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Review

Radiation-induced neuropathy in cancer survivors ☆

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ABSTRACT

Radiation-induced peripheral neuropathy is a chronic handicap, frightening because progressive and usually irreversible, usually appearing several years after radiotherapy. Its occurrence is rare but increasing with improved long-term cancer survival.

The pathophysiological mechanisms are not yet fully understood. Nerve compression by indirect extensive radiation-induced fibrosis plays a central role, in addition to direct injury to nerves through axonal damage and demyelination and injury to blood vessels by ischaemia following capillary network failure.

There is great clinical heterogeneity in neurological presentation since various anatomic sites are irradiated. The well-known frequent form is radiation-induced brachial plexopathy (RIBP) following breast cancer irradiation, while tumour recurrence is easier to discount today with the help of magnetic resonance imaging and positron emission tomography. RIBP incidence is in accordance with the irradiation technique, and ranges from 66% RIBP with 60 Gy in 5 Gy fractions in the 1960s to less than 1% with 50 Gy in 2 Gy fractions today. Whereas a link with previous radiotherapy is forgotten or difficult to establish, this has recently been facilitated by *a posteriori* conformal radiotherapy with 3D-dosimetric reconstitution: lumbosacral radiculo-plexopathy following testicular seminoma or Hodgkin's disease misdiagnosed as amyotrophic lateral sclerosis.

Promising treatments via the antioxidant pathway for radiation-induced fibrosis suggest a way to improve the everyday quality of life of these long-term cancer survivors.

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Long-term cancer survivors have an unavoidable tissue trace of their previous treatment, especially radiotherapy (RT), which is most often clinically asymptomatic [1]. Some patients have radiation damage in normal tissues affecting the functional or vital prognosis. The symptoms are related to the irradiated volume and their severity depends on the intensity of the underlying fibrotic process, combined with direct toxicity of RT for specific cells, depending on the organ concerned. Involvement of the peripheral nervous system structures is rare, although state-of-the-art epidemiological studies are lacking [2], but has a considerable impact on quality of life in patients considered to be cured of their cancer.

Radiation-induced peripheral neuropathy (RIPN) is better understood today through recognition of various clinical presentations corresponding to different damage to nerve roots, nerve plexus or nerve trunks, and using radiological methods to discount tumour recurrence including magnetic resonance imaging (MRI), positron emission tomography (PET) and *a posteriori* conformal RT with 3D-dosimetric reconstitution [3]. Recent histological forms in addition to the classic fibrosis, consist in description of multiple cavernomas of the nerve roots [4].

In the first part of the paper, we review the mechanisms of RIPN, particularly focusing on the mechanisms of fibrosis, which is a main causative factor and therapeutic target. In the second part, we review the general context of RIPN diagnosis and then describe the specific clinical and laboratory features according to the anatomic site of injury. The last part of the article considers existing and future treatment options.

Literature chosen in this article explore several decades of papers, not written with the same requirements and technical details: old clinical series with many uncertainties, drove us to choose the very plausible and appropriate explanations.

Mechanisms underlying RIPN

Pathophysiology

RIPN is delayed local damage to mature nerve tissue which is partly attributable to initial microvascular injury, then *radiation-induced fibrosis* (RIF) combined with specific neurological injury [5]. RIF is a dynamic process related to perturbations at various

☆ Search strategy and selection criteria: PubMed was searched for articles published in English (or French) using search terms including "radiotherapy injury" "radiation-induced" "peripheral nerve" "fibrosis" "brachial plexopathy or plexitis" "lumbosacral radiculopathy". We included papers and book chapters of particular relevance published between 1948 and 2010.

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levels of physiological homeostasis [1,6] varying from inflammation to sclerosis (Fig. 1), and is characterised by gradual stepwise worsening over a period of several years: an early asymptomatic prefibrotic phase with chronic inflammation, then an organised fibrotic phase of extracellular matrix deposits, and a late fibroatrophic poorly vascularised phase with retractile fibrosis [1]. The mechanisms consist of a *vicious circle* built on several imbalances including fibroblast proliferation, extracellular matrix deposition, amplified by cytokines such as TGFß$_1$ and CTGF. The smallest chief participant has been identified as oxygen free radicals (reactive oxygen species). Radicals are normally involved in physiological functions such as cell differentiation, proliferation and inflammation, but excess production may result in pathological stress to tissues as induced by physicochemical damage, infectious agents and deficient antioxidant defences. When the damage level rises so much that the oxidative stress response is transiently overwhelmed, fibrogenesis becomes possible. Subsequent additional stress, chronic or brief and repeated resulting in abnormal radical concentrations, may enhance production of reactive oxygen species, thus helping to extend and intensify the fibrotic process.

RIF pathogenesis [review in 1] has been highly debated. An old *vascular concept* based on a theory of gradual ischaemia–hypoxia was developed to account for capillary network destruction after RT. More recent ideas consider reactions of endothelial cells to RT with procoagulant pro-inflammatory effects of thrombin, and changed microvascularisation in relation to intermittent rather than chronic hypoxia, inducing hypoxic inducible factor, then neoangiogenesis possibly leading to telangiectasia [6]. However, although these vascular dysfunctions are involved in generating RIF, their role seems indirect in the established fibrotic phase. The fibroblastic stromal concept sheds further light on RIF, in terms of continuous attack by reactive oxygen species leading to fibrogenesis [1].

Sensitivity of the peripheral nerves to radiation. Early descriptions of RIPN lesions were based on experimental data using single high-dose RT with a pattern of damage in a direct dose–effect relationship [2]. In the acute phase, the irradiated nerve shows transient electrophysiological and biochemical changes combined with an altered vascular permeability. Delayed effects enhance a disorganised patchwork structure in the irradiated volume including direct axonal injury and demyelination, extensive fibrosis within and surrounding nerve trunks, and ischaemia by injury to capillary networks supplying the nerves compensated for by neovascularisation.

