

# **RADIATION IN METASTATIC BREAST CANCER**

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# Metastatic breast cancer

incidence of MBC interests 25–28% as **de novo metastatic**, **Metastatic recurrence** is reported in 20–30% of patients

Metastatic breast cancer is variable in disease extent  
a single metastasis to diffuse disease involving multi Organs

**oligometastatic disease (OMBC)** is a subset of metastatic breast characterized by single or few detectable metastases

The generally accepted definition is **five or less metastases confined to a single organ**. Some studies use less than five metastases and metastatic deposits **less than 5 cm in size**

The most common sites being **bone, liver and lung and brain** •  
presence of metastases generally is **non-curable disease** •

current standard of treatment aimed at **palliative** or **disease** •  
**control** (the delay or prevention of disease progression)  
rather than cure

**But OMBC** may signify less aggressive tumor behavior and •  
be **potentially curable** with aggressive treatment of the  
limited metastases

**systemic therapy** is first-line treatment for most patients with metastatic disease

**BUT local therapies** such as **surgery and/or radiation** TO the breast/chest wall, regional lymph nodes or to distant metastatic sites may be used for symptom **palliation** or **prolonging survival** in situations of oligometastatic disease

considerations for radiation therapy (RT) vary depending on **what the therapeutic goal is**

# palliation

whole brain radiation therapy (**WBRT**) considered an important **palliative** procedure in management of **multiple symptomatic brain** metastases that are **not amenable** to stereotactic radiosurgery (SRS) and/or surgery, or in presence of **leptomeningeal** disease

local adjuvant therapy in **bone metastases**

**radioisotopes** may be used in patients with **diffuse bone pain** that is not eligible for palliative RT

# Definitive therapy

RT is an option to potentially improve survival for patients with oligometastatic disease goal of potentially prolonging survival

Factors associated with longer survival include

limited metastatic disease:  $<5$

younger age

better performance status:  $p.s < 2$

bone-only metastases

and long disease free interval:  $. > 2-5$  years

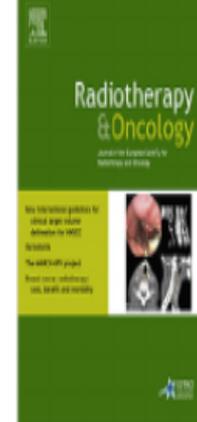


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Phase II trial

## Radical radiation therapy for oligometastatic breast cancer: Results of a prospective phase II trial



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## Methods and materials

Inclusion criteria were the following: oligometastatic breast cancer with  $\leq 5$  metastatic sites, FDG-PET/CT staging, no brain metastases, primary tumor controlled. Radiotherapy could be delivered using stereotactic body radiotherapy (SBRT) technique or fractionated intensity modulated radiotherapy (IMRT). SBRT consisted of 30–45 Gy in 3 fractions, while IMRT was delivered to a total dose of 60 Gy in 25 fractions. We hypothesized that radical radiation therapy could increase the PFS from 30% (according to the published literature) to 50% at two years.

## Results

54 Patients with 92 metastatic lesions were enrolled. Forty-four were treated with SBRT, and 10 with IMRT. Forty-eight (89%) patients received a form of systemic therapy concomitantly to radiation therapy. Sites of metastatic disease were the following: bones 60 lesions, lymph nodes 23 lesions, lung 4 lesions, liver 5 lesions. After a median follow-up of 30 months (range, 6–55 months), 1- and 2-year PFS was 75% and 53%, respectively. Two-year LC and OS were 97% and 95%, respectively. Radiation therapy was well tolerated, and no Grade  $\geq 3$  toxicity was documented. Grade 2 toxicity were pain and fatigue in 2 cases.

## Conclusions

Patients with oligometastatic breast cancer treated with radical radiotherapy to all metastatic sites may achieve long-term progression-free survival, without significant treatment-related toxicity. While waiting for data from randomized trials, the use of radical radiation therapy to all metastatic sites in patients with oligometastatic breast cancer should be considered a valuable option, and its recommendation should be individualized.

# Treatment Types

Radiation treatment modalities often based on **intent** and treatment **location**

## palliative radiation therapy:

- commonly performed with 2D or conformal radiation therapy (3D-CRT)
- intensity modulated radiation therapy (**IMRT**) can be considered in cases of **reirradiation** (repeat radiation

1-delivered in 1 or multiple fractions

2-considered **standard treatment** in patients with **bone metastases**, **pathologic fractures**, **spinal cord compression**

# Treatment Types

## Oligometastatic disease

### -SBRT

stereotactic body radiation therapy (**SBRT**) is an external beam radiotherapy used to deliver high dose of radiation to a precise intra- or extracranial target

### -IMRT

# SBRT

Used for definitive intent in select patients with **oligometastatic** disease if metastatic sites are potentially amenable for local treatment

1-deposited in 1 or multiple fractions with **maximum sparing of normal tissue**

2-may be considered **ablative** when biologically effective dose (BED) > 100 Gy

3-risks for **morbidity** and mortality correlate with targeted disease **site** and **dose** delivered

# SBRT

≥ grade 3 toxicities reported in pulmonary and hepatic oligometastases; adverse events in lesions within close proximity to chest wall may include chest wall pain, rib fractures, and skin toxicity

# RT ON PRIMARY(symptomatic)

The **primary role** of local treatment to the breast and/or regional nodes in patients with stage IV breast cancer is **Palliation**

Metastatic patients **should be evaluated** for possible management of the primary and/or regional nodes for **debilitating symptoms** from the cancer

(eg, locally advanced breast tumors causing **pain, bleeding, ulceration, infection**, and poor wound healing; or regional nodal disease causing pain, motor weakness, and sensory deficits from brachial plexus invasion, or lymphedema

## RT on primary (Asymptomatic)

However, **in general**, for patients who are **asymptomatic** at the site of their locoregional disease, locoregional treatment with **surgery and/or radiation** therapy is **not standard-of-care** treatment given **lack of clear evidence** that this improves Survival

Deviations to this approach may be rarely made on a case-by-case basis in a **multidisciplinary setting**, although these instances are **exception**.

