ANTICANCER RESEARCH *38*: 4977-4985 (2018)
doi:10.21873/anticanres.12816

Review

Whole Lung Irradiation in Patients with Osteosarcoma and Ewing Sarcoma

LETIZIA RONCHI[1], MILLY BUWENGE[1], ANNALISA CORTESI[2], ILARIO AMMENDOLIA[1], REZARTA FRAKULLI[1], MASSIMO E. ABATE[3], ALESSANDRA ARCELLI[1], COSTANZA M. DONATI[1], GABRIELLA MACCHIA[4], ALESSIO G. MORGANTI[1*] and SILVIA CAMMELLI[1*]

[1]*Radiation Oncology Center, Department of Experimental, Diagnostic and Speciality Medicine –DIMES, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy;*
[2]*Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) S.r.l. Sede legale, Meldola, Italy;*
[3]*Chemotherapy Section, Istituto Ortopedico Rizzoli , Bologna, Italy;*
[4]*Radiotherapy Unit, Department of Oncology, "Giovanni Paolo II" Foundation, Catholic University of Sacred Heart, Campobasso, Italy*

Abstract. *Background/Aim: Whole lung irradiation (WLI) represents standard therapy for patients with pulmonary metastases from Ewing sarcoma although the impact on clinical outcomes and toxicity is still unclear. The aim of this study was to evaluate toxicity after WLI in patients with Ewing sarcoma and osteosarcoma as well as overall survival (OS) and event-free survival (EFS). Materials and Methods: A systematic review of studies on bilateral pulmonary irradiation treatments for prophylactic or curative therapy was performed based on PRISMA methodology. Data base searches on PubMed and Cochrane Library from the earliest time possible through 31st March 2018 were carried out. Combination with other treatments, such as chemotherapy and surgery were allowed. Only articles published in English were considered. Results: Toxicity was evaluated in 13 of the 14 analyzed studies (640 patients). Reported lung acute toxicity grade ≥3 ranged between 0.0 and 12.2%. Three studies reported 12 cases (1.8%) of severe pneumonitis. Grade ≥2 late toxicity was mainly recorded in patients who received boost irradiation, previous thoracic surgery, chemotherapy or who were smokers. Lack of a significant impact of WLI on OS was reported in comparative studies although patients treated with WLI showed higher survival in most individual studies. Conclusion: Although the rate of severe toxicity was very low, the real impact of WLI on patients' outcomes remains unproven, probably due to the narrow dose limits that can be delivered to the whole lung parenchyma. New strategies to prevent or treat lung metastases in these patients should be tested. Ultra-fractionated radiotherapy concurrent with modern chemotherapy protocols could be tested in this setting due to the chemo-sensitizing effect and negligible radio-induced toxicity of fraction doses <0.5 Gy.*

*These Authors contributed equally to this study.

Correspondence to: Milly Buwenge MSc, Department of Experimental, Diagnostic and Speciality Medicine – DIMES, University of Bologna, S. Orsola-Malpighi Hospital, via Giuseppe Massarenti 9, 40138, Bologna, Italy. Tel: +39 0516363136, Fax: +39 0516364336, e-mail: mbuwenge@gmail.com.

Key Words: Whole lung, Ewing, sarcoma, radiation therapy, review.

Primary bone and joints malignancies are ranked as the third leading cause of cancer-related death in patients younger than 20 years old and account for approximately 0.2% of all malignancies (1). From 0.9 (United States) to 1.44 (China), new bone tumor cases are diagnosed per 100,000 persons/year (2, 3). In 90% of cases, primary bone tumors are diagnosed in children and young adults (2), and the lung is the most common site of metastatic involvement followed by bone (3).

Whole lung irradiation (WLI) has been demonstrated beneficial in several pediatric tumors with propensity for lung metastases (3). Furthermore, WLI has been pivotal since 1969 in the treatment of lung metastases for patients with primitive bone sarcoma and particularly Ewing Sarcoma (ESa) (4) despite reported severe toxicities (5, 6). Two initial randomized trials in the pre-chemotherapy (CT) era showed improved outcomes with WLI (7, 8). Subsequently, the results of the EORTC/SIOP (7) phase III trial which enrolled 240 patients with localized bone sarcoma randomized in

three arms: CT, WLI (20 Gy), or both were published. No significant differences between arms were reported in terms of outcomes (7). Based on these results, WLI was progressively less used as reported in a non-systematic narrative literature review published in 2002 (9).

However, WLI is still included in international guidelines as a treatment option in patients with pulmonary metastases from ESa despite conflicting results (8, 10, 11) of randomized trials. Therefore, the aim of this study was to systematically review, based on the PRISMA methodology (12), the available evidence on WLI results in terms of treatment-related toxicity and clinical outcomes.

Materials and Methods

Inclusion criteria. Prospective and retrospective studies on WLI as curative, palliative, or prophylactic therapy were included. Only studies enrolling patients with sarcoma of the bone (ESa or osteosarcoma (OSa)) with or without pulmonary metastases at time of diagnosis were included in this analysis. Studies on WLI combined with CT and/or surgery were not excluded. Less than 10 study participants, case-reports, editorials, letters, reviews and planning studies were excluded. Only studies published in English were considered. Furthermore, external beam radiotherapy (RT) studies irrespective of technique, dose and fractionation that targeted both lungs were assessed for inclusion. Concurrent or sequential and single or multiple drug CT regimens were eligible. Up-front metastasectomy or metastasectomy of lung nodules not completely responding to WLI +/– CT was allowed.