Risk factors

Factors affecting the risk, severity, and nature of RIPN in patients are not specific. Several *RT-related factors* have been identified: fifty years ago low-energy machines used a short source-to-skin distance (cobalt 60 cm), alternating treated fields with steep dose gradients within the body, and body position displacement (the RT machine did not turn around the patient) between each RT field favouring overlapping fields with a three-field technique [7,8]; large total dose (>50 Gy to plexus, >60 Gy to cranial nerves) [9–11], large dose per fraction ($\geqslant$2.5 Gy, stereotactic radiosurgery) [10,12], RT volume including a large proportion of nerve fibres [13], heterogeneous high-dose distribution [3], hot spot high dose (field junctions), salvage RT of previously treated areas, in intracavitary radium source [14], or after IORT boost.

Combined treatment-related factors are the following: surgery in the case of haematoma or chronic infection and extended lymph node dissection (axillary, retroperitoneal or iliac nodes); concomitant or previous neurotoxic chemotherapy (cisplatin, vinca alkaloids, taxanes) or concomitant chemotherapy with intrathecal methotrexate. *Patient-related factors* are: young or advanced age, obesity, co-morbidity factors such as high blood pressure, diabetes mellitus, dyslipidaemia, combined peripheral neuropathy (diabetic, alcoholic, genetic...) or arteritis (smoking, multiple sclerosis), pre-existing collagen vascular diseases and hypersensitive patients [1].

Clinical and paraclinical neurological features

Experience shows that when complications arise years later, in cancer survivors, the link with previous RT is forgotten or difficult to establish since symptoms are nonspecific, and so the diagnosis is made after a long series of medical consultations and tests, sometimes invasive (lumbar puncture, nerve biopsy, etc.). In the absence

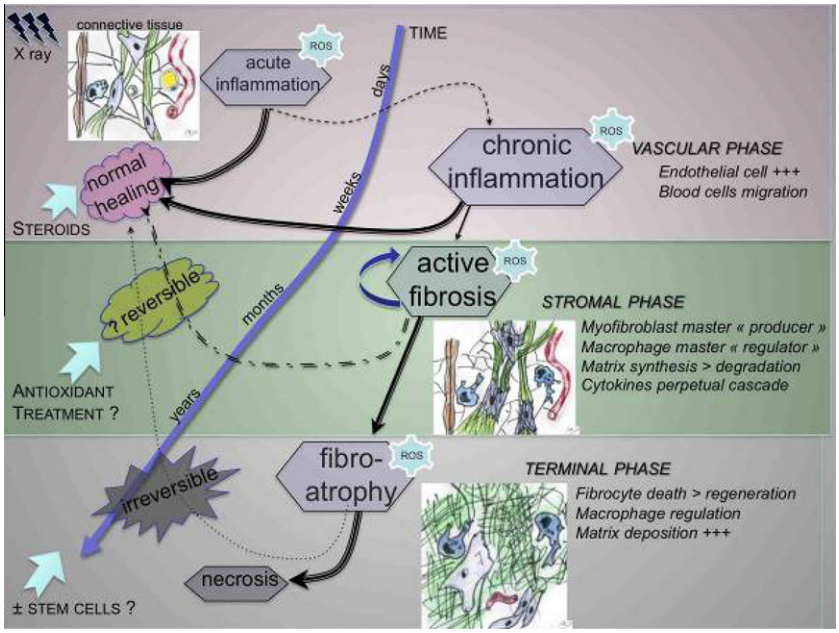

Fig. 1. Radiation-induced fibrosis: pathophysiology.

of specificity, the diagnosis is based on neurological expertise by analysis of symptoms, electrophysiological findings, MRI and PET scan. Collaboration between the neurologist and the radiotherapist allows determination of whether the neurological symptoms can be related to nerve damage within the irradiation volume, namely with a dosimetric reconstitution [3]. The diagnosis is guided by cutaneous atrophy with subcutaneous fibrosis and tattoo marks identifying the previous irradiated fields, and possible combined extra-neurological complications as sterno-clavicular osteoradionecrosis, radiation-induced cardiopathy, enteritis or multiple basal cell skin carcinoma. The diagnostic work-up aims to eliminate a cancer recurrence, but the clinical picture may also mimic many neurological diseases. Exceptional cases of peripheral nerve tumour, especially schwannoma, [15] with a developing painful mass in the irradiated volume and a rapidly (months) increasing neurological deficit, have been reported from 4 to 40 years after RT [16].

Neurotoxicity depends on the affected anatomic site of previous irradiation: we describe and classify these various topographic forms [17].

Cranial nerve injury predominantly involves the optic nerve

Cranial nerve injury is described after RT for intracranial and extracranial tumours: central nervous tumours as pituitary adenoma, craniopharyngioma, chiasmal glioma, frontal meningioma, orbit tumours, and head and neck cancers [18]. Technical progress in RT protocols has reduced its incidence in the last decades [9]. When radiation-induced optic neuropathy affects the anterior part of the optic nerve, ophthalmological findings are those of acute ischaemic anterior optic neuropathy with acute loss in visual acuity. However, chronic damage to the posterior portion of the optic nerve or chiasma is the most frequent (posterior radiation-induced optic neuropathy), with gradual impairment of visual acuity over 1–14 years after RT [18]. Hypoglossal palsy is the second most frequently reported cranial neuropathy: 19 out of 35 patients (54%) after RT in the 1960s [19]. Classically, patients develop tongue hemiatrophy, fasciculations and deviation when protracting the tongue, 1–10 years after RT for head and neck cancer, especially rhinopharynx lymphoepithelioma after combined chemotherapy [20]. Other injuries involve the glossopharyngeal nerve with swallowing impairment; vagus nerve after thoracic RT for breast [20] and head and neck cancers [11]; recurrent laryngeal nerve with larynx palsy after thoracic RT for thyroid tumour and spinal accessory nerve with sternocleidomastoid and trapezius muscle palsy [21]. Facial paralysis occurs after RT for parotid cancer [22]. Trigeminal neuropathy develops after cavernous sinus tumour irradiation, mainly meningioma and chordoma [23], or essential trigeminal neuralgia.

Cranial nerve neuromyotonia is a rapid muscular contracture, tonic, progressive and involuntary, with relaxation delayed by radiation-induced neuronal hyperexcitability, comparable to myokymia observed in plexopathy with complex repetitive electromyogram discharges in muscles. It is characterised by contraction lasting from a few seconds to minutes several times a day, sometimes with a trigger factor [22], corresponding to damage to the neuronal membrane which leads to cellular hyperexcitability and abnormal repeated discharges.

