**. [31]

7–14 days later, administer RIGVIR **peritumourally** (subcutaneously) (0.5–2.0 ml, the dose depends on the size of the metastasis or the recurrence) around one or two of the most recent metastatic nodules or around the recurrence. If there is anything left of the dose, administer it intramuscularly regionally **closer to the subcutaneous metastases or the recurrence**.

One week later, administer RIGVIR **intratumourally**. The dose depends on the size of the metastasis or the recurrence (0.5–2.0 ml). If there is a leftover dose, administer it intramuscularly regionally **closer to the subcutaneous metastases or the recurrence**.

These local virotherapy (**peritumoural and intratumoural**) and intramuscular regional injections (if there is a leftover dose) **closer to the subcutaneous metastases or the recurrence** are repeated every week.

Upon observing process regression, continue the local virotherapy with 2–3-week intervals.

If in 2–3 months there are no signs of process regression, surgical treatment is necessary. Afterwards, continue virotherapy, choosing a relevant protocol to decrease melanoma progression.

ATTENTION!

For peritumoural/intratumoural injections use a new needle for every injection site.

PROTOCOL 5

RIGVIR IN CASE OF BRAIN METASTASES

1st YEAR

Start virotherapy as follows: [30; 32]

On Day 1, make a regional injection in the lymph node region that is most distant from the brain metastases, e.g. in the **right *musculus gluteus maximus*** (see Example 4).

On Day 2, make a regional injection (1.0–1.5 ml) in the **left *musculus gluteus maximus*** (see Example 4). Administer the leftover dose intranasally (to bypass the blood–brain barrier), observing a 5–15-minute interval between every drop. Depending on the patient's overall state of health, the dose for intranasal administration is 0.5–1.0 ml.

On Day 3, make a regional injection (1.0–1.5 ml) again in the **right *musculus gluteus maximus*** (see Example 4). Administer the leftover dose intranasally. Depending on the patient's overall state of health, the dose for intranasal administration is 0.5–1.0 ml.

A week later, continue virotherapy weekly for 1–3 months, making 1.0–1.5 ml regional injections in the lymph node regions that are closer to the brain metastases, i.e. in the **right and left *musculus deltoideus*** (see Example 4). Administer the leftover dose intranasally. Depending on the patient's overall state of health, the dose for intranasal administration is 0.5–1.0 ml.

If it is decided that virotherapy may be continued, in the first year continue making regional injections once a month in the lymph node regions that are closer to the brain metastases, i.e. in the **right and left *musculus deltoideus***, and make intranasal administration.

2nd YEAR

Make regional injections in the lymph node regions that are closer to the brain metastases – in the **right and left *musculus deltoideus***, and make intranasal administration:

- every 6 weeks in the first half of the year;
- every 2 months in the second half of the year.

3rd YEAR

Administer RIGVIR in the same way as in the 2nd year, but with 3-month intervals.