Outcome measures. The primary outcome was treatment-related lung toxicity. The secondary objectives were pulmonary functional test (PFT), event-free survival (EFS), pulmonary relapse rates (PRR) and overall survival (OS).

Search methods for identification of studies. Literature search in PubMed database and Cochrane Library to select studies up to 31st March 2018 was performed. PubMed search details were (whole [All Fields] AND ("lung"[MeSH Terms] OR "lung"[All Fields]) AND ("radiotherapy"[MeSH Terms] OR "radiotherapy"[All Fields] OR "irradiation"[All Fields])) AND ("sarcoma"[All Fields] OR "Ewing"[All Fields]).

Trial selection and quality assessment. Titles and abstract screening, selection of studies, full text retrieval and data extraction were independently carried out by two authors (LR, AC) and any disagreements were resolved by the senior author (AGM). The following data from each study were obtained: authors and year of publication, medical center, Country, number of patients, median RT dose and fractionation, inclusion criteria, CT regimens, surgical treatment of metastases, PFT, risk factors related to lung toxicity, lung acute and late toxicity, EFS, PRR, and OS. Quality assessment of the selected studies was performed using the Cochrane Risk of Bias (ROB) tool.

Our systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) on April 2017 (registration number: CRD42017062604).

Results

Description of studies. From the literature search, 107 studies were from PubMed, 25 from Cochrane library and 5 from other manual searched reference lists. A total of 14 full text articles including 696 patients met the established inclusion criteria and were analyzed (Figure 1). The studies were mainly conducted in Europe and USA. Five studies were randomized controlled trials (7, 8, 10, 11, 13), 3 were phase I/II studies (5, 14, 15), 3 were phase II trials (16-18) and 3 were retrospective series (19-21). Three studies (17, 18, 22) were considered at low risk of bias while 6 studies were considered at high to serious risk of bias (5, 7, 10, 11, 15, 16).

Type of Interventions

Radiotherapy. In ten studies (7, 8, 10, 11, 14, 16-20), total RT prescribed doses ranged from 12 to 20 Gy in daily dose per fraction between 1.5 to 2.0 Gy using LINACs or Cobalt-60 units. Two studies (19, 20) reported different fractionation of 1.25 and 1.5 Gy delivered twice a day in some patients. Marinova and colleagues reported 12-15 Gy total RT dose delivered to bilateral lungs adapted to children's age without mentioning dose per fraction (21). In one study, WLI was administered with a total dose ranging from 22.5 to 27 Gy delivered in 6-16 weeks (13). WLI aim was prophylactic in 10 trials (7, 8, 10, 11, 13, 14,16-18) and curative in 4 series (5, 15, 19, 20). Air correction for increased radiation transmissibility was performed in two studies (7, 16). Air correction was not carried out in 3 studies (8, 18, 21) and this issue was not mentioned in the other papers.

Chemotherapy. Different multidrug schedules were used: (i) mitomycin C, vincristine, doxorubicin, dacarbazine and cyclophosphamide (18); (ii) high-dose methotrexate, vincristine, mitomycin C, doxorubicin, dacarbazine and cyclophosphamide (16); (iii) cyclophosphamide, doxorubicin, and methotrexate (7); (iv) vincristine, doxorubicin, cyclophosphamide, etoposide, ifosfamide and doxorubicin (5, 10, 19, 20); (v) vincristine, doxorubicin, cyclophosphamide and actinomycin D (21); (vi) cisplatin with doxorubicin or epirubicin or etoposide (13).

High-dose CT with busulfan and melphalan as consolidation treatment before WLI was used by Luksch and colleagues (15) and Paulussen and co-authors (5). Three studies reported a single agent regimen using actinomycin D (11) or doxorubicin (14, 17). One study did not mention the use of CT (8).

Surgery. Metastasectomy of lung nodules was performed before WLI in 2 studies (5, 15). In 2 studies it was not specified if surgery was performed before or after WLI (7, 19). Improved OS was reported after metastasectomy in one study (p=0.0002) (7) while EFS was similar in patients with or without pulmonary surgery (p=0.411) in another study (5).