Axial neurological injury is a rare complication

Dropped head syndrome, late-onset cervico-scapular muscle atrophy combined with cervical paraspinal and shoulder girdle muscle weakness, has been reported up to 25 years after upper diaphragmatic RT for lymphoma in a small series of 2–15 patients [24,25]. Apart from cervical pain, sensory function is preserved. We have recently reported the case of a patient who developed a radiation-induced camptocormia after total lymphoid RT for lymphoma [26]. Asymmetric diaphragmatic weakness secondary to phrenic nerve paralysis is very rare, initially described after cervical high-dose RT for head and neck cancer or more recently low-dose mantle RT for Hodgkin's disease [27].

Upper limb injury with classic progressive brachial plexopathy

The main upper limb RIPN is chronic brachial plexopathy.

Delayed progressive radiation-induced brachial plexopathy (RIBP)

RIBP is a progressive injury in the axillary-supraclavicular ipsilateral node volume after RT for breast cancer (Fig. 2). Time to onset ranges from several months to decades with a mean incidence of 1.8–2.9% per year [7,28]. During past decades, three waves of RIBP incidence occured in accordance with the irradiation technique at that period (Table 1a and b): 1950s with 60 Gy total dose axillary-supraclavicular delivered using 5 Gy/fr followed by 66% RIBP [10,12]; 1960s with 45–50 Gy using 4 Gy/fr and patient removal between each RT field (overlapping) followed by 50% RIBP [8,12]; 1970s–1980s with 45–50 Gy using 3 Gy/fr followed by 10–15% RIBP [12,28–30], then less than 5% [31]. The incidence of RIBP today is <1–2% in patients receiving usual plexus total doses <55 Gy [7,32].

More rarely RIBP is seen in apical lung [33] or head-neck [34] cancers after hot spot total dose in relation to intensity-modulated radiation therapy (IMRT) or stereotaxic body radiation therapy (SBRT) and in Hodgkin's disease with bilateral neuropathy after mantle irradiation with only 40 Gy using 2 Gy/fr but a large volume [35–38] (Table 1c).

Several neurological publications have reported RIBP [36,37,39–43]. Clinically, RIBP begins with subjective paraesthesia or dysaesthesia which usually decreases with the development of hypoaesthesia then anaesthesia. The pressure of a zone of axillary and/or supraclavicular induration can trigger this paraesthesia (Tinel's sign). Neuropathic pain is generally rare and moderate, except after failure of neurolysis. Motor weakness is progressive, often delayed by several months, and then associated with fasciculations and amyotrophy. The topography of symptoms varies with the level of plexus damage, in relation with the irradiation technique used, predominating at the upper or lower plexus. It frequently starts at the median nerve, simulating carpal tunnel syndrome, before spreading progressively to the forearm and then the upper arm. Onset is often insidious, occurring over several months or years. Intensity is variable, but progressively increases, and after several years may result in paralysis of the upper limb in a range of 0.2–5 years from the first signs to hand paralysis [43]. Rapid neurological worsening is possible after trauma such as unusual traction on the affected limb, notably carrying of heavy loads [2], thorax parietal surgery or upper limb lymphangitis. Skin and muscular atrophy are combined, notably after previous orthovoltage or cobalt RT, with subcutaneous fibrosis of the axillary-supraclavicular area, and subcutaneous calcifications or sterno-clavicular osteonecrosis (Fig. 2a). Arm lymphoedema, which was frequent in older studies, is strongly linked to combined extensive lymph node dissection and high RT dose and is not predictive of RIBP, but may enhance upper limb nerve compression.

Electroneuromyography identifies the level of plexus injury [44]. The initial anomaly is an alteration of the sensory potentials of the median nerve in the fingers, which discounts an involvement proximal to the dorsal root ganglia (cervical) where the sensory potentials are preserved. The decrease in amplitude of the motor potentials generally starts in the thenar muscles (thumb). The nerve conduction is normal or slightly reduced, compared with axonal loss. A proximal conduction block of the motor fibres is often detected [41,45], reflecting focal demyelination whose origin may