Example 4

Injection sites in the 1st therapy year in case of brain metastases

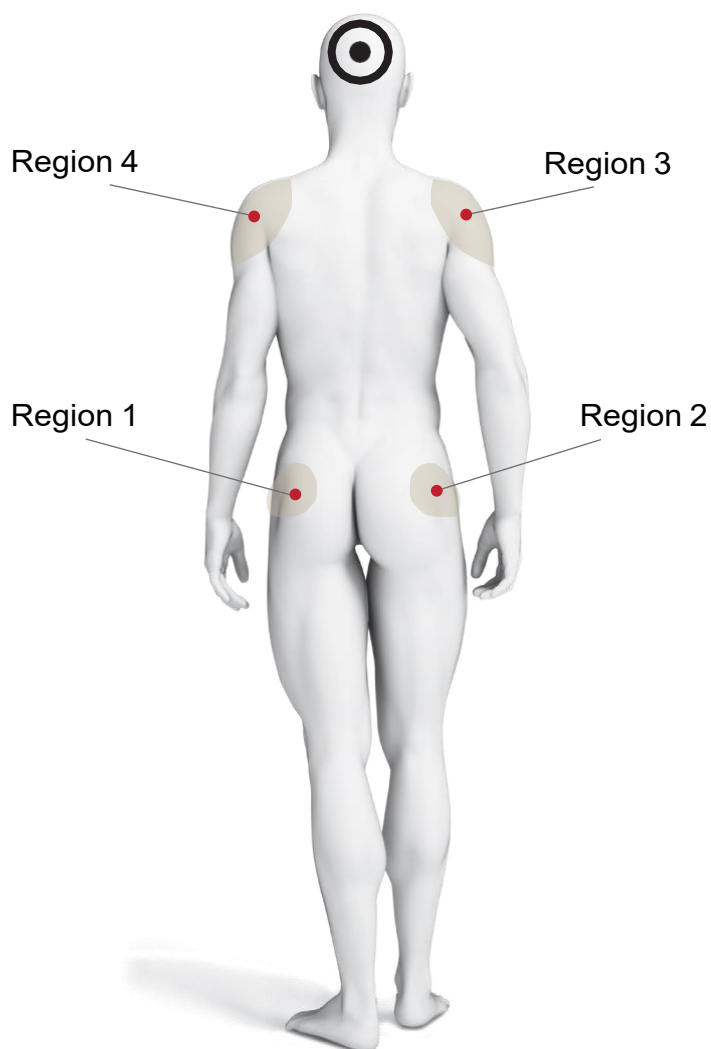
Month I, Week 1 – Regions 1 and 2 interchangeably (1 injection per day for 3 consecutive days)

Week 2–4 – Regions 3 and 4 interchangeably (1 injection per week)

Months II, III – Regions 3 and 4 interchangeably (1 injection per week)

Months IV–XII – Regions 3 and 4 interchangeably (1 injection per month)

At the same time, make intranasal administration.



PROTOCOL 5 THERAPY SCHEDULE

Year, month, day	Date	Injection site
1 st year		
Month I	Day 1	
	Day 2	
	Day 3	
	Once a week	
	Once a week	
	Once a week	
Month II	Once a week	
	Once a week	
	Once a week	
	Once a week	
Month III	Once a week	
	Once a week	
	Once a week	
	Once a week	
Month IV		
Month V		
Month VI		
Month VII		
Month VIII		
Month IX		
Month X		
Month XI		
Month XII		
2 nd year, first half		
	6-week interval	
	6-week interval	
	6-week interval	
	6-week interval	
2 nd year, second half		
	2-month interval	
	2-month interval	
	2-month interval	
3 rd year		
	3-month interval	
	3-month interval	
	3-month interval	
	3-month interval	

PROTOCOL 6

RIGVIR IN COMBINATION

WITH CHEMOTHERAPY AND/OR RADIOTHERAPY, IMMUNOTHERAPY

ATTENTION!

Virotherapy cannot be used simultaneously with chemotherapy and radiotherapy, as the activity of the virus may be affected.

Before chemotherapy and/or radiotherapy

5–10 days before starting a course of chemotherapy and/or radiotherapy, make a regional injection **diagonally opposite to tumour localisation**. [28; 31]

In between chemotherapy courses

If the intervals between chemotherapy courses are at least 3 weeks long, administer RIGVIR at the end of the 2nd week of the interval (**at least 5 days prior** to the following chemotherapy course).

The regional injection is made **closer to the tumour localisation**.

Virotherapy diminishes the immunosuppression and side effects caused by chemotherapy and radiotherapy.

After chemotherapy and/or radiotherapy

Virotherapy may be started 2–4 weeks after chemotherapy and/or radiotherapy.

Alongside immunotherapy

Virotherapy may be used alongside immunotherapy courses (both administrations should not be on the same day), as both therapies together may show a synergistic effect. [45]

1st YEAR

Make 2 regional injections (1 per day for 2 consecutive days) **closer to the primary tumour localisation**. Continue the therapy with **immunisation** once a month – a regional injection, activating also the more distant lymph nodes.

2nd YEAR

Continue the therapy, every 2 months making a regional injection **closer to the primary tumour localisation**.

3rd YEAR

Administer RIGVIR in the same way as in the 2nd year, but with 3-month intervals.

The treatment schedule should be developed according to individual patient needs, taking into account the timing of other therapies.

ATTENTION!