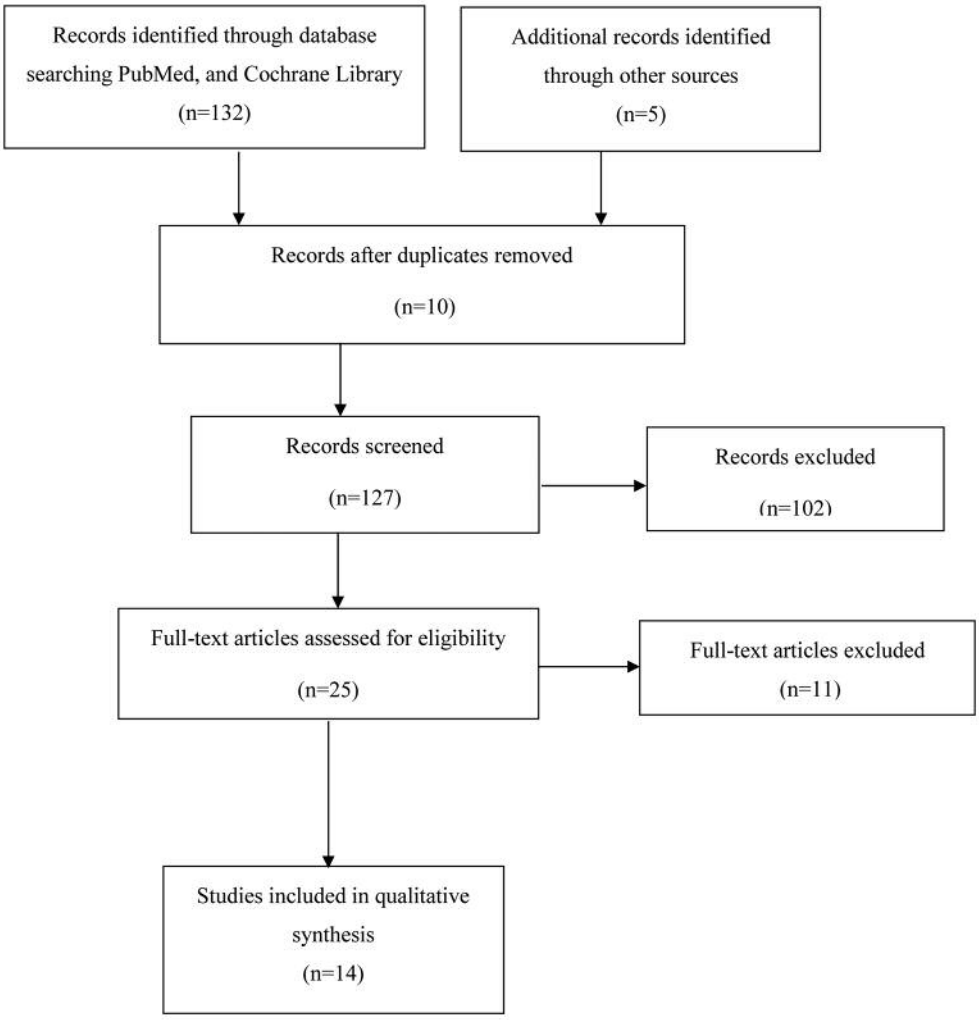

Figure 1. *Process of article selection.*

Toxicity. All but one paper (10) analyzed toxicity (640 patients). Table I shows the toxicity results in more details. Reported lung acute toxicity grade ≥3 ranged between 0.0 and 12.2% (5, 7, 8, 10, 11, 13-16, 18-21). Toxicity scales were not reported in all but 2 studies (7, 18). From our analysis, clinical mild and moderate dyspnea and cough were reported in 6 studies including 29 (4.5%) patients (5, 15, 16, 18-20). Three studies reported 12 cases (1.8%) of severe pneumonitis (5, 15, 19). In 2 studies increased toxicity compared to the rest of the study population were reported in active smoker patients (16, 20). No skeletal deformities or growth retardation were reported in any paper.

Pulmonary Function Tests. PFTs were performed in 10 studies including 217 patients (5, 7, 14-21) (Table I). Normal tests were reported in 3 studies ranging between 40.5 and 100% (17, 19, 21). Restrictive disorders were reported in 6 studies ranging from 19.0 to 100% (5, 14-16, 18, 20). Late lung function impairment was reported in one study in 14.3% of patients (7) and one study recorded severe impairment in 10.8% of patients (19). None of the studies reported the used modalities and timing to evaluate lung impairment. In 3 studies (5, 8, 15) only partial data were reported regarding PFTs. Breur and co-workers stated that PFTs were optional and performed only in a small number of patients in whom no clinical evidence of decreased pulmonary function was found (8). In one series with 75 patients, restrictive lung disease was reported in 7 (9.3%) patients and one case of restrictive defect with less than 50% of vital capacity was reported in 1 (1.3%) patient who received RT boost (5). In another series with 70 patients, 3 restrictive syndromes three months after WLI were recorded as severe and moderate in 1 and 2 patients, respectively. The authors reported a preexisting mild restrictive syndrome worsening after WLI in 1 case (15).

Table I. *Toxicity.*

Authors (year)	Medical center	WLI patients	Median dose, Gy (Gy/Fract)	Boost N (Gy)	Chest/lung surgery N	Chemotherapy	Pulmonary function tests N n results	Pulmonary function tests % toxicity %	Risk factors related to lung	Lung acute toxicity G ≥3%
Rab (1976) (11)	Mayo Clinic, Rochester, USA	26	15 (1.5)	0	0	A	n.r.	n.r.	n.r.	0.0
Breur (1978) (8)	A. van Leeuwenhoek Hospital, Amsterdam, The netherlands	44	17.5 (1.75)	0	0	No	n.r.	n.r.	n.r.	0.0
Razek (1980) (10)	Radiation Oncology, Washington, USA	56	15 (1.5)	0	0	V-A-C +/– D	n.r.	n.r.	n.r.	n.r.
Jasmin (1982) (16)	Hopital Paul Brousse, France	21	17.5 (1.75)	0	0	MTX-V-M; D-C; Da	21	Restrictive: 19.0	Smoker: 4.8 Polychemo-therapy + WLI: 4.8	0.0
Zaharia (1986) (17)	Instituto Nacional Neoplasicas, Lima, Perù	36	20 (1.5)	0	0	D	6	Normal: 100	n.r.	0.0
Trifaud (1988) (18)	French Bone Tumor Study Group, France	41	20 (2)	0	0	M-C-V-MTX; V-Da	41	Normal: 0.0	n.r.	12.2
Burgers (1988) (7)	Netherlands Cancer Institute, Amsterdam, The Netherlands	140	20 (2)	0	0	C-D-V-MTX	56	Late lung function impairment: 14.3	n.r.	0.0
Ellis (1992) (14)	University of Florida College of Medicine, Gainesville, USA	57	16 (1.6)	0	0	D	28	Restrictive: 100	n.r.	0.0
Pochanugool (1997) (13)	Ramathibodi Hospital Mahidad University, Bangkok, Thailand	36	24.8§ (n.r.)	0	0	C +D or E or Epirubicin	n.r.	0.0	n.r.	0.0
Paulussen (1998) (5)	Munster University, Germany	75	15-18 * (n.r.)	1 (45)	20	BuMel; V-D-C-A-E	8	Restrictive: 100	n.r.	5.3
Bolling (2008) (19)	Munster University, Germany	70	12-21 * (1.5)	13 (50-54)	12	V-D-I-A E-V-D-I-A	37	Normal: 40.5 Mild: 24.4 Moderate: 21.6 Severe: 10.8	Thoracic surgery: 66.7	7.1
Luksch (2012) (15)	Italian and Scandinavian, Sarcoma Group	57	15.0 (1.5)	0	6	V-D-C-E-BuMel	4	Restrictive: 100	n.r.	1.8
Casey (2014) (20)	Sloan Kettering Cancer Center, New York, USA	26	15 (1.5)	2 (45) 1 (21)	1	V-D-C-I-E	5	Restrictive: 20.0 Reductions residual volume: 40.0 Interstitial disorder: 40.0	Smokers: 73.0 Non-smokers: 36.0	0.0
Marinova (2015) (21)	Medical University, Varna, Bulgaria	11	12-15 * (n.r.)	0	0	V-A-C-D	11	Normal: 100	n.r.	0.0

