Dual impact from coincide potential complications of cancer therapy and sarcopenia: a narrative review

ABSTRACT
Sarcopenia is a disorder of progressive loss of skeletal muscle mass and strength that is linked with multiple complications, decreased physical activity, lower quality of life and accelerated mortality rate. It is more common among cancer patients and identified with reduced tolerance by the toxic effects from cancer therapy, negative outcomes, lowered response and overall survival rate. This narrative review aims to demonstrate the dual impact from the co-occurrence of cancer therapy; chemotherapy, radiotherapy, immunotherapy, and sarcopenia alongside the potential complications from their coincide effects on cancer prognosis. By searching through data sets, all articles that focused on sarcopenia and cancer therapy were collected in the indexed journals between the years 2000 and 2021 that could provide findings for the potential complications from the coinciding effects of cancer therapy and sarcopenia in cancer patients receiving chemo-radio- and immunotherapy. Outcome measures were the rate of studies showing potential complications from the co-occurrence of cancer therapies and sarcopenia. A total of hundred-two cohort studies were enrolled. The majority were about chemotherapy and sarcopenia (45%). About 56.9% of the studies designed as retrospective analysis, and a high proportion were about chemotherapy and sarcopenia (21.6%). About 63.7% of the studies reported skeletal muscle index as the primary marker. Lower than half of the reviewed studies revealed a significant increase in the rate of sarcopenia (47%). The direct toxic effects of chemotherapy on skeletal muscle were reported in 13.7% of the studies. Studies that reported the impact of sarcopenia on a reduction in chemotherapy cycles were about 10.8%. About 11.8% and 14.7% of the studies showed lowered overall survival by the coinciding impact of chemotherapy/radiotherapy and sarcopenia, respectively. In conclusion, the evaluation of sarcopenia in cancer patients should be considered a primary part of oncological care in cancer patients as there are potential complications and poor survival from the co-occurrence of sarcopenia and different cancer therapies.

Key words: cancer, chemotherapy, immunotherapy, radiotherapy, skeletal muscle, sarcopenia

Introduction
Sarcopenia term first took its place in medical literature in the late 1980s by Rosenberg and consists of two words: “sarx (muscle)” and “penia (loss)”. It is defined as a progressive generalized loss of muscle mass and strength as a secondary complication to chronic disease conditions, sedentary lifestyle, and malnutrition [1–3]. Sarcopenia is strictly correlated with increased risk of functional impairment, disability, physical insufficiency, falls and fractures, low quality of life, poor patient outcomes, and a high rate of mortality [3]. It is categorised into three stages based on the definition of the European Working Group on Sarcopenia in Older People (EWGSOP). A pre-sarcopenia stage is characterized by a decrease in muscle mass. This stage does...
not affect muscle strength and physical performance and can be identified by accurate measuring of muscle mass. A sarcopenia phase is manifested by a decrease in muscle mass, strength, or physical performance. In severe sarcopenia, there is an obvious decrease in muscle mass, strength, and physical performance [4, 5].

In sarcopenia, potential components for loss of muscle quality, mass, and strength include a diminished skeletal muscle innervation and capillary density and the specific decay of type II muscle filaments; that is, a decrease in the motor units involved in the binding of neurons and muscle fibres [6]. The immediate result of sarcopenia is the loss of skeletal muscles, which are not just an essential piece of the motor system but also, modulate immune and inflammatory processes by secreting multiple cytokines, such as tissue necrosis factor-α (TNF) to promote systemic inflammation. Along these lines, sarcopenia may bring down natural killer (NK) cells in cancer patients, thereby debilitating the anti-tumour immune response and worsening patient prognosis [7–9]. Myokines, like interleukin (IL)-6, can have anti-tumorigenic impacts by interacting with NK cells and actuating the production of IL-1 receptor antagonist and IL-10 by the molecules with anti-inflammatory effects [10, 11]. On the other hand, the pro-inflammatory factors delivered by both immune cells and tumour cells advance muscle tissue disintegration and restrain skeletal muscle cell differentiation which can inhibit protein synthesis and muscle regeneration, ultimately prompting muscle atrophy [12]. Besides, TNF-α can straightforwardly instigate muscle atrophy through the ubiquitin-proteasome system (UPS) [13].