Due to the lasting effect of radiotherapy on the immunopoiesis, in the first months after radiotherapy, there may be immunoactivation (radiation-caused inflammation). To monitor the immune status, for example, immunosuppression (radiation-caused lymphopenia and immunoglobulin discorrelation; increase of IgA level in the serum, decrease of IgM level in the serum) – regular blood tests are done every 10 days. In case of lymphopenia, it is first advised to normalise the lymphocyte count as much as possible, e.g. by using medicines for thymus gland stimulation and vitamins A, C, E in therapeutic doses; and then start virotherapy.

PROTOCOL 7

RIGVIR AT DISSEMINATION

Based on RIGVIR clinical experience, as a result of the therapy, patients with widely disseminated process may experience life quality improvement, the reduction of bleeding and pains, the shrinking of the primary tumour, process stabilisation, and increased survival. [28; 33]

1st YEAR

If cancer dissemination has been diagnosed, start virotherapy with 3 regional injections (1 per day for 3 consecutive days) in the **region of non-excised lymph nodes, that is closer to metastases** (see Example 5).

Depending on the patient's overall and immunological state, as well as on the healthcare specialist's experience, virotherapy is continued with **immunisation** (more distant lymph node activation), making a regional injection every 1–3 weeks for up to 3 months (see Example 5). Depending on the patient's condition being evaluated as fair to serious, the interval between injections may be increased (at serious patient condition, the interval is longer).

If the patient's condition improves, continue in the 1st year with **immunisation** once a month – a regional injection, activating also the more distant lymph nodes (see Example 5).

If the patient's condition has improved and stabilised at the end of the 1st therapy year, see Protocol 7 Therapy Schedule, the 2nd and 3rd therapy years (p. 25).

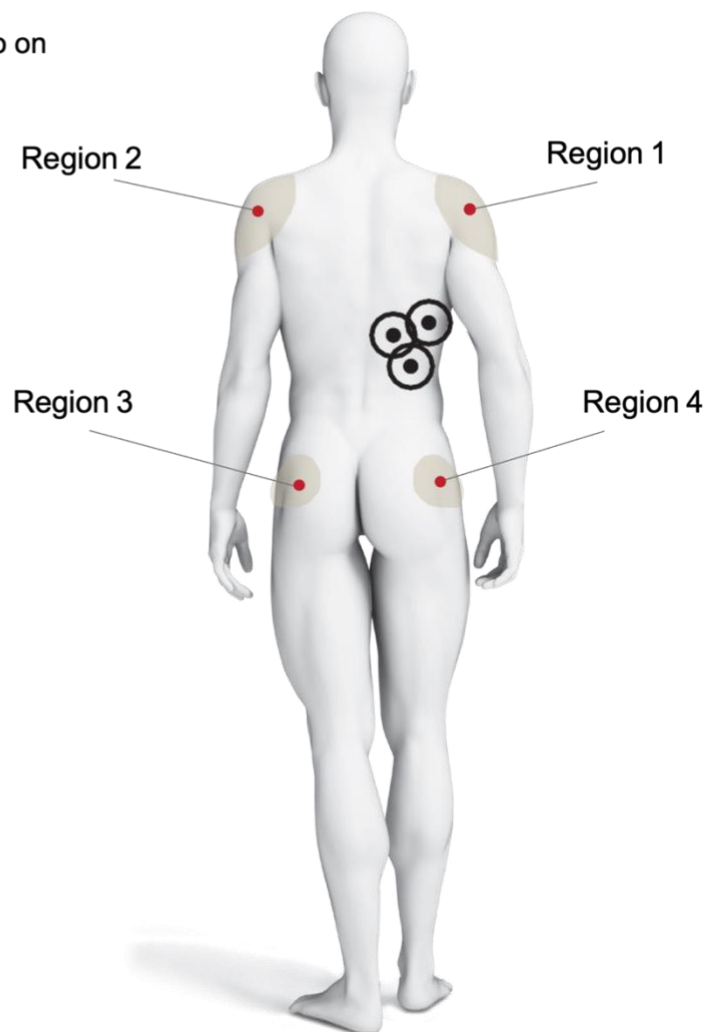
Example 5

Possible injection sites in the 1st therapy year in case of liver metastases. The patient's overall condition is evaluated as fair.