A: Actinomycin; BuMel: busulfan and melphalan; D: doxorubicin; Da: dacarbazine; E: etoposide; I: ifosfamide; LT: lung toxixity, M: mitomycin C; MTX: methotrexate; V: vincristine; m: months; N: number of patients; n.r.: not reported; Ref: Reference; *dose given in range only; §mean dose.

Table II. *Outcome in studies on prophylactic WLI in osteosarcoma.*

Authors (year)	Medical center	Number of patients	Median age (years)	Median WLI dose (Gy) (fractionation)	Chemotherapy	Event-free survival	Pulmonary relapse rate	Overall survival
Jasmin (1982) (16)	Hopital Paul Brousse, France	21	15	17.5 (1.75)	MTX-V- M-D	16 m: 80%	11 m*: 11.1%	16 m: 90%
Zaharia (1986) (17)	Instituto Nacional Enfermedades Neoplasicas, Lima, Perù	29	15.3	20.0 (1.5)	D	372 d*	n.r.	843 d*
		6	15.3	20.0 (1.5)	no	118 d*	n.r.	241 d*
Trifaud (1988) (18)	French Bone Tumor Study Group, France	41	18-23	20.0 (2.0)	M-C-V-MTX V-Da	1 y: 87%; 2 y: 70% 3 y: 58%	60.6 m*: 100%	1 y: 95%; 2 y: 75%; 3 y: 61%

A: Actinomycin; D: doxorubicin; C: cyclophosphamide; MTX: methotrexate; M: mitomycin; n.r: not reported; V: vincristine; Da: Dacarbazine; d: days; m: months; y: years; *median.

During follow-up no further impairment deterioration in pulmonary function was detected (15).

Outcome measurements

Outcome in studies on prophylactic WLI in osteosarcoma. Six studies reported EFS and OS after WLI with prophylactic intent in patients with OSa (7, 8, 11, 16-18). Three studies were randomized trials and they will be analyzed later (7, 8, 11). Three papers are analyzed in this paragraph (Table II).

In the report of Jasmin with a median follow up of 16 months, EFS and OS were 80% and 90%, respectively and PRR was 11.1% (16).

Zaharia and coworkers reported 118 days median EFS in patients treated with WLI alone and 372 days in patients treated with WLI and CT ($p \leq 0.003$). Furthermore, OS was significantly better in the group treated with CT and WLI (median: 843 days) compared to the group treated with WLI alone (median: 241 days) ($p<0.03$) (17).

Trifaud and colleagues reported 87%, 70% and 58% of patients had 1-, 2-, and 3-year EFS, respectively and 95%, 75%, 61% of patients had 1-, 2-, and 3-year OS, respectively. The authors reported that all patients experienced pulmonary relapse at a median time of 60.6 months. In the same study, multiparametric analyses revealed age as a significant prognostic factor for patients younger than 15 years old. Five-year OS was observed in 41% of patients younger than 15 years old and in 75% of patients older than 15 years old ($p<0.001$) (18).

Outcome in studies on prophylactic WLI in Ewing Sarcoma. Two papers reported patients' outcome after prophylactic WLI in ESa (10, 21): one randomized trial (10) [described in next paragraph] and 1 retrospective study (21). Marinova and co-workers reported 3- and 5-year EFS in 40% and 34% of patients, respectively. The authors also reported that 7 patients out of 11 who underwent prophylactic WLI were alive without lung metastases at a follow-up between 5 and 12 years. In this study WLI was for patients who had achieved primary tumor local control (21).

Outcome in studies on curative WLI in Ewing Sarcoma. Four studies reported outcome after curative WLI in ESa (5, 15, 19, 20) (Table III). In the study of Paulussen and colleagues, 5-year EFS in patients treated with neoadjuvant therapy and local treatment of the primary tumor with WLI and without WLI was 38% *vs*. 27% ($p=0.0022$), respectively. Five-year OS was 46% for both groups and PRR was 40% in patients who did not receive WLI and 20% after WLI ($p=0.046$) (5).

Bolling and co-workers reported 5-year EFS in 39% of patients who received also WLI and 37% in patients without WLI ($p=$n.s.). After exclusion of patients with progressive disease before the start of the scheduled therapy, 5-year OS was 61% in patients treated with WLI *vs*. 49% in patients without WLI ($p=0.363$). At 5-years, PPR occurred in 48.5% of patients receiving WLI *vs*. 38.8% in patients without WLI ($p=0.46$) (19).