Furthermore, many risk factors are associated with the development of sarcopenia. They include age-related changes in tissue secretion or responsiveness to trophic hormonal factors, nutritional insufficiency, a diet poor in protein, muscle fibre count, genetic factors, immobility, post-traumatic, smoking, alcohol, sedentary lifestyle and acute and chronic co-morbid disease conditions such as obesity, osteoporosis and type 2 diabetes mellitus, insulin resistance and underlying malignancy [14, 15].

This narrative review aims to demonstrate the bimodal impact from the co-occurrence of cancer therapy; chemotherapy, radiotherapy, immunotherapy, and sarcopenia alongside the potential complications from their coincide effects on cancer prognosis.

**Methods**

Search and data extraction

By searching through data sets within PubMed, Google Scholar, ISI, Scopus, and Embase, all articles that focused on sarcopenia and cancer therapy were gathered in the indexed journals between the years 2000 and 2021 that could provide information on the correlated effects of different therapeutic agents used in cancer therapy and sarcopenia. The search strategy for this study was performed utilizing the terms of medical subject headings (MeSH) and combinations of the keywords according to the following: sarcopenia, cancer, chemotherapy, radiotherapy, chemo-radiotherapy, immunotherapy, immune checkpoint inhibitors, skeletal muscle, and body mass index. Inclusion criteria were all articles that focused on the co-existence of cancer therapy and sarcopenia regarding the potential impact of cancer therapy (chemo-radio-and immunotherapy)-induced toxicity on the incidence and prognosis of sarcopenia and vice versa. These included randomised clinical trials, case-control, and retrospective studies; while the titles, abstracts, and full texts of all imported studies were screened by the researchers. Data were extracted from included studies for the following evidence: author, country, year of publication, type of study, sample size, cancer type, cancer therapy, duration of therapy in days, body composition marker, rate of sarcopenia evaluation, and summary of main outcomes. The accuracy and quality of the included data were additionally checked and the review process excluded irrelevant studies and articles, and those not in the English language (Fig. 1).
## Table 1. Summary of findings for the reviewed cohort studies

| Variable                                      | Number of reviewed studies (n = 102) | Percentage |
|-----------------------------------------------|-------------------------------------|------------|
| **Studies-related cancer therapy**            |                                     |            |
| Chemotherapy                                  | 46                                  | 45.0       |
| Chemo-radiotherapy                            | 28                                  | 27.5       |
| Immunotherapy                                 | 28                                  | 27.5       |
| **Study design**                              |                                     |            |
| Retrospective                                 | 58                                  | 56.9       |
| Prospective                                   | 44                                  | 43.1       |
| **Cancer diagnosis**                          |                                     |            |
| Oesophagogastric carcinoma                    | 14                                  | 13.7       |
| Non-small cell lung carcinoma (NSCLC)         | 15                                  | 14.7       |
| **Anticancer therapy**                        |                                     |            |
| Platinum-based compounds                      | 14                                  | 13.7       |
| Pembrolizumab                                  | 16                                  | 15.7       |
| Nivolumab                                      | 16                                  | 15.7       |
| **Surrogate for skeletal muscle mass**        |                                     |            |
| Skeletal muscle index (total)                 | 65                                  | 63.7       |
| Skeletal muscle index (chemotherapy)          | 29                                  | 44.6       |
| Skeletal muscle index (chemo-radiotherapy)    | 18                                  | 27.7       |
| Skeletal muscle index (immunotherapy)         | 18                                  | 27.7       |
| **Rate of sarcopenia**                        | 48                                  | 47         |
| **Impact of chemotherapy on sarcopenia incidence** | 14                                  | 13.7       |
| **Impact of sarcopenia on administration of chemotherapy schedules** | 11                                  | 10.8       |
| **Lowered overall survival by coincide impact of chemotherapy and sarcopenia** | 12                                  | 11.8       |
| **Lowered overall survival by coincide impact of radiotherapy and sarcopenia** | 15                                  | 14.7       |
| **Impact of sarcopenia on administration of immunotherapy schedules** | 8                                   | 7.8        |
| **Overall outcome**                           | 95                                  | 93.1       |