## RT on primary (Asymptomatic)

For example, we have offered local management of the primary to patients with (HER2)-positive disease who have a brisk and dramatic response to systemic therapy, but the primary site is progressing.

Or asymptomatic patients but we are concerned may be symptomatic if they do not respond quickly

multidisciplinary setting and patient preferences are important

# EVIDENCE

In the Turkish trial, 274 women with **de novo metastatic breast** cancer were randomly assigned to local management (**mastectomy, or BCS with radiation**) followed by systemic therapy, versus systemic therapy only

patients who received locoregional therapy experienced an **improvement in five-year survival** (42 versus 24 percent; HR 0.66, 95% CI 0.49-0.88). However, the **arms were not balanced** according to biologic subtypes

Patients randomized to **locoregional therapy had lower rates of triple-negative disease**, and higher rates of hormone receptor-positive disease and solitary bone metastases raising the concern that they were in better prognostic categories before the intervention.

In a post-hoc subgroup analysis, patients **with hormone receptor-positive, HER2-negative disease**; age **younger than 55** years; and those **with solitary bone metastases** appeared to derive the greatest **benefit from local management**.

# Selection of patients for local therapy to the metastasis

1 - **intractable pain** in spite of systemic therapy for metastases, are usually considered candidates for radiation therapy to the affected site

2 - **medical emergencies**: **spinal cord** or cauda equina compression, mass effect due to **brain metastases**, and impending or present **pathologic fracture** due to a bony metastases

3- **Metastases to the chest wall** are also usually treated with locoregional therapy, principally with the intent of avoiding future symptoms. **Local therapy such as excision and radiation** may also be helpful in patients with hemorrhagic chest wall lesion

# BRAIN METASTASIS

## Brain :

For most patients with brain metastases, a **local approach** such as **surgical resection**, stereotactic radiosurgery (**SRS**), or whole-brain radiotherapy should be employed, **irrespective of whether the patient is symptomatic or not**, often prior to or in conjunction with systemic therapy

an **exception** may be made in select patients with **limited intracranial disease** from (HER2)-positive breast cancer, as **systemic therapy alone** may be a reasonable option in some cases

**solitary brain metastasis:** options include **surgical resection** or **SRS**

Due to the high risk of **recurrence after surgery**, typically  
.post operative **SRS** is offered

**multiple metastases:** (typically  $> 4-5$ )  
**WBRT** remains the therapy of choice.

Open Access | Review

# Diagnosis and management of brain metastases: an updated review from a radiation oncology perspective

Views: 7937 | Downloads: 762 | Citations:  Crossref 1

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**treatment of cerebral edema:** with systemic steroids such as dexamethason is important

Even though there is not a defined dexamethasone scheme, the **most utilized dose** in patients with clinical cerebral **edema is 4 to 8 mg/day**

**Management of seizures:** In patients who have not presented with seizures, the use of an antiepileptic agent in a prophylactic manner is currently **not recommended** :

**Initial assessment:** adequate assessment of the patient's condition, evaluating parameters such as **functional status** and **extracranial disease**

Table 2  
RPA classes

<b>Prognostic factors</b>	<b>Class I</b>	<b>Class II*</b>	<b>Class III</b>
Age (years)	< 65	Any	Any
Controlled primary tumor	Yes	Any	Any
KPS	> 70	> 70	<7 0
Extracranial metastasis	No	Any	Any
Estimated survival (months)	7.1	4.2	2.3

Abbreviations: RPA: recursive partition analysis; KPS: Karnofsky performance score. \*All patients not in class I or III.

Patients with a class III RPA are usually candidates for only supportive care, with local management performed either through surgery or radiotherapy for patients with classes I and II<sup>[40,41]</sup>.

# Whole-brain radiotherapy

-WBRT has been considered a **mainstay treatment** for brain Metastases

-irradiating the whole brain through two **opposed lateral** fields  
-from the **supraorbital ridge** through the **external auditory meatus** to the foramen magnum; the other margins of the rectangular field project 2 cm beyond the forehead, vertex, and occiput

**Dose and fractionation.** .

30 Gy/2 weeks/20 Gy/1 week

37.5 Gy/3 week//40 Gy/4 week

Because the primary objective of this type of treatment is the **palliation of symptoms**, the **most common prescription** is **3000 cGy in 10 fraction**

**RTOG COMPARISON** four different radiation schemes reported **no differences** in survival, time to progression, and symptom relief

**physician decision**: **patient's performance** status, estimated **survival**, and **histology** of the primary tumor

# WBRT

20 Gy in 1 week is preferable for most patients with poor performance status

37.5 Gy in 3 weeks is recommended in patients who have received a stereotactic radiosurgery boost with one metastatic lesion and should be considered in patients with one to three lesions

**Adv:** lower intracranial relapse

**Dis adv:** greater cognitive deterioration (reflected as short-term memory loss), especially in patients with a longer life expectancy (> 6 months)

# Role of radiosurgery in the treatment of brain metastases

- uses **multiple rays** of radiation, which converge three-dimensionally on a **localized objective**, either static or mobile, giving a **high dose to a unique fraction** with a high fall-off. This **minimizes the damage to the adjacent tissue**
- has been demonstrated that **both surgical treatment and SRS** lead to **longer overall survival** in these patients, especially for **lone lesions smaller than 30 mm**, where SRS has an overall survival comparable to microsurgery.

adjuvant treatment with radiotherapy after surgery is imperative because of high local recurrence

Then “: reduce cognitive impairment in such patients, the use of SRS has grown in use as an alternative to WBRT in the first 6 weeks following surgery, with the goal being to maintain local control in surgery and preserve neurocognitive functions without lowering quality of life

but when do we use srs??????