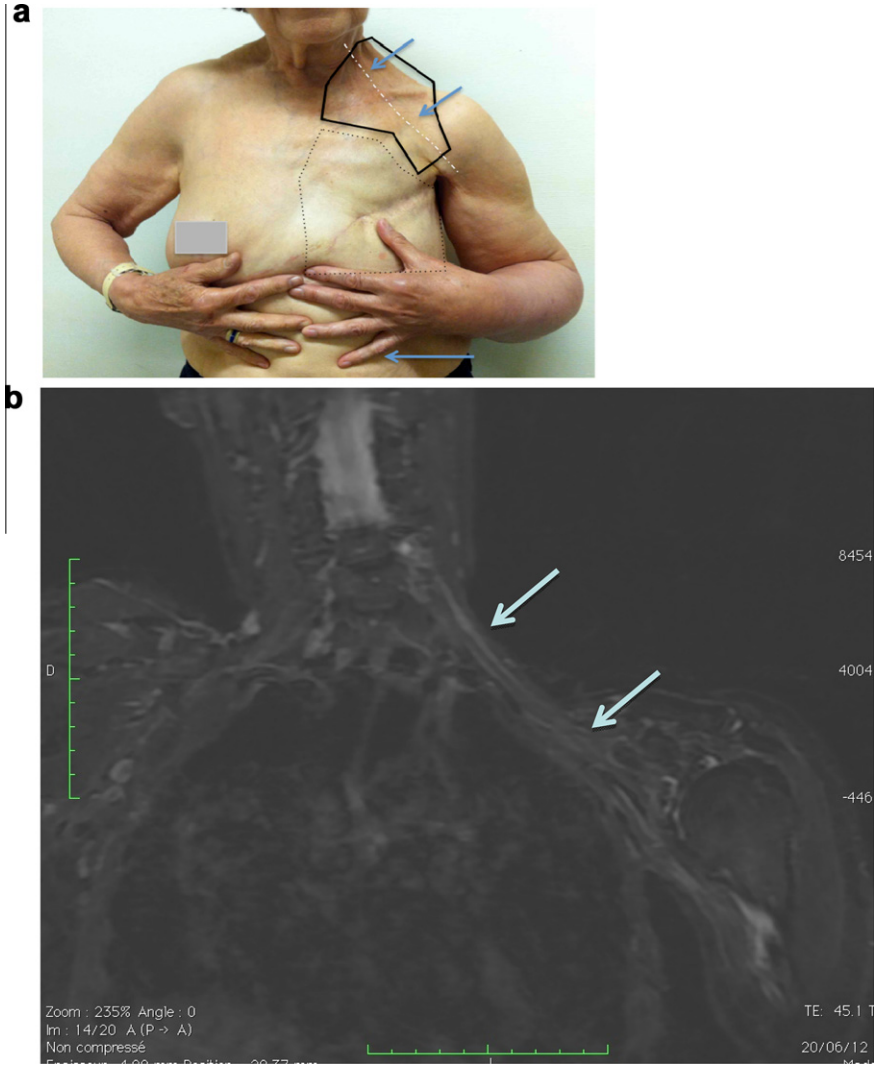

Fig. 2. Radiation-induced brachial plexopathy (RIBP): (2a) a 74-year-old woman with left breast cancer 41 years ago was treated by breast (RT field black dotted line) and axillary-supraclavicular (RT field black full line) irradiation followed by mastectomy: she developed arm lymphoedema, supraclavicular fibrosis and RIBP (plexus along the white dotted line) showing progressive sensory and motor upper limb signs for 4 years. (2b) Corresponding MRI in frontal view with supraclavicular and axillary compressive fibrosis without cancer recurrence.

be compression by fibrosis but also direct damage of myelin by RT: its role in the motor deficit may explain why in some cases there is a contrast between the severity or weakness and the absence of axonal loss, either clinically (absence of amyotrophy) or electrophysiologically. Myokymic discharges are of great diagnostic value when present as they are highly suggestive of a radiation-induced effect. The main differential diagnosis of axillary tumour is based on MRI (STIR sequence) (Fig. 2b) and PET-scan to rule out a tumour recurrence characterised by an intense hypermetabolic zone in the plexus and, if any, combined sites of metastatic cancer [13,46,47].

Early transient RIBP

Early transient RIBP occurring within the year following breast cancer irradiation is rare: 8 women with acute brachial plexopathy out of 565 in a range of 2–14 months after an average supraclavicular-axillary dose of 50 Gy in 1970s RT [48] and in 16 women with acute RIBP out of 1117. 80% of these acute RIBP completely resolved [49]. A case of transitory RIBP has been reported, after 43 Gy mantle irradiation for Hodgkin's disease, at one month (duration of symptoms 6 months) and at 17 months (duration of symptoms 6 months) with complete recovery [50]. Initial signs include distal paraesthesia with proximal pain. Moderate motor deficit occurs straight away or in the following months, with worsening. After 3 to 6 months of stability, neurological signs regress, often completely. The direct and transient effect on Schwann cells, which causes reversible demyelination, may be causal, as suggested by some experimental data [51], while another hypothesis concerns the role of compression caused by reversible radiation-induced oedema.

Ischaemic RIBP

Ischaemic RIBP is an exceptional neuropathy of sudden onset, with absence of secondary worsening. Only two cases of ischaemic RIBP following RT related to acute ipsilateral occlusion of the subclavicular artery have been reported [52].

Lower limb injury

Less known, lower limb RIPN is rare, and was first described after testicular irradiation.

Delayed progressive lumbosacral radiculoplexopathy (RILP)

The term lumbosacral radiculoplexopathy is preferred to lumbosacral plexopathy, which is used by analogy with brachial

Table 1
Chronic radiation-induced brachial plexopathy (RIBP) after shoulder girdle radiotherapy.

(1a) For breast cancer: incidence in large retrospective trials

Series Breast cancer [Ref.]	Supraclavicular-axillary RT: total dose (size: dose/fraction) [±reconstructed plexus dose]	RIBP incidence: number BP/total patients (%)	RIBP latency period (years) median
Stoll 66 [10] RT (1958–62) 2 series	(a) 63 Gy/12fr/25d (5.25 Gy/fr) Co [55 Gy] (b) 57.7 Gy/11fr (5.25 Gy/fr) [51] comorbidity: RM, compressive lymphoedema in 58%(a)25%(b)	(a) 24 BP/33 pts (73%) *complete paralysis and sensory signs in* 6 (b) 13 BP/84 pts (15%) *complete paralysis in* 1	(a) 14 mths (b) 19 mths 1.3 y (0.5–2.5 y)
Westling 72 [8] RT (1963–65)	44 Gy/11fr/23d (4 Gy/fr) isodose 130%/plexus. Axillar field with elevated arm [54] comorbidity: RM, lymphoedema	31 BP/71pts (44%) sensorimotor signs	3 y 1–4 y for 20 5–9 y for 8 10–22y for 6
Johanson 02 [12] RT (1963–68) 3 series	(a) 44 Gy/11fr/3wk (4 Gy/fr) [80] (b) 44 Gy/11fr (4 Gy/fr) Co-e^{-} [82] (c) 45 Gy/15fr (3 Gy/fr) Co-e^{-} [63] Gyeq in smaller field sizes comorbidity: RM	(a) 45 BP/71 pts (63%) (b) 11 BP/23 pts (48%) (c) 8 BP/56 pts (14%) *complete paralysis/150 pts: 30% at 5 y, 50% at 15 y, 67% at 30 y*	(a) 3y (1–19) (b) 4 y (1–12) (c) 5 y (1–18) (a) Incid 41%/y
Basso-Ricci 80 [31] RT 1965–72	RM 55 Gy/?fr/40d (>2 Gy/fr) [60]	16 BP/490 pts (3.2%) + others 26 BP drugs test (worse/vasodilators)	<2 y for 19 2–4 y for 10 >4 y for 13
Pierce 92 [45] RT (1968–85)	RT 2- or 3-field technique: 48–54 Gy/25fr (2–2.5 Gy/fr) [50] comorbidity: SM + CT	(a) 0 BP/507 pts 2-fields (b) 20 BP/1117 pt (0.2%) 3fields 16 acute + *chronic and severe in 4*	0.9 y (0.1*–6.4 y)
Rawlings 83 [32] RT 1967–74 RT 1967–74 RT 1969–80	45 Gy/18fr (2,5–3.3 Gy/fr) ± boost – exclusive RT [79] french technic – SM + RT [51] – BCS + RT [51] overlapping post field/supraclav	25 BP/1354 pts (1.8%) 9/245 (3.7%) for D > 60 Gy 11/650 (1.7%) 5/459 (1.1%) sensorimotor neurolysis in 6	0.5–10 y 3.5 y 4.5 y 3 y
Olsen 90 [29] RT (1977–82)	36.6 Gy/12fr/40d (3 Gy/fr); 2fr/wk comorbidity: SM (N dissection > 6), concomitant CT	(a) 28 BP/79 pts (35%) Mild in 13 Severe in 15	0.3*–5 y
Olsen 93 [30] RT (1982–90)	SM (11 nodes), sequential CT 50 Gy/25fr/38d (2 Gy/fr)	(b) 19 BP/161 pts (12%) Mild in 12 Severe in 7	Months?
Powell 90 [7] RT (1982–84) 2 series	SM or BCS + RT 3- or 4-field technique (80% isodose) pt turned (a) 51 Gy/15fr/6wk(3.4 Gy/fr) [46] (b) 60 Gy/30fr (2 Gy/fr) [54]	0 BP with 2 Gy/fr and 4-fields (a) 17 BP/338pts (5%)13BP/3-fd (b) 1 BP/111pts (3-fd)	0.8–4 y incidence 1.8%/y
Bajrovic 04 [28] RT (1980–93)	SM or BCS, sequential CT 60 Gy/20fr (3 Gy/fr) Co with [52] 2.6 Gy/fr plexus	19 BP/ 140 pts (14%) severe in 2% at 5 y; 5.5% at 10 y; 12% at 15 y; 19% at 19 y	7.3y (2.5–18 y) incidence 2.9%/y 5 y:4%; 10 y:25%