Data presented as number (n) and percentage (%); *A significant negative impact to the co-existence of sarcopenia and cancer therapy

## Results

A review of hundred-two cohort studies conducted on the potential complications from coinciding effects of cancer therapy and sarcopenia in cancer patients receiving chemo-radio- and immunotherapy revealed varied results. Most of the reviewed studies were about the potential impact of cancer chemotherapy and sarcopenia (45%) (Tab. 1 and 2); while an equal proportion of the reviewed studies was about the impact of sarcopenia in chemo-radiotherapy and immunotherapy (27.5%), as shown in Tables 1, 3 and 4.

The present study showed that a total of 58 studies (56.9%) were designed as retrospective analyses, and a high proportion of these retrospective studies was about cancer chemotherapy and sarcopenia (n = 22) (Tab. 1 and 2). Nearly an equal proportion of the reviewed studies were conducted among patients who suffered from oesophagogastric carcinoma received chemotherapy and non-small cell lung cancer patients received immunotherapy (NSCLC) (13.7%, 14.7%), respectively (Tab. 1, 3 and 4). Furthermore, platinum-based compounds represented the most common chemotherapeutic agents administered within the scope of chemotherapy and sarcopenia (13.7%) (Tab. 1 and 2); while both pembrolizumab and nivolumab represented the most common immune checkpoint inhibitors (15.7%) administered within the scope of immunotherapy and sarcopenia, as shown in Tables 1, 3 and 4.