- good functional status
- one to three metastases at diagnose
- limited extracranial disease

ASTRO and NCCN guidelines agree in recommending management with SRS in patients with a limited number of brain metastases (up to four metastases for SRS protocols)

it is necessary to continue surveillance using serial MRI when only SRS is used, with the intention of identifying the progression



VitalBeam Linac

Machines used to focus highly targeted radiation or radiosurgery (SRS or stereotactic radiosurgery)



Cyberknife



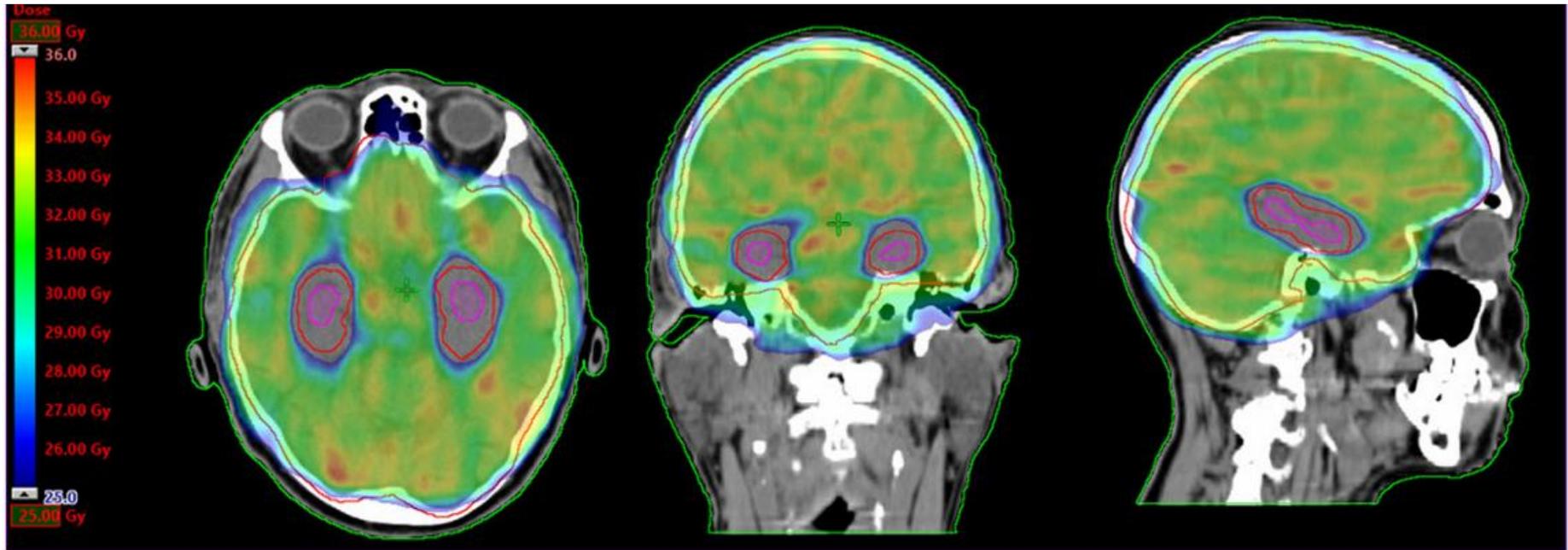
Gamma Knife



Tomotherapy

# Hippocampal Avoidance During Whole-Brain

- Radiation dose to the neuroregenerative zone of the **hippocampus** has been found to be associated with cognitive toxicity
- **Hippocampal avoidance (HA)** using intensity-modulated radiotherapy during whole-brain radiotherapy (WBRT) is hypothesized to preserve cognition
- **HA-WBRT plus memantine** better preserves cognitive function and with **no difference in intracranial PFS and OS**, and should be considered **a standard of care for patients with good performance status**.



tion in axial, coronal and sagittal view for a patient planned with HS WBRT with  $10 \times 3$  Gy

# Bone Metastases in Breast Cancer

- Up to 70% of women with advanced breast cancer may develop bone metastases
  - Early site of spread
  - 20% of women have “bone only” disease
  - More common if tumor is hormone receptor positive
- Cancer cells target bones with an extensive blood supply: arms, legs, ribs, spine, pelvis. Tend not to travel to hands and feet.
- Breast cancer growth in bone is typically slow; therefore optimizing treatment is crucial

# Radiation Therapy

- Radiation therapy can be used to treat painful bone metastases refractory to systemic therapies
  - 80-90% of breast cancer patients experience relief of symptoms
  - 40-46% experience full relief
  - 70% never have pain in that region again
  - May take months before full pain relief is realized

# Radiation Therapy: Specifics

- Can take 1-4 weeks; 2 weeks is most common
- Chemotherapy is usually on hold during RT
- Side effects: nausea, diarrhea, low blood counts  
fatigue
- Typically radiation is not used again in the same place