(1b) For breast cancer: incidence in case reports

Cases Breast cancer [Ref.]	Supraclavicular-axillary RT: total dose (dose/fraction)	RIBP incidence number BP/total patients	RIBP latency period (years) median
Pritchard 01 [39] RT 1970–95?	Various postoperative techniques with lymphoedema including R.A.G.E. patients *HBO test*	34 BP	3 y ⩽4 y for 20 5–9 y for 8 >10 y for 6
Kori 81 [36]	6000R? *neurological serie*	13 BP sensorimotor	<1 y for 4? >1 y for 9?
Roth 88 [41] RT 1973	59 Gy (2.5 Gy/fr) RM + carpal tunnel syndrome traumatic stretching disclosure *neurological series*	1 BP sensorimotor cramps, myokymia, pain, conduction blocks on EMG neurolysis (worse)	9 y
Fardin 90 [42] RT 1964–81	RM 50 Gy/30d (2.5 Gy/fr) *neurological series*	10 BP sensorimotor and progressive + 3 acute sensitive	7 y (3–15 y) ⩽8 mths for 3
Killer 90 [37]	? *Neurological series*	7 BP sensorimotor plexus surgery test	2 y (0.5–7)
Fathers 02 [43]	BCS 50 Gy/16fr (3 Gy/fr) *neurological series*	33 BP sensorimotor and proximo/distal *time to hand weakness : 1.2 y (0.2–5 y)*	1.5 y 0.5–20 y

(continued on next page)

Table 1 (continued)

(1c) For head-neck and lung cancers, for Hodgkin's disease

Irradiated cancer	Series/cases [Ref.] RT date	Supraclavicular-axillary RT: total dose, dose/fraction [±plexus dose]	RIBP incidence nb BP/total (%)	RIBP latency period (years) median
Hodgkin disease	Pezzimenti 73 [35]	Subclavicular ± salvage	2 BP	0.2 y
	Kori 81 [36]	?	3 BP	?
	Killer 90 [37]	? + lymphoedema in 3/5	5 BP sensorimotor	Median 6 y (2–18 y)
	Wadd 98 [38]	40 Gy/20fr mantle RT ± salvage lumbar RT/chemotherapy	2 BP nilat or bilat sensorimotor	12–19 y
Lung apical Ca	Kori 81 [36]	?	3 BP/lung Ca 2 BP/thyroid Ca	
	Forquer 08 [33]	57 Gy (18 Gy/fr) 3–4fr/8d SBRT stereotaxic	7 BP/37 pts (19%)	Median 0.6 y (6–23 mths)
Head Neck Ca	Chen 10 [34] RT (2007–10)	69 Gy [63–78] exclusive or IMRT postoperative [Dmax > 74 Gy]	22 BP/145 pts (15%) sensorimotor	Median 1.5 y (6–30mths)

RM, radical mastectomy with extended lymph node dissection; SM, simple mastectomy with lymph node dissection levels I–II; BCS, breast conserving surgery with lymph node dissection levels I–II; CT, adjuvant chemotherapy; Co, cobalt 60; Gy, gray; d, day; fr, fraction; 3-fd, three-field technique (with patient move and overlap risk); y, year.
* means: acute BP.

plexopathy, but does not correspond to the clinical reality of the anatomic lesions that simultaneously affect in a given volume the lumbosacral spinal cord, the nerve roots, the lumbosacral plexus and the large nerve trunks.

Some 75 RILP cases of the lower limbs (Table 2a) have been reported in a range of 0.4–25 years after external RT for testicular cancer [11,53–63] and a range of 1–24 years after RT for lymphoma [3,13,59,62,64–67]. The current "over-representation" of Hodgkin's disease seems to be related to the efficacy of older treatments. These survivors are then susceptible to late-onset neuropathy, delayed further because the total irradiation dose was moderate (40–45 Gy using 2 Gy/fr) but sufficient to be toxic, given the large field volume covering the lumbo-aortic, iliac and inguinal lymph node chains, emphasising the importance of the volume of nerve irradiated in generating radiation-induced neuropathies (Fig. 3).