Regarding the marker of body composition (a surrogate for skeletal muscle mass), skeletal muscle index...
| Author/Country          | Year   | Study design          | Sample size | Cancer type            | Chemotherapy          | Duration (pre-post therapy in days) | Main outcomes                                                                 |
|------------------------|--------|-----------------------|-------------|------------------------|-----------------------|------------------------------------|--------------------------------------------------------------------------------|
| Awad et al./UK/2012    |        | Observational study   | 47          | Oesophago-gastric       | Epirubicin/Cisplatin/5-fluorouracil | 107                                 | Baseline sarcopenia (57%)          | Post-therapy sarcopenia (79%) Neoadjuvant chemotherapy was associated with an increase of sarcopenia [32] |
| Yip et al./UK/2014     |        | Prospective study     | 35          | Oesophageal             | Multiple chemotherapy  | 60                                 | Baseline sarcopenia (26%)          | Post-therapy sarcopenia (43%) Sarcopenia increased following neoadjuvant chemotherapy [33] |
| Reisinger et al./Netherlands/2015 |        | Prospective study     | 114         | Oesophageal             | Multiple chemotherapy  | 111                                 | Baseline sarcopenia (56%)          | Post-therapy sarcopenia (67%) Measurement of muscle mass loss index provides assessment to identify unfavorable postoperative outcome [121] |
| Liu et al./Japan/2016  |        | NA                    | 84          | Oesophageal             | 5-fluorouracil, cisplatin | 56                                 | Baseline sarcopenia (56%)          | Post-therapy sarcopenia (NA) Decreased psoas muscle index correlates well with a poor prognosis [21] |
| Elliott et al./Ireland/2017 |        | Prospective study     | 252         | Oesophageal             | Multiple chemotherapy  | 365                                 | Baseline sarcopenia (87%)          | Post-therapy sarcopenia (18%) Sarcopenia is associated with an increased risk of major postoperative complications [122] |
| Paireder et al./Austria/2018 |        | Retrospective study   | 130         | Oesophageal             | Bone marrow            | NA                                 | Baseline sarcopenia (42.3%)        | Post-therapy sarcopenia (NA) Skeletal muscle index, skeletal muscle mass, and lean body mass provide assessment to identify unfavorable postoperative outcome [23] |
| Daly et al./Ireland/2018 |        | Prospective observational study | 225 | Foregut                 | Multiple chemotherapy  | 118                                 | Baseline sarcopenia (40%)          | Post-therapy sarcopenia (40%) Skeletal muscle index, skeletal muscle mass, and lean body mass provide assessment to identify unfavorable postoperative outcome [34] |
| Guinan et al./Ireland/2018 |        | Prospective observational study | 28 | Oesophageal             | Multiple chemotherapy  | 96                                 | Baseline sarcopenia (7%)           | Post-therapy sarcopenia (22%) Participants experience significant losses of muscle mass and strength during chemotherapy [35] |
Table 2. cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|-----------------------------------|-------------------------|-----------------------------|---------------|-----|
| Järvinen et al./Finland/2018 | Retrospective cohort study | 118 (115) Oesophageal | epirubicin–oxaliplatin–capecitabine | 33 | Skeletal muscle index | 80 | 80 | Loss of skeletal muscle tissue correlates with worse overall survival | [24] |
| Dijksterhuis et al./Netherlands/2019 | NA | 88 Oesophago-gastric | Capecitabine/oxaliplatin | 79 | Skeletal muscle index, reflecting muscle mass, and skeletal muscle density | 49 | 55 | Sarcopenia was not associated with survival or treatment-related toxicity | [123] |
| Ma et al./South Korea/2019 | Retrospective study | 198 Oesophageal cancer | Chemo-radiotherapy (multiple chemotherapy regimens) | NA | Skeletal muscle index | NA | NA | Sarcopenia can be a useful predictor for long-term prognosis | [22] |
| Ota et al./Japan/2019 | Retrospective study | 31 Oesophageal cancer | Cisplatin, 5-fluorouracil/cisplatin, 5-FU, and docetaxel | NA | Skeletal muscle index | 51.6 | NA | Potential utility of sarcopenia assessment | [124] |
| Voisinet et al./France/2020 | Retrospective study | 46 Oesogastric adenocarcinoma | NA | 180 Psoas, paraspinal, abdominal wall muscles | 6.7 | 60 | Feeding jejunostomy with enteral nutritional seemed to efficiently counteract sarcopenia occurrence | [125] |