Review

## Management of Metastatic Bone Disease Algorithms for Diagnostics and Treatment

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**Abstract.** *Background:* Bone is a frequent site of metastases in advanced cancer and is associated with significant skeletal morbidity. Current treatment options are aimed at preserving and improving functional independence and quality of life. *Materials and Methods:* A review of current literature focusing on diagnostic tools and treatment approaches of bone metastasis in advanced cancer was performed and conclusions were incorporated into diagnostic and treatment algorithms. *Results:* Radiologic imaging has added valuable tools for screening and diagnosis of bone metastasis

Structural integrity of the bone is meticulously regulated through the actions of osteoclasts and osteoblasts. The dynamics of bone resorption and formation in this context are determined by the stress and force bone is subjected to and orchestrated by cytokines and other factors. The healthy skeletal structure is lost if this balance is disturbed by the detrimental effects of either bone metastasis or cancer treatment (1). In cancer patients, the skeletal morbidity is conferred upon by the burden of bone metastasis and by cancer treatment induced bone loss (CTBL). Careful use of

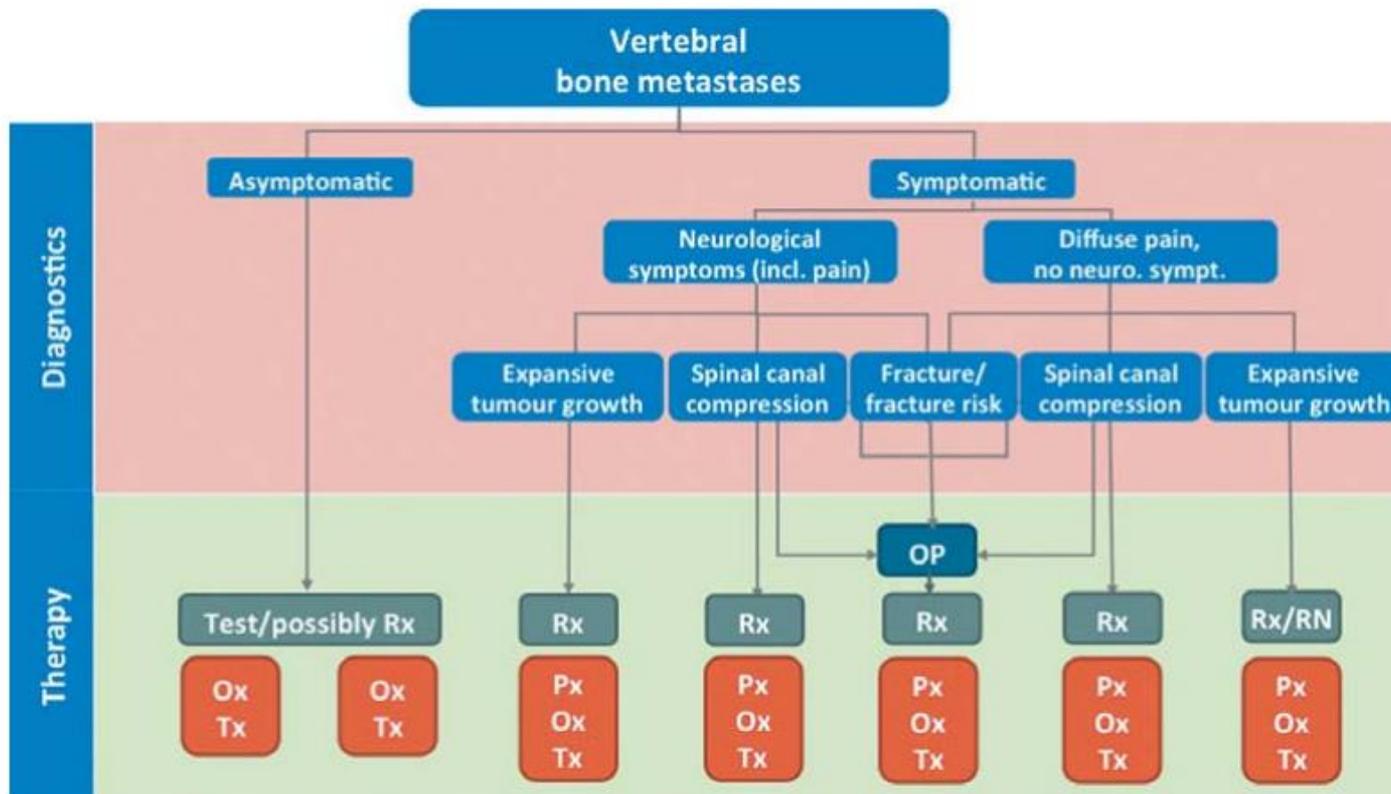


Figure 2. Treatment of vertebral bone metastases. OP, Surgical treatment; Ox, osteoprotective therapy; Px, pain therapy; Rx, radiotherapy; Tx, cancer treatment; Rx/RN, radiotherapy and/or radionuclide therapy. Osteoprotective therapy: denosumab or bisphosphonates (as approval), calcium and vitamin D supplementation (as prescribing information).