After pelvic RT (Table 2b) with more than 60 Gy, RILP cases include 24 after RT for cervical carcinoma with intracavitary radium, comorbidities or combined extensive node dissection [13,14,68–73], and cases for rectal [74,75] and bladder cancers [70]. In a long-term follow-up after a median dose of 73 "Gy-equivalents" in RT for retroperitoneal-paraspinal sarcomas, 13 out of 53 patients (25%) developed neurotoxicity in a mean time of 7 years [76]. Intraoperative radiotherapy (IORT) has yielded substantial experimental and clinical data. The high risk of RILP of sciatic and femoral nerves limits this technique because of the perioperative delivery of RT in a single high-dose fraction.

RILP occurs earlier after high-dose RT in a moderate volume and later with moderate doses in a large volume. Although irradiation was delivered around the body median line, the usual neurological deficits are bilateral and asymmetric with initial unilateral damage [59]. The onset of neurological signs is insidious, with damage that is largely motor [58]. Unlike RIBP, the sensory signs and paraesthesia are absent or noted very late, in contrast to signs of peripheral neurogenic motor involvement, such as amyotrophy and fasciculations. Central signs are lacking, apart from possible associated medullar damage, and the handicap progresses in severity after a few years. Subcutaneous paraspinal muscle atrophy often corresponds to the previous RT volume (Fig. 3a). Sudden worsening of the neurological deficit associated with lumbar pain may indicate vertebral compression with underlying radiation-induced vertebral osteoporosis, notably following a fall because of walking difficulties. Intestinal and/or urinary disorders are associated after pelvic RT, either by peripheral neurogenic damage or by pelvic fibrosis. Disease progression generally proceeds step-wise, with periods of stabilisation. Diagnosis, which is often difficult, requires neuroradiological examinations to rule out tumour invasion or narrowing of the lumbar canal [13]. In the case of pure motor forms, the main differential diagnosis is amyotrophic lateral sclerosis: it is not rare for this initial diagnosis to be questioned because there is no rapid progression of the motor deficit to new territories or the appearance of pyramidal syndrome. Electroneuromyography objectifies anomalies that usually affect several nerve roots, while the sensory potentials are preserved. Decrease in sensory potentials may be caused by radiation-induced damage to lymph nodes, but may also reflect sequelae of chemotherapy with cisplatin or taxol. Myokymia, as in RIBP, may indicate a radiation-induced origin [65]. Lumbar MRI usually shows lesions of osteoporosis of the vertebral bodies, which confirms that the adjacent nerve roots were included in the field of RT. MRI does not play a determinant role in a positive diagnosis, but does eliminate tumour invasion or lumbar canal stenosis (Fig. 3b): nodular enhancing lesions suggest leptomeningeal metastases. Biopsy of the nerve root of the cauda equina shows fibrotic lesions and vascular dilation corresponding to cavernomas [4]. Recently, a new technique of *a posteriori* conformal RT with 3D-dosimetric reconstitution has been used to confirm diagnosis of RILP of the lower limbs, and defines the anatomical regions that have received a high radiation dose. In one report, a patient had developed a pure, progressive motor deficit of the lower limbs, which was initially diagnosed as amyotrophic lateral sclerosis; 3D-dosimetric reconstitution showed that the spinal cord and the lumbosacral nerve roots had in fact received an unplanned dose of 52 Gy along a 7 cm segment [3].

Acute transient lumbosacral plexopathy

Transient lumbosacral plexopathy was recently described following L-field (12th thoracic–5th lumbar vertebrae) RT for testicular cancer, after mild RT doses in 11 out of 346 patients. Seven patients presented with bilateral paraesthesia, which lasted less than three months, in the 6 months after RT using a median total dose of 25 Gy, and four patients showed weakness lasting at least one year, in a range of 3–9 years after a total dose of 36–40 Gy [77]. As described for transient RIBP, symptoms worsened over a few months, then stabilised before regressing, often completely. A few single cases have been reported after pelvic or lumbar RT with 45–55 Gy [13,75].

Table 2
Chronic radiation-induced radiculoplexopathy (RILP) after lumbo-pelvic girdle radiotherapy.