Month I	Week 1 – Region 1 (1 injection per day for 3 consecutive days) Week 2 – Region 2 (1 injection) Week 3 – Region 3 (1 injection) Week 4 – Region 4 (1 injection)
Month II	Week 1 – Region 1 (1 injection) Week 2 – Region 2 (1 injection) Week 3 – Region 3 (1 injection) Week 4 – Region 4 (1 injection)
Month III	Week 1 – Region 1 (1 injection) Week 2 – Region 2 (1 injection) Week 3 – Region 3 (1 injection) Week 4 – Region 4 (1 injection)

If the patient's condition improves:

Months IV–XII – Regions 1, 2, 3, 4, and so on
(1 injection per month)



PROTOCOL 7 THERAPY SCHEDULE (intensive regimen)

Year, month, day	Date	Injection site
1 st year		
Month I	Day 1	
	Day 2	
	Day 3	
	Once a week	
	Once a week	
	Once a week	
Month II	Once a week	
	Once a week	
	Once a week	
	Once a week	
Month III	Once a week	
	Once a week	
	Once a week	
	Once a week	
Month IV		
Month V		
Month VI		
Month VII		
Month VIII		
Month IX		
Month X		
Month XI		
Month XII		
2 nd year, first half		
	6-week interval	
	6-week interval	
	6-week interval	
	6-week interval	
2 nd year, second half		
	2-month interval	
	2-month interval	
	2-month interval	
3 rd year		
	3-month interval	
	3-month interval	
	3-month interval	
	3-month interval	

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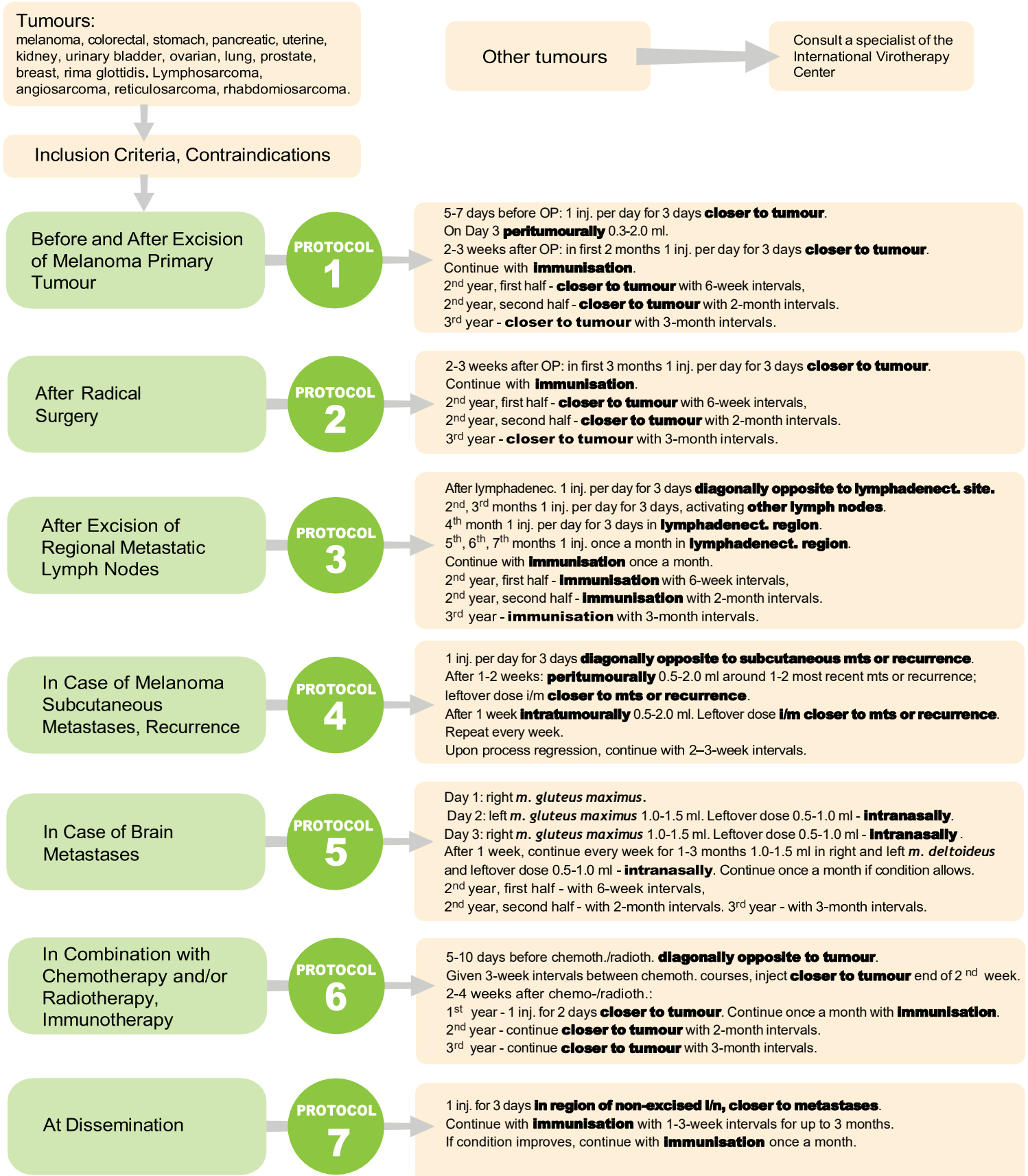
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VIROTHERAPY WITH RIGVIR SUMMARY