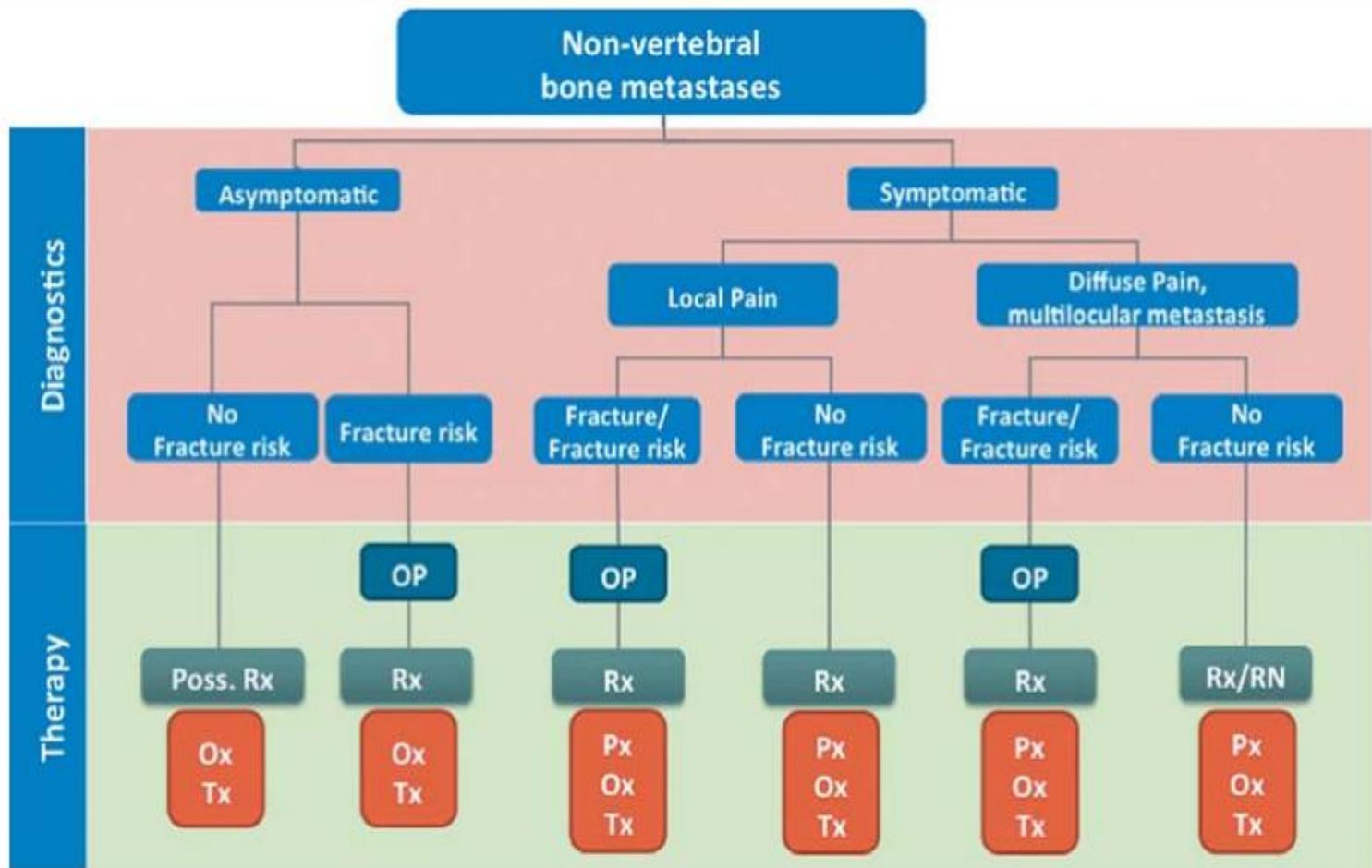


Figure 3. Treatment of non-vertebral bone metastases. OP, Surgical treatment; Ox, osteoprotective therapy; Px, pain therapy; Rx, radiot cancer treatment; Rx/RN, radiotherapy and/or radionuclide therapy. Osteoprotective therapy: denosumab or bisphosphonates (as approved and vitamin D supplementation (as prescribing information).

# Pall RT in bone metastasis

Systemic review of randomized Pall RT trials: SFs Vs MFs

SFs: 8Gy/1#

MFs: 20Gy/5# OR 30Gy/10# OR 40Gy/20#

16 RCTs since 1986

N=>5000

Intention to treat & accessible pt analysis done



# Pall RT in bone metastasis

Intention to treat analysis:

**Overall response:**

SF= 58% (1468 / 2513 pt)

MF= 59% (1466/ 2487 pt)

ODD's ratio= 0.99 (0.95-1.03)

**Complete response:**

SF= 23% (545/2375 pt)

MF= 24% (558/2351 pt)

ODD's ratio= 0.97 (0.88-1.06)

**Increased risk in SF arm:**

Pathological #: 3.2% SF Vs 2.8% MF (p=0.75)

Spinal cord compression: 2.8% SF Vs 1.9% MF (p=0.13)