Luksch and co-authors reported 53% and 66% 5-year EFS and OS, respectively in patients who received WLI combined with high dose CT with busulfan and melphalan (HDCT) schedule. They reported 13 months median time to progression and identified negative prognostic factors emerging from multivariate analysis as: unfavorable histology, unfavorable radiological response at the site of primary tumor and incomplete radiological remission of lung metastases after primary CT (15).

Table III. *Outcome of studies on curative WLI Ewing Sarcoma.*

Authors (year)	Center	Number of patients	Median age (years)	Median dose (Gy) (fractionation Gy)	Chemotherapy	Event-free survival (5-year) %	Pulmonary relapse (years) %	Overall survival (5-year) %
Paulussen (1998) (5)	Munster University, Germany	75	15	15-18 * (n.r.)	V-D-Dac-C; V-D-I-Dac; E-V-D-I-A; *vs*. V-D-I-A	38.0	5 y: 40.0	46.0
		39	15	No	V-D-C-A; V-D-I-A E-V-D-I-A; V-D-I-A	27.0	5 y: 20.0	46.0
Bolling (2008) (19)	Munster University, Germany	70	15	12 - 21 (1.5)	V-D-I-A+/–E	39.0	5 y: 48.5	61.0
		27	15	No	V-D-I-A+/–E	37.0	5 y: 38.8	49.0
Luksch (2012) (15)	Italian Sarcoma Group and Scandinavian Sarcoma Group	57	16	15 (1.5)	V-D-I-E; BuMel	53.0	n.r.	66.0
		45	16	15 (1.5)	V-D-I-E	43.0	n.r.	52.0
Casey (2014) (20)	Sloan Kettering Cancer Center, New York, USA	26	23	15 (1.5)	V-D-C-I-E	3y: 38.0	3 y: 55.0	3y: 45.0

A: Actinomycin; BuMel: busulfan and melfalan; C: ciclophosphamide; D: doxorubicin; Dac: dactinomycin; E: etoposide; I: ifosfamide; n.r: not reported; V: vincristine; y: year; *: dose given in range only.

In the paper published by Casey and co-authors, 3-year EFS, OS and PPR were 38%, 45% and 55%, respectively. In the same paper, patients with exclusively pulmonary metastases had better outcomes compared to patients with extra-pulmonary disease. EFS was 61% in non-smokers *versus* 11% in smokers (p=0.04). The authors also reported that patients who received 15 Gy WLI had an OS of 51% compared to 25% in those who received 12-13 Gy (20).

Outcome in randomized trials. Five randomized trials on prophylactic WLI in both ESa and OSa reporting EFS and OS have been published (Table IV).

Rab and co-workers enrolled 53 patients with localized OSa in two arms to compare adjuvant doxorubicin plus WLI *versus* a control group (no adjuvant therapy). The authors reported a median EFS of 18 months for both arms while median OS was 42 months for patients who got WLI plus CT *vs*. 25 months for the patients without adjuvant therapy (p=n.s). Two-year EFS and OS probability in the WLI plus CT and without adjuvant therapy were 42% *vs*. 38%, and 60% *vs*. 52%, respectively (11).

In 1978, Breur and colleagues (8) performed a multicenter study reporting 43% and 28%, 5-year EFS, respectively in patients with OSa treated with or without WLI (p=0.028). Five-year OS in patients treated with or without WLI was 55% and 40%, respectively (p=0.059). With 2 to 6 years of follow up, PRR in patients treated with and without WLI was 18.2% and 9.5%, respectively. In the same study, patients younger than17 years old had 5-year metastases free survival of 48% and 28% if treated with or without WLI, respectively (p=0.028). Moreover, 5-year OS in patients under 17 years of age was 59% and 35% if treated with or without WLI, respectively (p=0.052) (8).

Razek and colleagues published the results of a randomized trial comparing different treatment regimens for primary ESa: vincristine, actinomicin and cyclophosphamide (VAC) plus adriamycin (regimen I), VAC alone (regimen II), and VAC combined with WLI (regimen III). With median follow up of 83 weeks, EFS was 96%, 86% and 86%, respectively (p=n.s.). With a median follow up of 172 weeks, OS was 78%, 38%, and 55%, respectively. The p-value was 0.1, for regimen I *vs*. regimen II, 0.16 for regimen II *vs*. regimen III, and 0.61 for regimen I *vs*. regimen III. Adriamycin-VAC was superior to WLI-VAC in terms of OS. The authors reported that the addition of adriamycin to VAC in regimen I decreased the incidence of pulmonary metastases to 10% while in patients treated with VAC alone the incidence was 38% (p=0.001). Furthermore, WLI in regimen III reduced the incidence of pulmonary metastases to 20% (p<0.10) (10).

Burgers and colleagues reported the results of an EORTC randomized study stopped earlier due to the development of new promising multi-drug CT. They randomly compared 3 arms: CT, WLI, and both (CT plus WLI) in OSa. Four-year EFS and OS were 24% and 43%, respectively in all arms (p=0.76) and 5-year PRR was 62% in the three arms (7).