| Palmela et al./Portugal/2017 | Retrospective study | 48 Gastric | Multiple chemotherapy regimens | 86 | Skeletal muscle index, visceral fat index | 23 | 58 | Sarcopenia associated with early termination of neoadjuvant chemotherapy | [55] |
| Dalal et al./USA/2012 | Prospective cohort study | 41 Pancreatic | Bevacizumab, capecitabine | 104 | Skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue | 63 | 90 | Obese patients experience higher losses in weight | [126] |
| Fogelman et al./USA/2014 | Prospective study | 53 Pancreatic | Gemcitabine, erlotinib, MK-0646 | 60 | Skeletal muscle index | NA | NA | Metastatic pancreatic cancer patients can be expected to lose muscle mass | [127] |
| Choi et al./South Korea/2015 | Retrospective study | 484 Pancreatic cancer | Multiple chemotherapy regimens (Gemcitabine, FOLFIRINOX) | NA | Skeletal muscle index | 21 | 53 | Sarcopenia was poor prognostic factors in advanced pancreatic cancer | [25] |
Table 2. cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|-----------------------------------|--------------------------|-----------------------------|--------------|------|
| Cooper et al./USA/2015 | Prospective study | 89 | Pancreatic | Gemcitabine, cisplatin | 135 | Skeletal muscle, adipose tissue compartments | 52 | 59 | Further depletion of skeletal muscle occurred during neoadjuvant therapy | [36] |
| Benjamin et al./USA/2018 | Retrospective study | 24 | Pancreatic | Multiple chemotherapy regimens | NA | Total psoas area index | 38 | NA | A significant decrease in total psoas area index during treatment with received neoadjuvant chemotherapy | [37] |
| Sandini et al./Italy/2018 | Retrospective cohort study | 193 | Pancreatic | Multiple chemotherapy regimens | 180 | Total adipose tissue area, visceral adipose tissue area, skeletal lean mass | 43 | 41 | Patients experience a significant loss of adipose tissue during neoadjuvant chemotherapy | [38] |
| Prado et al./Canada/2007 | Prospective study | 62 | Colon cancer | 5-fluorouracil, leucovorin | 168 | Lean body mass | NA | NA | Lean body mass is a significant predictor of toxicity | [56] |
| Poterucha et al./USA/2012 | NA | 57 | Colorectal cancer | Multiple chemotherapy regimens, bevacizumab | 90 | Skeletal muscle index | NA | NA | Prescribed bevacizumab appear to lose weight and muscle in the absence of cancer progression | [39] |
| Barret et al./France/2014 | Prospective, cross-sectional, multicenter study | 51 | Colorectal cancer | Fluoropyrimidine ± oxaliplatin, irinotecan | 60 | Areas of muscle tissue, visceral adipose tissue, subcutaneous adipose tissue | NA | 70.6 | Sarcopenia significantly associated with severe chemotherapy toxicity | [57] |
| Jung et al./South Korea/2015 | Prospective study | 229 | Colon cancer | Oxaliplatin, 5-fluorouracil, leucovorin | 180 | Psoas muscle index | NA | NA | Decreased muscle mass was associated with increased risk of grade 3-4 toxicity and poor prognosis | [26] |
| Miyamoto et al./Japan/2015 | Retrospective study | 182 | Unresectable colorectal cancer | Oxaliplatin, irinotecan | 70 | Skeletal muscle index | 73 | NA | Skeletal muscle loss was an independent, negative prognostic factor | [27] |
Table 2. cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|-------------------------------------|-------------------------|-----------------------------|--------------|------|
| Ali et al./France, Canada/2016 | Prospective randomized clinical trials | 138 | Colon cancer | FOLFOX (Folinic acid, 5FU, oxaliplatin, irinotecan ± cetuximab) | 180 | Lean body mass | NA | NA | Low lean body mass is a significant predictor of toxicity | [54] |
| Blauwhoff-Buskermolen et al./Netherlands/2016 | Prospective study | 63 | Colorectal cancer | Multiple chemotherapy regimens | NA | Skeletal muscle index | 57 | 70 | Muscle area decreased significantly during chemotherapy and was independently associated with survival | [20] |
| Eriksson et al./Sweden/2017 | Retrospective study | 225 | Resectable colorectal liver metastases | Multiple chemotherapy regimens (majorly oxaliplatin-based) | 960 | Skeletal muscle index | NA | 61 | Skeletal muscle mass decreases during neoadjuvant chemotherapy and impairs the conditions for adjuvant chemotherapy | [40] |
| Antoun et al./France/2019 | Prospective multicenter, randomized, open-labeled, non-comparative phase II trial | 76 | Colorectal cancer | Multiple chemotherapy regimens | 120 | Skeletal muscle index | NA | NA | Skeletal muscle mass depletion was not associated with survival or chemotherapy toxicity | [128] |