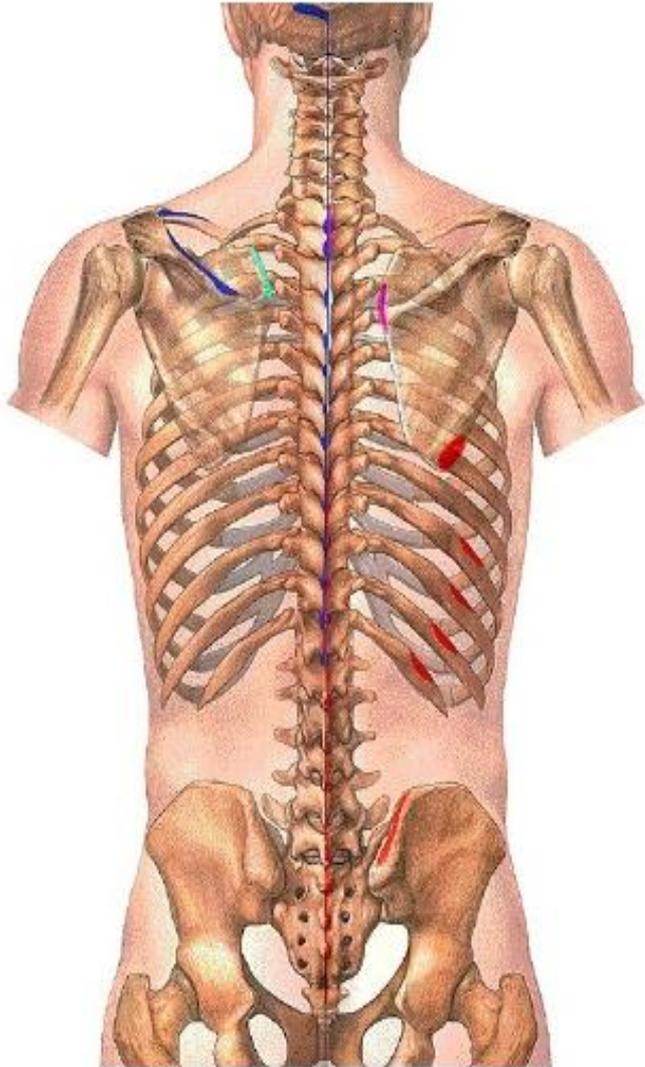
**Re-RT rate:**

SF= 20% Vs MF 8% (p=0.0001)