The summary is an assisting tool for healthcare specialists assigning virotherapy. It does not replace the guidelines and is intended for use only upon the completion of the full guideline course.



RIGVIR AVAILABILITY

 <p>The image shows the packaging for RIGVIR medicine. On the left is a white box with green and black text. The text includes 'RIGVIR®', 'Active substance - Rigvir Picornaviridae family Enterovirus genus ECHO group type 7', and 'Excipients - Sodium chloride, water for injection, MCM medium traces contains minerals, amino acids, vitamins, Thre xSP TCD, /us'. To the right of the box is a small glass vial with a green cap and a white label that says 'RIGVIR®'.</p>	<p>Medicine RIGVIR®</p> <p>The medicine RIGVIR® is available through distributors authorized by the manufacturer.</p> <p>In case of interest, please contact International Virotherapy Center at info@virotherapy.com.</p>
 <p>The image shows the packaging for ECHO-7 RIGVIR analogue. On the left is a white box with green and black text. The text includes 'RIGVIR®', 'Sterile solution - 2ml', and a list of characteristics: 'Non-toxic', 'Non-pathogenic', and 'Non-GMO'. There is a green circular logo with 'GMP' and 'STERILIZATION' text. To the right of the box is a small glass vial with a green cap and a white label that says 'ECHO-7 RIGVIR®'.</p>	<p>Analogue ECHO-7 RIGVIR®</p> <p>Analogue product ECHO-7 RIGVIR® has no medical status, but 100% corresponds to the medicine RIGVIR - it is produced under GMP conditions, it's safety, quality, sterility and testing does not change, but due to the requirements of the regulators, a lower permissible titer is indicated on the label - 10^5. ECHO-7 RIGVIR® for scientific needs can be freely purchased in the webshop www.echo7rigvir.com. The owner of the analogue product is "AramaPharm" Ltd, which received a license from Rigvir group in the non-medical segment. Rigvir group provides product quality monitoring and supervision in the market.</p> <p>In case of medical questions, please contact the International Virotherapy Center at info@virotherapy.com.</p>
 <p>The image shows the packaging for RIGVIR SE food supplement. It features three dark blue boxes with a starry space background and a large yellow sun or planet. The text on the boxes includes 'RIGVIR SE' and 'FOOD SUPPLEMENT'. In front of the boxes are two white capsules.</p>	<p>Food supplement Rigvir SE for Cancer prevention</p> <p>RIGVIR SE contains Vitamin B2, whey protein isolate and traces of a lyophilised non-genetically modified and non-pathogenic ECHO-7 virus Rigvir. RIGVIR SE ingredients are included in a capsule with special coating (hydroxypropyl methylcellulose) that allows it to cross the stomach and reach the intestine which is the most suitable environment for the ECHO-7 virus to provide its maximum benefit. The amount of ECHO-7 virus is multiple times smaller than the one used in the production of the RIGVIR® medicine.</p> <p>The manufacturer of RIGVIR SE is a UK-based company Smart Nanovirus Limited.</p> <p>RIGVIR SE can be purchased in the webshop www.smartnanovirus.com.</p> <p>In case of medical questions, please contact the International Virotherapy Center at info@virotherapy.com.</p>

RIGVIR INTRAMUSCULAR INJECTION STEP BY STEP



1. STORAGE

Rigvir must always be stored in the freezer at a temperature of $-20 \pm 2^{\circ}\text{C}$ (equivalent to -4°F to -7.6°F).