Pochanugool and coworkers prospectively randomized 130 patients with OSa of whom 36 received 22.5 to 27 Gy WLI in 6-16 weeks concomitant to postoperative CT. The 2-

Table IV. *Randomized trials on prophylactic WLI.*

Authors (year)	Medical center	Number of patients	Inclusion criteria (mean age)	Chemotherapy	Median WLI dose (Gy) (fractionation)	Event-free survival %	Pulmonary relapse %* median FU	Overall survival %	*p*-Value
Rab (1976) (11)	Mayo Clinic, Rochester, USA	26	OSa (15)	D	15 (1.5)	18 m*	18 m: 65.0	42m*: 54.0	*p*=n.s
		27	OSa (16.9)	No	No	18 m*	18 m: 59.0	25m*: 48.0	
Breur (1978) (8)	A. van Leeuwenhoek Hospital, Amsterdam, The Netherlands	44	OSa (<60)	No	17.5 (1.75)	≥2y: 43.0	≥2y: 18.2	>4y: 55.0	*p*=0.18
		42	OSa (<60)	No	No	≥2y: 28.0 *p*=0.028	≥2y: 9.5	>4y: 40.0	
Razek (1980) (10)	Radiation Oncology, Washington, USA	73	ESa	V-A-C-D (X)	No	83w: 96.0	83 w*: 10.0	172 w*: 78.0	X *vs*. Y: *p*=0.10
		64	ESa	V-A-C (Y)	No	83w: 86.0	83 w*: 38.0	172 w*: 38.0	Y *vs*. Z: *p*=0.16
		56	ESa	V-A-C (Z)	15 (1.5)	83w: 86.0	83 w*: 20.0	172w*: 55.0	X *vs*. Z: *p*=0.61
Burgers (1988) (7)	Netherlands Cancer Institute, Amsterdam, The Netherlands	67	OSa (1-16)	V-D-MTX	20 (2.0)	4y: 24.0	5y: 62.0	4y: 43.0	*p*=0.76
		65	OSa (1-16)	V-D-MTX	No				
		73	OSa (1-16)	No	20 (2.0)				
Pochanugool (1997) (13)	Ramathibodi hospital, Mahidad University, Bangkok, Thailand	36	OSa	C-D/E	24.8 (n.r.)	n.r.	16.0	9y: 70.0	*p*=0.05
		79	OSa	C- D/E	No	n.r.	49.0 p = 0.009	9y: 46.0	

A: Actinomycin; C: cisplatin; D: doxorubicin; E: etoposide; ESa: Ewing sarcoma; FU: follow-up; MTX: methotrexate; n.r: not reported; n.s: not significant; OSa: osteosarcoma; V: vincristine; w: weeks; y: years, *median.

, 3-, 5- and 9-year survival rates of the whole group were 76%, 65%, 55% and 55% respectively. Thirty-six patients treated with prophylactic WLI had a 9-year survival rate of 70% compared to 46% in 79 patients who did not receive WLI (p=0.05). The incidence of lung metastases was lower in the irradiated group. In fact, 16% and 49% developed lung metastases in the WLI arm and in the arm without WLI, respectively (p=0.009) (13).

Discussion

Lungs are radio-sensitive organs particularly in the case of large irradiated volumes. In fact, the mean doses that are correlated to a risk of 13% and 20% of symptomatic pneumonitis are only 10 and 20 Gy, respectively. For this reason, WLI is a challenging treatment for radiation oncologists due to the tight constraints for lung irradiation.

Despite this marked lung sensitivity, the incidence of severe pulmonary complications seemed relatively low in our analysis. One reason for this positive outcome could be the relatively homogeneous irradiation of the lungs without volumes receiving relatively high doses. Another reason could be the relatively short follow-up in most studies particularly in phase II trials or the non-systematic and non-prospective, in the case of retrospective studies, toxicity assessments. Moreover, different types of mild to intermediate lung damage were described with variable incidences in individual studies that could probable be attributed to underestimation given the limited use of PFT.

Our analysis has clear limits related to the different study designs, lack of treatment homogeneity in terms of both integrations with surgery, CT, and RT doses and fractionation. Furthermore, the inclusion criteria are inhomogeneous in particular with regard to age. Overall, only 3 out of the 14 analyzed studies were considered at low risk of bias.

In terms of toxicity, it can be observed that although the median incidence of severe (G ≥3) pulmonary toxicity was 0%, some authors reported incidences above 5% (5, 18, 19). In addition, other authors reported lung impairments mainly of a restrictive type based on PFTs with a prevalence of 100% (5, 14-16). The negative impact of CT (16), thoracic surgery (19) and smoking habits (16, 20) were reported sporadically. The actual impact of these factors is unclear considering the lack of evaluation in studies not reporting on these relationships. The impact of dose and fractionation are not evident based on our analysis. In particular, the highest

incidence of severe pulmonary side-effects (12.2%) was recorded in the study of Trifaud and collaborators (18) who administered 20 Gy in 2 Gy fractions in their series of 41 patients. In contrast, Burger and colleagues (8) did not observe cases of severe toxicity in their series of 140 patients despite the delivery of the same dose and fractionation.

From the studies on prophylactic WLI in OSa, few conclusions can be drawn due to the lack of homogeneity in describing the results. The only evident aspect is the improvement of EFS and OS in patients undergoing WLI + CT compared to WLI alone as recorded in the study by Zaharia and colleagues (17). The efficacy of combination therapy in this setting was confirmed by the study of Trifauld and collaborators (18) who recorded a median survival of more than 3 years in patients who underwent WLI + CT.

In the series on curative WLI in ESa, it can be observed that only two studies compared patients who got CT alone with those who got both CT plus WLI (5,19). In the first study, patients who got also WLI showed better results in terms of EFS (5-year: 38.0% *vs*. 27.0%) and pulmonary relapse (5-year: 40.0% *vs*. 20.0%) (5). In the second study, a 9.7% reduction of pulmonary relapse at 5 years and 12% improvement of 5-year OS were observed (19).