Likelihood ratio 2.5

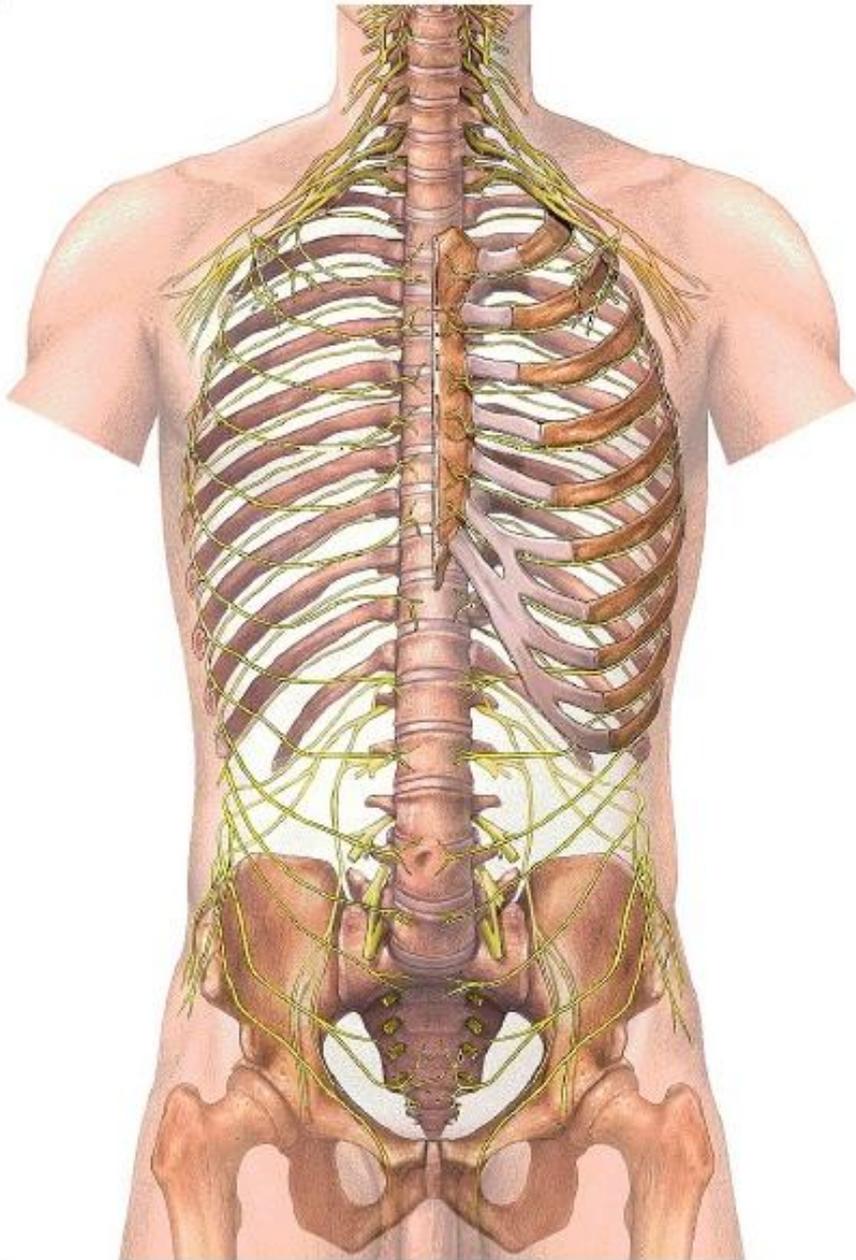


# Side Effects of Radiation for Bone mets



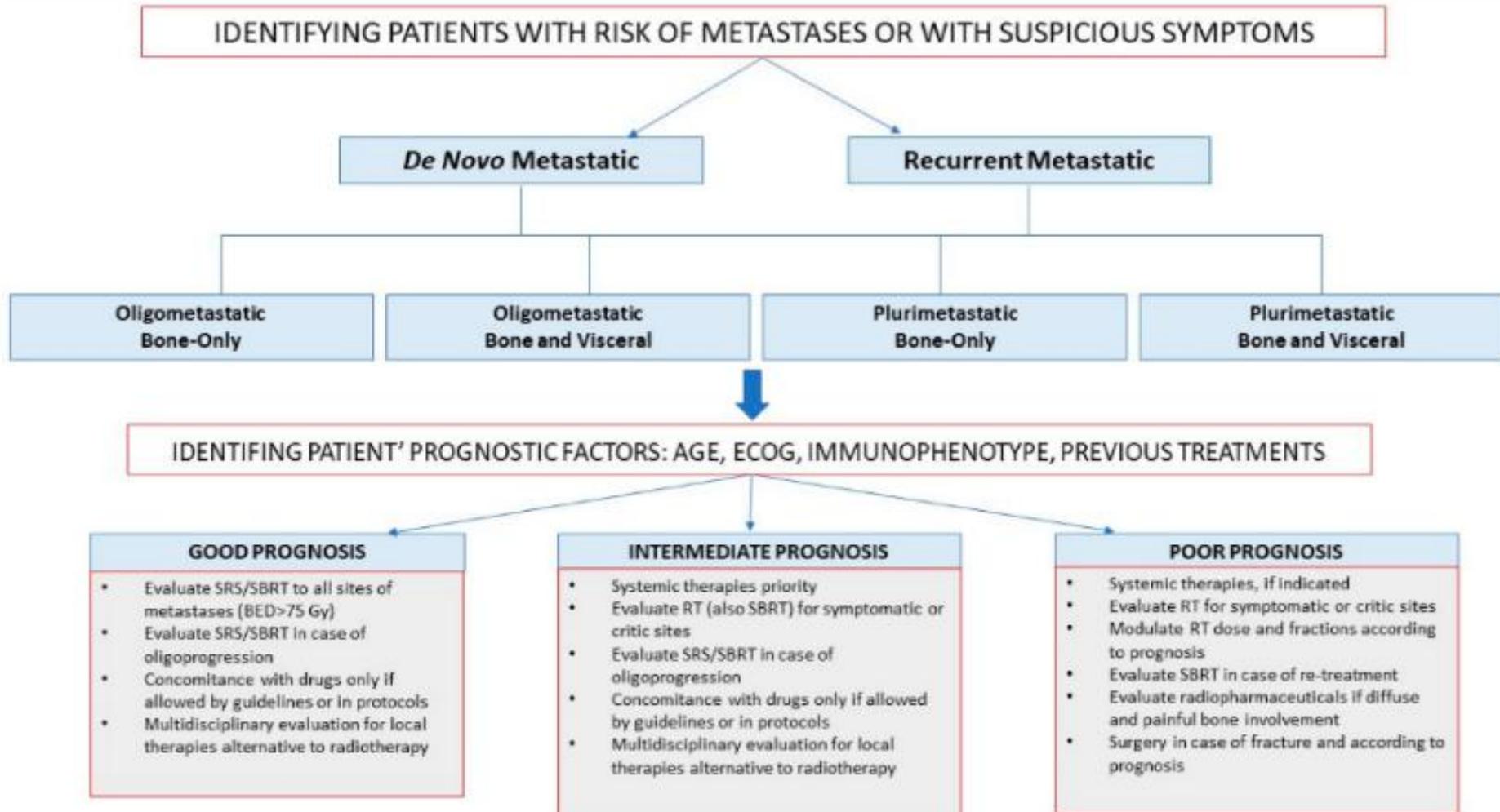
- **Mild fatigue**
- **Local skin irritation**
- **Lower the blood count (anemia or white count)**
- **The bone can temporarily get weaker before strengthening**

# Radiation Results



- **80 - 90% of the time the symptoms improve**
- **Complete relief in 54%**
- **Most respond by 10-14 days, 70% by 2 weeks, 90% by 3 months**
- **55 - 70% pain benefit is sustained for life**

**Figure 2.** Therapeutic algorithms approach to patients with Bone metastases from breast cancer according to good, intermediate or poor prognosis.



**Table 2.** Ongoing trials of oligometastatic and oligoprogressive breast cancer patients.

Reference	Setting	Intervention	Radiotherapy Dose/Volumes	Primary Endpoints
CLEAR, Jeong J, NCT03750396	Oligometastatic breast cancer recurrence (>12 months) All site of metastases	Surgery or radiotherapy or radiofrequency on metastasis	Total radiation dose and fractions are various according to metastatic lesions (57–97.5 Gy/8–10 Fraction)	PFS
NRG Oncology, NCT02364657	Limited MBC	SBRT +/- Surgery	Radiosurgery in 1, 3 or 5 fractions (according to discretion of physician)	PFS OS
STEREO- SEIN, NCT02089100	De novo Oligometastatic Breast Cancer, excluding triple negative subtype	SBRT	SBRT with radical intent to all sites of metastases	PFS
MSKCC, NCT03808337	Metastatic NSCLC or TNBC	SBRT concurrently to systemic therapy	SBRT with a minimum BED of 48 Gy to all sites	PFS
NCI, NCT00182793	Stage IIIb-IV BC	RT on primary site or on site of metastasis (oligometastatic), High-dose chemotherapy, autologous stem cells transplant	Tomotherapy on site of disease with standard fractionation	5-year Relapse- Free-Survival 5-year Overall, Survival-Rate
CIMER, NCT04220476	Oligometastatic, Luminal BC	SBRT (Immune-SBRT every 48 h)	SBRT every 48 h, to all sites of metastases 50GY in 5 fractions	ORR PFS OS
MSKCC NCT03808862	Oligoprogressive NSCLC or TNBC	SBRT	SBRT 9–10 Gy × 3 or 10 Gy × 5 fractions given every other day to all sites	PFS