Irradiated cancer (total)	Series/cases [Ref.] RT date	Lumbo-sacral (volume) radiotherapy total dose, dose/fraction, [±plexus dose]	RIRP incidence number/total patients (%)	RIRP latency period (years) median
(a) Low and moderate dose levels in extended volume irradiation for testicular cancer and Hodgkin's disease				
Testicular Ca (n = 54)	Maier 69 [11]	Retroperitoneal node dissection	15 RP motor/313pts (5%)	Mean 2y (0.4–13 y)
	Greenfield 48 [63] RT (1944–65)	lumbo-iliac [T_{11}–L_4] 200 KV #48–53 Gy/12 wk		
	Schiodt 78 [53] RT (1965–74)	>55 Gy/6 wk lumbar [T_{11}–L_5] Cobalt	5 RP/99pts (5%) alive/156 treated + 5 acute*	Mean 1.5 y mean 4 mths
	Grunewald 92 [54] RT (1964)	49 Gy (1.4 Gy/fr)/7 wk lumbar + pelvis	1 RP motor	23 y
	Kristensen 77 [55] RT (1968–75)	#55 Gy/6 wk lumbar [T_{11}–L_5] 6 MV	4 RP motor	0.4–1.3 y
	Knap 07 [56] RT (1964–73)	36–51 Gy (3 Gy/fr) [#60] lumbar and 59 Gy (2 × 1.6 Gy/d) in 1 pt	6 RP/94pts (6%) + 1 acute * ± 9 mixte	14 y (10–20 y) 9 mths ?
	Horowitz 83 [57] RT 1977	25 Gy lumbar-pelvis + salvage 30 Gy postop coeliac and CT	1 motor	0.7 y/2nd RT 2 y/1st RT
	Feistner 89 [58] RT (1977–82)	45 Gy (2–3Gy/fr)/3–4 wk lumbar + iliac/mediastine	3 RP motor	3–9 y
	Lamy 91 [59] RT (1970)	30 Gy lumbar and 30 Gy mantle	1 RP motor	12 y
	Bowen 96 [60] RT (1966–88)	40–50 Gy (1.7–2.2 Gy/fr) lumbar T_{10}–L_4 ± iliac/mediastine	6 RP motor	Mean 11 y (3–25 y)
	Tallasken 97 [61] RT (1981–84)	36 Gy (2 Gy/fr)/3.5 wk lumbar + salvage 32 Gy/4 wk (0.9 Gy/fr)	1 RP motor	0.8 y/2nd RT 3.8 y/1st RT
	Mathis 07 [62] RT (1983)	Dose? mantle–lumbar RT	1 RP motor	13 y
Hodgkin's disease (n = 20)	DeGreve 84 [64]	40 Gy/4 wk (2 Gy/fr) mantle + lower-diaphragmatic	1 RP acute*	1.8 y regressive after 5 mths
	Thomas 85 [13] RT (1965–83)	40–50 Gy lumbar (2 Gy/fr)	5 RP	Median 5 y
	Lamy 91 [59] RT (1974–82)	40 Gy mantle + lower-diaphragmatic	2 RP motor	1.5–9 y
	Lalu 98 [65]	>40 Gy mantle + lower-diaphragmatic	4 RP motor	Mean 16.5 y (6–24 y)
	Hsia 03 [66] RT (1978–84)	mantle 50 Gy + lower-diaphragmatic 44 Gy	3 RP motor	17–24 y
	Mathis 07 [62] RT (1975–96)	40–44 Gy/16fr (2.5 Gy/fr) mantle + lower-diaphragmatic	2 RP motor	8.5–21y
	Delanian 08 [67] RT (1985–88)	36–40 Gy (2 Gy/fr) mantle + lower-diaphragmatic co-morbidity	2 RP motor	9–10 y
	Delanian 10 [3] RT (1993)	45 Gy (2 Gy/fr) mantle + lower-diaphragmatic heterogeneity in volume [#52]	1 RP motor	10 y
(2b) High dose level in lumbo-pelvic volume irradiation for pelvic cancers				
Gynaeco-logical Ca (n = 24)	Aho 1983 [64] RT (1964–68)	Hysterectomy-node dissection + 50 Gy pelvis + radium ± 34 Gy parameter (1pt/2)	2 RP motor	8–14 y
	Georgiou 93 [65] RT?	50 Gy pelvis [#73 sacral] + 30 Gy radium (brachytherapy)	4 RP motor/2410pts (0.15%)	0.8*–2 y
	Ashenhurst 77 [13] RT 1969	40 Gy/14fr (2.85Gy/fr) pelvis + radium cervix 67 Gy/T [#82 ptA]	1 RP sensorimotor	0.5 y
	Pettigrew 84 [66] RT (1970–79)	50 Gy pelvis + radium [#80]	2 RP motor	3.5–11.5 y
	Thomas 85 [12] RT (1965–83)	>50 Gy (2–3.5Gy/fr) pelvis ± radium	9 RP sensorimotor	Mean 5 y
	Glass 85 [67] RT 1972	40 Gy pelvis [#80] + radium (lateral deviation)	1 RP unilateral	12y
	Saphner 89 [68] RT 1972–86	Uterine RT technique?	2 RP motor/1219pts (0.15%)	0.8 y*–14 y
	Stryker 90 [69] RT 1973–84	Lumbar node dissection 51 Gy/30fr (1.7Gy/fr) pelvis L_4–L_5 + 36 Gy/ptA brachytherapy (caesium)	1 RP/313 pts sensorimotor	1 y
	Lalu 98 [61]	⩾45 Gy lumbar + pelvic ± brachytherapy	2 RP sensorimotor	9–15 y
Rectal Ca	Frykholm 96 [70] RT 1979–93	25 Gy/5d (5 Gy/fr) 3 post fields	4 RP/443 pts 5 RP/59 pts	<1 y
	Dahele 06 [71]	Comorbidities (postop/CT/age): + 45 Gy + diabetes/rectal Ca + 55 Gy/anal Ca	2 RP motor	0.4 y*

(*continued on next page*)

Table 2 (*continued*)

Irradiated cancer (total)	Series/cases [Ref.] RT date	Lumbo-sacral (volume) radiotherapy total dose, dose/fraction, [±plexus dose]	RIRP incidence number/total patients (%)	RIRP latency period (years) median
Sarcoma	Pieters 06 [72]	Combined RX-protons in (L_2-coccyx) [# 73 CGE Gy équivalents]	13 RP/53 pts (25%)	5 y
Bladder Ca	Ashenhurst 77 [13] RT (1965)	Alternated fx 67 Gy/24fr (2.8 Gy/fr)	1 RP sensorimotor	4 y

* Early transitory neurological symptoms followed by partial recovery.

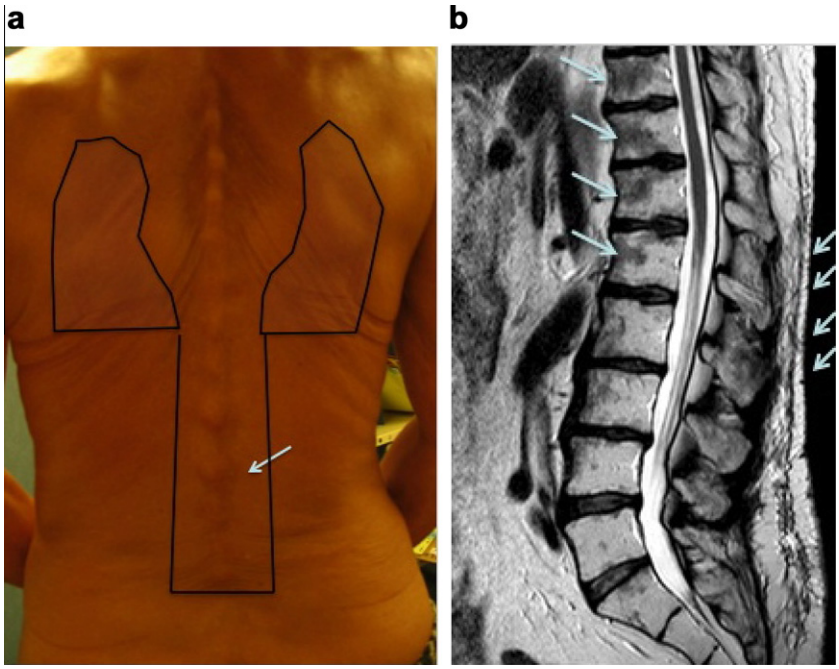

Fig. 3. Lower limb radiation-induced radiculoplexopathy (RILP): (3a) clinical history: this 51-year-old man treated by 40 Gy total lymphoid irradiation for Hodgkin's disease, 26 years ago, has RILP corresponding to lumbar muscle-subcutaneous atrophy (RT field black full line); (3b) corresponding MRI in sagittal view with subcutaneous atrophy (arrow), pagetoid vertebra (arrow), without cancer recurrence.