| Derksen et al./Netherlands/2019 | Randomized controlled phase III trial | 300 | Colorectal cancer | Multiple chemotherapy regimens | 126 | Skeletal muscle index | NA | NA | Skeletal muscle index loss was associated with lifestyle-related as well as tumour and treatment-related factors | [28] |
| Kurk et al./Netherlands/2019 | Observation trial study | 414 | Colorectal cancer | Capecitabine, bevacizumab, oxaliplatin | NA | Skeletal muscle index, body mass index | 54, 46 | NA | Sarcopenia and/or muscle loss was associated with an increased risk of dose-limiting toxicities | [58] |
| Kobayashi et al./Japan/2018 | Retrospective study | 102 | Hepatocellular carcinoma | Transcatheter arterial chemembolization and transcatheter arterial infusion multiple chemotherapy | 180 | Skeletal muscle index | NA | NA | Rate of change in skeletal muscle mass was an independent prognostic factor | [129] |
Table 2. cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|------------------------------------|--------------------------|-----------------------------|-----------------|------|
| **Lung**            |              |             |             |              |                                     |                          |                             |                 |      |
| Stene et al./Norway/2015 | Pilot observation-al cohort study | 35 | Non-small cell lung carcinoma cancer (NSCLC) | Carboplatin Vinorelbine Gemcitabine | 88 | Skeletal muscle index | NA | NA | Almost half of the patients had stable or increased muscle mass during chemotherapy | [21] |
| Go et al./Korea/2016 | Retrospective study | 117 | SCLC | Chemotherapy (Etoposide, platinum/Irinotecan, cisplatin) or chemo-radiotherapy | NA | Skeletal muscle index | 24.8 | NA | Baseline sarcopenia is associated with poor prognosis and a high incidence of dose-limiting toxicity of the standard first-line treatment | [29] |
| Atlan et al./France/2017 | Retrospective study | 64 | NSCLC | NA | 133 | Skeletal muscle index, total adipose tissue | 49 | 48.1 | Skeletal muscle mass is wasting is lower when initial skeletal muscle mass and BMI values are low | [130] |
| Nattenmüller et al./Germany/2017 | Retrospective single centre study | 200 | NSCLC | Multiple chemotherapy regimens | 125 | Visceral, subcutaneous-fat-area, inter-muscular-fat-area, muscle-density, muscle-area, skeletal-muscle index | NA | NA | After chemotherapy, patients exhibited sarcopenia with decreased muscle | [41] |
| Goncalves et al./USA/2018 | Retrospective study | 88 | NSCLC | Taxane, gemcitabine, bevacizumab | 120 | Skeletal muscle index 2-[18F]-fluoro-2-deoxy-d-glucose | NA | NA | During chemotherapy skeletal muscle volume and metabolism are altered | [42] |
| Kakinuma et al./Japan/2018 | Retrospective study | 44 | NSCLC | Not-specified (Poly-chemotherapy) | 152 | Skeletal muscle index | NA | NA | Skeletal muscle loss was higher in patients receiving cytotoxic chemotherapy | [131] |
| **Breast and ovarian** |              |             |             |              |                                     |                          |                             |                 |      |
| Prado et al./Canada/2009 | Prospective Study | 55 | Breast cancer | Capecitabine | 30 | Skeletal muscle index | 25 | 50 | Sarcopenia is a significant predictor of toxicity and tumour progression | [30] |
| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|------------------------------------|------------------------|-----------------------------|---------------|------|
| Prado et al./Canada/2011 | Prospective study | 132 | Breast cancer | 5FU, epirubicin, cyclophosphamide | 180 | Lean body mass | NA | NA | Lean body mass was lower for patients presenting with toxicity | [59] |
| Mazzuca et al./Italy/2018 | Retrospective study | 21 | Breast cancer | Anthracycline-based chemotherapy | NA | Skeletal muscle index | 38 | 48 | Lean body mass loss is associated with higher grade of toxicity | [60] |
| Rier et al./Netherlands/2018 | Single-centre, retrospective study | 98 | Metastatic breast cancer | 5-fluorouracil, doxorubicin, cyclophosphamide/Paclitaxel | 118 | Lumbar skeletal muscle index | NA | NA | Muscle attenuation decreased during treatment | [62] |
| Rutten et al./Netherlands/2016 | Retrospective study | 123 | Ovarian cancer | Multiple chemotherapy regimens | 84 | Surface areas of skeletal muscle | NA | NA | Patients with ovarian cancer have a worse survival when they lose skeletal muscle | [31] |