# **Metastatic spinal cord compression**

7 (ALL) >



# Presentation

- ◆ Depends on level (77% in T spine) <sup>(1)</sup>
- ◆ Radicular back pain in 85-95%
- ◆ Worsened by lying flat, weight bearing, coughing and sneezing, relieved by sitting

# Presentation

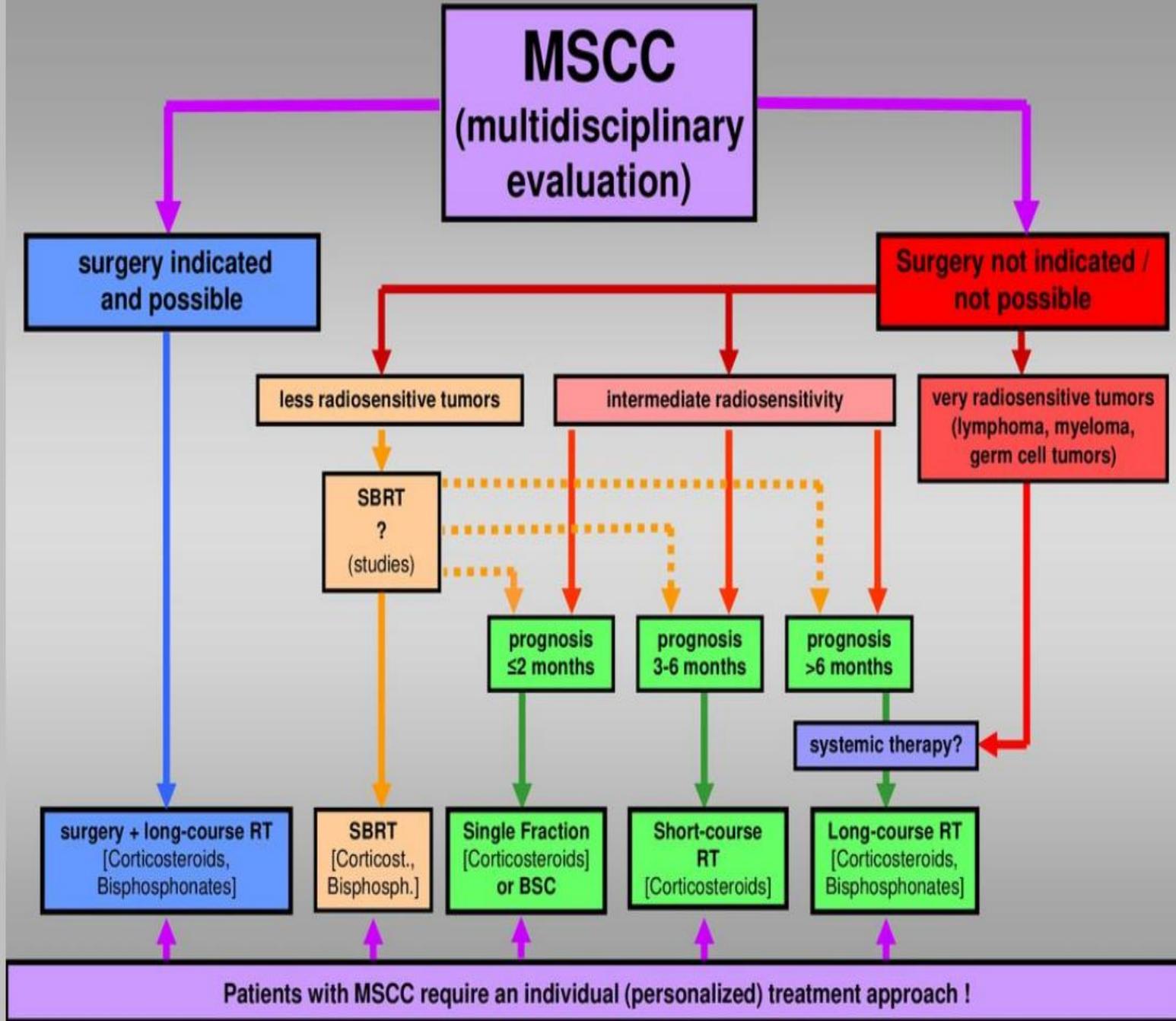
- ◆ Motor weakness
- ◆ Sensory disturbance
- ◆ Sphincter disturbance
- ◆ However localisation of pain poorly correlates with site of disease – 16%

# Diagnosis

- ◆ *In the history* - especially in a known cancer patient.
- ◆ MRI spine – urgent
- ◆ Referral to Oncology - urgent

# Treatment options include:

1. Steroids & gastric protection
2. Analgesia
3. Surgery – decompression & stabilisation of the spine
4. Radiotherapy



Patients with MSCC require an individual (personalized) treatment approach !

# Lung metastases

## palliation

- mediastinal/hilar masses causing extrinsic airway obstruction
- peripheral or pleural disease causing chest wall pain
- or apical masses extending into spinal canal or brachial plexus
- endobronchial brachytherapy for intrinsic bronchial obstruction;

# SBRT

For patients with a limited number of lung metastases who **meet the criteria for resection**, particularly in those with significant medical comorbidity. results suggest that SBRT provides **equivalent local control to surgical resection**; thus, SBRT may be an alternative to surgery in patients with oligometastatic disease

SBRT offers a survival benefit relative to surgery  
long-term follow-up data **are not available**. There **are no results from randomized clinical trials** comparing SBRT with surgery or other ablative techniques such as radiofrequency ablation



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Thank You  
For Your  
Attention