Nerve trunk damage

The most common aetiology of neuropathy after lower limb irradiation is tumour recurrence and radiation-induced fibrotic compression, best discriminated by MRI. Severe isolated cases of radiation-induced injury of the nerve trunk (sciatic, crural) after external irradiation of the thigh have been reported [78]. In one case, *a posteriori* 3D-dosimetric reconstitution identified risk factors such as irradiation (66 Gy) over a 25 cm stretch of a nerve and large surgical sarcoma resection of the thigh, exposing the sciatic nerve at the surface of the irradiated volume [79]. In another case, salvage RT (30 Gy) overlapped the volume irradiated postoperatively (50 Gy) one year before. Other cases of RIPN have been reported in the long-term follow-up to conservative treatment of extremity sarcomas: with brachytherapy implants in four cases (9%) at 6–20 months [80]; after 20 Gy single-dose boost electron IORT in combination with external 45 Gy RT in nine out of 15 patients at 10 years [81]; after 15 Gy IORT in 24 out of 195 survivors at 94 months [82]. Moreover, indirect femoral nerve paresis by scar tissue compression has also been described in patients irradiated along the inguinal region and thigh nerve trajectory [83,84].

RIPN treatments

In today's clinical practice, RIPN treatment is symptomatic. A curative strategy has yet to be defined; however the best approach is always prevention in respect of RT limits [85] by reducing total RT dose, dose per fraction and RT volume every time if possible, while identifying patients with serious comorbidities.

Symptomatic treatment

Pain, if any, is usually treated with non-opioid analgesics, benzodiazepines, tricyclic antidepressants and anti-epileptics. Benzodiazepines are used for paraesthesia and quinine for cramps. Membrane-stabilising drugs (carbamazepine) may reduce nerve hyperexcitability, like myokymia. Neurolysis is an additional surgical manipulation that can worsen nerve wall ischaemia, whereas mechanical separation from compressive fibrosis may in theory release trapped nerves; and surgical methods have never proven useful in the management of RIPN. Vitamins B1–B6 are often used routinely, but detailed data are lacking. Physical therapy is valuable in maintaining function and preventing joint complications, which cause pain and hamper movement. It is important to prevent any stretching of a plexus immobilised by fibrosis, notably by avoiding the carrying of heavy loads and extensive movements, which are likely to cause sudden neurological decompensation.

Restriction of aggravating factors

Removal of inciting stimuli is helpful in controlling the progression of RIPN [85]. First, *removing co-morbidity factors* by (i) general

measures as controlling diabetes and high blood pressure; (ii) stopping alcohol abuse, avoiding fibrogenic drugs and statins (potential neuromuscular toxicity); and (iii) by local measures consisting in avoiding any local trauma in the irradiated volume, such as new surgery or biopsy (haematoma, infection). Second, *controlling acute inflammation* with corticosteroids, which are of value in reducing the acute inflammation associated with RIF and should first be used to circumscribe the fibrotic volume and density, despite lack of any objective efficacy in reduction of fibrosis and nerve lesions [86,87].

Disease-modifying agents

The literature is poor concerning the treatment of RIPN.

Vascular approach

Evidence for the benefit of hyperbaric oxygen (HBO) in RIF is not apparent [85,88] and the literature is dominated by small trials with ill-defined recording of complications. HBO reduces tissue oedema and stimulates angiogenesis, fibroblast proliferation and collagen formation in irradiated hypoxic tissue, which paradoxically may enhance fibrotic properties. In a study of 32 women who underwent breast-conserving irradiation and 12 controls, after 25 HBO sessions and median follow-up of 9 months, significant reduction in pain, oedema and erythema was observed, but fibrosis and telangiectasia were not affected [89]. There was no evidence that HBO was clinically beneficial in 34 patients with RIBP at 12 months of follow-up, although it may improve the warm sensory threshold [39]. Because of vascular changes and ischaemia, heparin and warfarin have been used in an attempt to halt progression of radiation necrosis [90].

Fibrosis/atrophy

Although pathogenesis of RIPN initially involves vascular mechanisms, fibrosis and atrophy are the main targets for therapeutic interventions. It has been known for two decades now that combined pentoxifyllin-tocopherol (PE) significantly reduces RIF due to their synergistic clinical and biological properties [91,92]. In a series of patients treated with PE for superficial fibrosis, 8 patients with RIBP showed neurological symptom stabilisation, but no improvement at 18 months [85]. More recently, 10 out of 11 patients treated for cerebral radionecrosis after stereotactic RT showed significant improvement after PE combination [93]. Clodronate, a bisphosphonate, inhibits osteoclastic bone destruction with anti-inflammatory effects, and inhibits macrophagic myelin nerve destruction in rats [85]. Recently, clodronate, when combined with pentoxifylline-tocopherol (PENTOCLO), healed 54 patients with refractory osteoradionecrosis in a median of 9 months [94]. Moreover, neurological symptoms were reduced by half in two patients with progressive RILP after 3 years of PENTOCLO treatment [67], results that have led to an ongoing phase III randomised clinical trial in France (NCT01291433).

Conclusion

Knowledge of RIPN complications has improved and we can now distinguish sub-types and unravel the complex pathophysiology. However, more systematic descriptions of the epidemiology and history of these neuropathies are required, and we need longitudinal studies in large cohorts of patients. Diagnostically, progress in structural and functional imaging techniques has enabled better differentiation between radiculopathy and a recurrent tumour. Improved understanding and earlier diagnosis of these complications, before the lesions become progressive and irreversible, is particularly important given the recent emergence of new therapeutic leads. Cancer patients are surviving for many years and so the management of late treatment-related complications that reduce their quality of life has become a public health priority.

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