2. PREPARATION

Before use, take the vial out of the freezer and carefully inspect it for any visible damage.



3. WARMING THE VIAL

Hold the Rigvir vial in your hands for approximately 3 to 5 minutes until the solution becomes fully liquid. The injection should be administered within 3 hours after the solution has completely thawed.



4. REMOVING THE CAP

Remove the green protective cap from the vial to prepare it for use.



5. DISINFECTING THE STOPPER

Using an alcohol pad, thoroughly disinfect the grey rubber stopper on top of the vial.



6. DRAWING THE SOLUTION

Intramuscular injections are performed using a syringe fitted with a 23G needle. Each 2 ml vial of Rigvir is intended for single use. Withdraw the full content of the vial, ensuring a clean and steady draw.
Note: If drawing Rigvir with a 23G needle is difficult, use an 18G needle, then switch back to 23G before injection.



7. NEEDLE AND INJECTION SITE PREPARATION

Before each injection, disinfect both the needle and the injection site. Make sure to expel any air from the syringe to prevent air bubbles from entering the muscle.



8. INJECTION PROCEDURE




Administer the intramuscular injection as directed by a healthcare professional. The injection should be given into either the musculus deltoideus (shoulder) or the musculus gluteus maximus (buttock). Insert the needle fully into the muscle.



9. AFTERCARE

After removing the needle, disinfect the injection site again and apply a medical patch to protect the area.

SPECIAL ADMINISTRATION CASES

	<p>If local therapy is performed with multiple sequential injections administered peritumorally (around the tumor, subcutaneous metastases, or recurrence), the injection should be performed obliquely, with a depth of approximately 5 mm. The injection site should be within healthy tissue, at least 1 cm away from the outer edge of the tumor.</p>
	<p>If local therapy is performed intratumorally (directly into the tumor, subcutaneous metastases, or recurrence), it is recommended to administer the injection at the outer edges of the tumor. A new needle should be used for each injection to ensure sterility and minimize the risk of tissue contamination.</p> <p>Note: One 2 ml vial of Rigvir can be used to perform an average of 4–5 local injections.</p>
	<p>Rigvir may be administered intranasally in cases of brain metastases. If possible, the solution should be dropped into both nostrils. A 5–15 minute interval should be observed between each drop. The total volume should be 0.5–1 ml. Any remaining Rigvir may be refrozen and used for the next administration.</p>

IMMUNITY CHANGES ALONG WITH TUMOUR PROGRESSION

Author of the table – Professor, *Dr. Habil. Med.*, virologist, immunologist Aina Muceniece.
Table published in A. Muceniece and D. Venskus book "How to Assess Immunity – Melanoma Model".

Changes	Compensation phase		Immunodiscorrelation phase		Immunodiscorrelation in certain organs			
	Activation	Normalisation	Moderate suppression	Hyper-activation	Reactive lymph nodes	Lymph node metastases	Liver	Lungs
↑	CD8=CD38		Mo	Mo=Ly CD4 CD8 < CD38 HLA-DR	Ly CD4 CD8, CD38 CD19 CD16 HLA-DR	Mo	HLA-DR	
N	Ly, Mo CD4	Ly, Mo CD8 = CD38 HLA-DR			CD8 = CD38	Ly CD8 = CD38 HLA-DR		Ly, Mo HLA-DR CD19, CD16
↓			Ly CD8 = CD38 CD4		Mo	CD4, CD19 CD16	Ly, Mo CD4 CD8 < CD38 CD19 CD16	CD4 CD8 < CD38
Virotherapy use	Yes	Yes	Yes	Symptomatic, disintoxication therapies additionally	Yes	Yes	Yes	Yes

If Mo = Ly, there is total progression
Recurrence – the most severe stage of suppression

Description:

- ↑ – cell count above the norm for 27% and more;
- N – cell count within the normal reference ranges;
- ↓ – cell count below the norm for 27% and more;
- = – cell count equation phenomenon.



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