In the randomized studies on prophylactic WLI, we can observe that 4 of these involved patients with OSa. In all studies, an improvement of some end-points was observed in patients treated with WLI in particular EFS (8), Pulmonary Relapse (13) and OS (11, 13). In the only study on ESa, WLI + VAC showed superior results compared to VAC alone in terms of pulmonary relapse and OS. However, regarding the same end-points, VACD alone was superior to WLI + VAC (10).

To summarize the results of this analysis, the risk of complications is at least non-negligible based on PFTs evaluation despite a minimum percentage of severe pneumonia. According to some sporadic reports, this risk is higher in some patients' categories and difficult to stratify the patients most susceptible to toxicity and clearly understand the relationship between dose and complications.

Concise evaluation of clinical outcomes picture is even more complex. Non-randomized studies indicate clear superiority of combination with CT in prophylactic WLI for OSa patients. Randomized trials show a positive impact on at least some end-points. In terms of survival, the Pochanugool study (13) showed a close to significant improvement in 9-year survival (70.0% *vs*. 46.0%; p=0.05). The Rab study (11) showed a similar improvement with median survival of 42 months *vs*. 25 months. This difference was not significant probably due to the low number of patients (total: 53 patients). Similar considerations can be made regarding the Breur study (8) in which a 15% improvement in OS was not statistically significant probably also due to the analyzed patients size. Therefore, the use of prophylactic WLI in OSa can be justified especially in patients with greater risk of metastatic diffusion.

Regarding curative WLI for ESa patients with lung metastases, the results are substantially similar with several studies showing some improvement of the different end-points. Also, in this case it could be reasonably concluded that the use of WLI can be justified especially in patients with higher risks to metastases.

The results of this treatment do not seem optimal due to the marginal impact on survival in most studies and the risk of toxicity. Therefore, the use of WLI should be individualized based on the risk of lung metastases and the presence of respiratory comorbidities. Furthermore, its use should be reserved for centers with considerable experience in the management of these patients and in particular of possible treatment related complications.

From a scientific point of view, it is evident that there is need to identify alternative treatments possibly less toxic and more effective especially in terms of OS and quality of life. For example, in oligometastatic lung patients, the combination of CT and stereotactic RT seems less toxic and more effective compared to CT plus WLI (22). This data requires further validation in prospective studies.

In patients treated with WLI for prophylactic purposes, the use of ultra-fractionated regimens (dose per fraction<0.5 Gy) administered concomitantly with CT could be tested as an alternative. In fact, RT is traditionally used with conventional fractionation (1.8-2 Gy/fraction). Lower fraction doses were found more effective than predicted by the linear-quadratic model (23). Survival curves for some irradiated cell populations show a steeper slope in the initial phase (between 0.0 and 0.5 Gy). This phenomenon is known as Hyper Radiation Sensitivity (HRS) and has been confirmed in several cell lines (24, 25) and in vivo studies (26). Moreover, some preclinical studies show that lower-fraction RT dose increases the biological efficacy of CT suggesting a synergistic effect between this fractionation modality and CT probably by increasing apoptosis and thus improving the global efficacy (27, 28). At the same time applying low total dose, very low RT dose per fraction and very prolonged treatment time (the same of CT) would be potentially less toxic. For all these reasons, the prophylactic treatment of lung metastases from ESa or OSa seems to be an ideal setting to test ultra-fractionated RT plus CT.

Conflicts of Interest

The Authors have no actual or potential conflicts of interest regarding this study.

The abstract has been previously presented as an oral poster at the 36th Annual meeting of the ESTRO (European Society for Radiotherapy & Oncology), Vienna, Austria, May 5-9, 2017 and at Congresso AIEOP (Associazione Italiana di Oncoematologia Pediatrica) Bologna, Italy, May 27-29, 2018 as an oral communication.

References

1 Siegel RL, Miller KD and Jemal A: Cancer Statistics, 2017. CA Cancer J Clin *67*: 7-30, 2017.

2 Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL and Bunin GR (eds). Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999.

3 Halperin EC, Wazer DE, Perez CA and Brady LW: Perez and Brady's Principles and Practice of Radiation Oncology. Sixth edition, Lippincott Williams and Wilkins., pp. 161, 2013

4 Margolis LW and Phillips TL: Whole lung irradiation for metastatic tumor. Radiology *93*: 1173-1179, 1969.

5 Paulussen M, Ahrens S, Burdach S, Craft A, Dockhorn-Dworniczak B, Dunst J, Fröhlich B, Winkelmann W, Zoubek A and Jürgens H: Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies. European Intergroup Cooperative Ewing Sarcoma Studies. Ann Oncol *9*: 275-281, 1998.

6 Caldwell WL: Elective whole lung irradiation. Radiology *120*: 659-666, 1976.

7 Burgers JM, van Glabbeke M, Busson A, Cohen P, Mazabraud AR, Abbatucci JS, Kalifa C, Tubiana M, Lemerle JS, Voûte PA *et al*: Osteosarcoma of the limbs. Report of the EORTC-SIOP 03 trial 20781 investigating the value of adjuvant treatment with chemotherapy and/or prophylactic lung irradiation. Cancer *61*: 1024-1031, 1988.

8 Breur K, Cohen P, Schweisguth O and Hart AMM: Irradiation of the lungs as an adjuvant therapy in the treatment of osteosarcoma of the limbs. An EORTC randomized study. Cancer *14*: 461-471, 1978.