### Bladder

| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|------------------------------------|------------------------|-----------------------------|---------------|------|
| Zargar et al./USA/2017 | Retrospective study | 60 | Bladder cancer | Multiple chemotherapy regimens (majorly gemcitabine-cisplatin) | 126 | Bilateral total psoas muscle volume | NA | NA | A decline in psoas muscle volume during neoadjuvant chemotherapy and associated with the need for dose reduction/dose delay | [43] |
| Rimar et al./USA/2018 | Retrospective study | 26 | Bladder carcinoma | Methotrexate, vindesine, doxorubicin, cisplatin/gemcitabine, cisplatin/gemcitabine, capecitabine | 110 | Lumbar skeletal muscle index, visceral adipose index, subcutaneous, intramuscular adipose index | 69 | 81 | A significant decrease in lean muscle mass with an associated increase in the prevalence of sarcopenia | [44] |

### Others

| Author/Country/Year | Study design | Sample size | Cancer type | Chemotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|--------------|------------------------------------|------------------------|-----------------------------|---------------|------|
| Xiao et al./USA/2016 | Retrospective cohort study | 191 | Diffuse large B-cell lymphoma | Cyclophosphamide, doxorubicin, vincristine/prednisone, ± rituximab | 90 | Muscle, subcutaneous fat, visceral fat areas | NA | NA | Survivors undergo unfavorable long-term body composition changes | [132] |

NA — non-available
| Author/country/year | Study design | Sample size | Cancer type | Radiotherapy or chemoradiotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|-------------|-------------|-------------|----------------------------------|-----------------------------------|-----------------------|--------------------------|----------------|-----|
| **Head and neck carcinoma (HNC)** | | | | | | | | | |
| Grossberg et al./USA/2016 | Retrospective study | 2840 | HNC | Radiotherapy | 2058 | Skeletal muscle index | 35.3 | 65.8 | Diminished skeletal muscle mass | [133] |
| Cho et al./South Korea/2018 | Retrospective study | 221 | HNC | Chemo-radiotherapy | NA | Skeletal muscle index | NA | 48 | Sarcopenia is associated with significantly inferior overall survival, progression-free survival and RT interruption more frequently | [80] |
| Ganju et al./USA/2019 | Retrospective study | 246 | HNC | Chemo-radiotherapy (cisplatin, cetuximab) | 1053 | Lumbar skeletal muscle index | NA | 58.1 | Sarcopenic patients are more likely to require radiation treatment breaks and suffer chemotherapy toxicity | [73] |
| van Rijn-Dekker et al./Netherlands/2020 | Prospective study | 750 | HNC | Chemo-radiotherapy (cisplatin, carboplatin/5-FU or cetuximab) | 720 | Skeletal muscle index | NA | NA | Sarcopenia is an independent prognostic factor for worse survival outcomes and is associated with physician-rated toxicity | [82] |
| Chauhan et al./India/2020 | Short-term, longitudinal cohort study | 19 | HNC | Chemo-radiotherapy | 49 | Skeletal muscle index | 31.5 | 89.4 | Patients showed clinically significant increases in the incidence of sarcopenia | [134] |
| Thureau et al./France/2020 | Observational prospective, unicentric study | 243 | HNC | Chemo-radiotherapy (Cisplatin, cetuximab) | NA | Skeletal muscle index | NA | 41.7 | Pretherapeutic sarcopenia remains frequent and predicts overall survival and disease-free survival | [83] |
| **Respiratory** | | | | | | | | | |
| Op den Kamp et al./Netherlands/2014 | Retrospective cohort study | 203 | Non-small cell lung carcinoma (NSCLC) | Chemo-radiotherapy | NA | Limb muscle strength | NA | NA | Weight loss starts early and requiring timely and intense nutritional rehabilitation | [135] |
| Sanders et al./Netherlands/2016 | Retrospective study | 287 | Non-small cell lung carcinoma (NSCLC) | Chemo-radiotherapy (majorly platinum-based chemotherapy + etoposide) | NA | Early weight loss | NA | NA | Early weight was found to be associated with worse prognosis | [84] |
| Kiss et al./Australia/2019 | Prospective study | 41 | Non-small cell lung carcinoma (NSCLC) | Multiple chemotherapy regimens | 150 | Muscle area, muscle density | 61 | 85 | Significant loss of muscle area and muscle density occurs early during therapy | [136] |
Table 3. cont. Summary of clinical cohort studies regarding the potential impact of radiotherapy/chemo-radiotherapy and sarcopenia