9 Whelan JS, Burcombe RJ, Janinis J, Baldelli AM and Cassoni AM: A systematic review of the role of pulmonary irradiation in the management of primary bone tumours. Ann Oncol *13*: 23-30, 2002.

10 Razek A, Perez CA, Tefft M, Nesbit M, Vietti T, Burgert EO, Kissane J, Pritchard DJ and Gehan E: Intergroup Ewing's sarcoma study local control related to radiation dose, volume, and site of primary lesion in Ewing's sarcoma. Cancer *46*: 516-521, 1980.

11 Rab GT, Ivins JC, Childs DS, Cupps RE and Pritchard DJ: Elective whole lung irradiation in the treatment of osteogenic sarcoma. Cancer *38*: 939-942, 1976.

12 Moher D, Liberati A, Tetzlaff J and Altman DG: PRISMA Group.Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol *62*: 1006-1012, 2009.

13 Pochanugool L Subhadharaphandou T, Dhanachai M, Hathirat P, Sangthawan D, Pirabul R, Onsanit S and Pornpipatpong N: Prognostic factors among 130 patients with Osteosarcoma. Clin Orthop Relat Res *345*: 206-214, 1997.

14 Ellis ER, Marcus RB Jr., Cicale MJ, Springfield DS, Bova FJ, Graham-Pole J, Enneking WF, Spanier SS and Million RR: Pulmonary function tests after whole-lung irradiation and doxorubicin in patients with osteogenic sarcoma. J Clin Oncol *10*: 459-463, 1992.

15 Luksch R, Tienghi A, Hall KS, Fagioli F, Picci P, Barbieri E, Gandola L,Eriksson M, Ruggieri P, Daolio P, Lindholm P, Prete A, Bisogno G, Tamburini A, Grignani G, Abate ME, Podda M, Smeland S and Ferrari S: Primary metastatic Ewing's family tumors: results of the Italian Sarcoma Group and Scandinavian Sarcoma Group ISG/SSG IV Study including myeloablative chemotherapy and total-lung irradiation. Ann Oncol *23*: 2970-2976, 2012.

16 Jasmin C: A Strategic Adjuvant therapy of osteosarcoma. Recent Results Cancer Res *80*: 108-114, 1982.

17 Zaharia M, Caceres E, Valdivia S, Moran M and Tejada F: Postoperative whole lung irradiation with or without adriamycin in osteogenic sarcoma. Int J Radiation Oncology Biol Phys *12*: 907-910, 1986.

18 French Bone Tumour Study Group. Age and dose of chemotherapy as major prognostic factors in a trial of adjuvant therapy of osteosarcoma combining two alternating drug combination and early prophilactic lung irradiation. Cancer *61*: 1304-1311, 1988.

19 Bolling T, Schuck A, Paulussen M, Dirksen U, Ranft A, Konemann S, Dunst J, Willich N and Jurgens H: Whole lung irradiation in patients with exclusively pulmonary metastases of ewing tumors, toxicity analysis and treatment results of the EICESS-92 Trial. StrahlenterOnkol *184*: 193-197, 2008.

20 Casey DL, Alektiar KM, Gerber NK and Wolden SL: Whole lung irradiation for adults with pulmonary metastases from Ewing sarcoma. Int J Radiation Oncol Biol Phys *89*: 1069-1075, 2014.

21 Marinova L, Hristozova I, Mihaylova I and Perenovska P: Protective, elective lung irradiation in non-metastatic Ewing's sarcoma. Radiat Prot Dosimetry *165*: 492-494, 2015.

22 Frakulli R, Salvi F, Balestrini D, Parisi A, Palombarini M, Cammelli S, Rocca M, Salone M, Longhi A, Ferrari S, Morganti AG and Frezza G: Stereotactic radiotherapy in the treatment of lung metastases from bone and soft-tissue sarcomas. Anticancer Res *35*: 5581-5586, 2015.

23 Joiner MC, Marples B, Lambin P, Short SC and Turesson I: Low-dose hypersensitivity: current status and possible mechanisms. Int J Radiat Oncol Biol Phys *49*: 379-389, 2001.

24 Marples B and Joiner MC: The response of Chinese hamster V79 cells to low radiation doses: evidence of enhanced sensitivity of the whole cell population. Radiat Res *133*: 41-51, 1993.

25 Wouters BG, Sy AM and Skarsgard LD: Low-dose hypersensitivity and increased radioresistance in a panel of human tumor cell lines with different radiosensitivity. Radiat Res *146*: 399-413, 1996.

26 Beauchesne PD, Pedeux RM, Bonmartin A, Bertrand S, Jouvet A, Kirchner AL, Revel R, Mornex F and Dore JF: Intracerebral C6 glioma model in female hairless rats: assessment by using MRI and follow-up of irradiation. Anticancer Res *23*: 3755-3760, 2003.

27 Dey S, Spring PM, Arnold S, Valentino J, Chendil D, Regine WF, Mohiuddin M and Ahmed MM: Low-dose fractionated radiation potentiates the effects of Paclitaxel in wild-type and mutant p53 head and neck tumor cell lines. Clin Cancer Res *9*: 1557-1565, 2003.

28 Gupta S, Koru-Sengul T, Arnold SM, Devi GR, Mohiuddin M and Ahmed MM: Low-dose fractionated radiation potentiates the effects of cisplatin independent of the hyper-radiation sensitivity in human lung cancer cells. Mol Cancer Ther *10*: 292-302, 2011.

Received July 13, 2018
Revised August 9, 2018
Accepted August 10, 2018