| Author/country/year | Study design | Sample size | Cancer type | Radiotherapy or chemo-radiotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|-----------------------------------|-------------------------------------|------------------------|--------------------------|-----------------|------|
| Shen et al./China/2013 | Retrospective cohort study | 2433 | Nasopharyngeal carcinoma (NPC) | Radiotherapy | 60-3750 | High weight loss, low weight loss | NA | High weight loss was independently associated with poor survival in NPC | [85] |
| Li et al./China/2017 | Retrospective study | 322 | NPC | Radiotherapy | 2190 | Body weight loss | NA | Acute radiation toxicities had significant and independent impact on weight loss | [75] |
| Gastrointestinal | Olson et al./Portland/2020 | Retrospective study | 245 | Oropharyngeal squamous cell carcinoma | Radiotherapy | NA | Third lumbar skeletal muscle index | NA | Sarcopenia has a negative association with survival for patients | [86] |
| Murimwa et al./USA/2017 | Retrospective study | 56 | Oesophageal cancer | Chemo-radiotherapy | NA | First full slice of the L4 vertebral, psoas muscle | NA | Sarcopenia was associated with a significant increase in acute grade ≥3 toxicity | [137] |
| Panje et al./Switzerland/2019 | Prospective Study | 61 | Oesophageal cancer | Chemo-radiotherapy (multiple chemotheraphy regimens) | 90 | Skeletal muscle index | 29.5 | Neoadjuvant chemoradiation increased the percentage of sarcopenia. Sarcopenic patients are at higher risk for increased toxicity during therapy | [76] |
| Ma et al./South Korea/2019 | Retrospective study | 287 | Oesophageal cancer | Chemo-radiotherapy | 90-180 | Skeletal muscle index | NA | Sarcopenia can be a useful predictor for long-term prognosis | [87] |
| Yoon et al./Korea/2020 | Retrospective study | 248 | Oesophageal cancer | Chemo-radiotherapy (5-fluorouracil, cisplatin) | 35 | Skeletal muscle index | 62.9 | Excessive muscle loss was a significant prognostic factor for overall survival and recurrence free survival | [88] |
| Mallet et al./France/2020 | Retrospective study | 97 | Oesophageal cancer | Chemo-radiotherapy | NA | Skeletal muscle index | 56 | Sarcopenia is a powerful independent prognostic factor, associated with a rise of the overall mortality | [81] |
| Liang et al./China/2021 | Retrospective study | 100 | Oesophageal cancer | Radiotherapy | 360 | Skeletal muscle index | NA | Sarcopenia can independently predict the survival of patients | [89] |
| Shiba et al./Japan/2018 | Retrospective study | 68 | Hepatocellular carcinoma (HCC) | Radiotherapy | 1005 | Skeletal muscle index | NA | Sarcopenia was not a prognostic factor for patients with HCC treated with C-ion RT | [138] |
| Lee et al./South Korea/2019 | Retrospective study | 156 | Hepatocellular carcinoma (HCC) | Radiotherapy | 279 | Skeletal muscle index | 63.5 | Sarcopenia, was associated with poor survival | [90] |
| Author/country/year | Study design | Sample size | Cancer type | Radiotherapy or chemo-radiotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|-----------------------------------|-------------------------------------|------------------------|---------------------------|--------------|-----|
| Lin et al./China/2016 | Retrospective study | 364 | Rectal cancer | Chemo-radiotherapy (oxaliplatin, capecitabine/oxaliplatin, leucovorin, 5-FU) | NA | Body mass index | Baseline sarcopenia (%) 66.2 | Post-therapy sarcopenia (%) 100 | Severe weight loss compromises survival outcome | [91] |
| Park et al./South/Korea/2018 | Retrospective study | 104 | Rectal cancer | Chemo-radiotherapy (5FU, capecitabine) | NA | Skeletal muscle index | 36.7 | 40 | Sarcopenia is a poor prognostic factor in older patients | [92] |
| Cervical Kiyotoki et al./Japan/2018 | Retrospective study | 60 | Cervical cancer | Chemo-radiotherapy (cisplatin, nedaplatin/ifosfamide + nedaplatin) | 1005 | Skeletal muscle, iliopsoas muscle | NA | NA | Sarcopenia was revealed to be an important prognostic factor | [93] |
| Matsuoka et al./Japan/2019 | Retrospective study | 236 | Cervical cancer | Chemo-radiotherapy (cisplatin, nedaplatin/ifosfamide + nedaplatin) | 30-4950 | Psoas muscle index, skeletal muscle index | NA | NA | Sarcopenia is not a predictive factor of outcome | [139] |
| Others Couderc et al./France/2020 | Prospective study | 31 | Prostate cancer | Androgen deprivation therapy + radiotherapy | NA | Appendicular skeletal muscle mass | 25.8 | NA | A high prevalence of muscle disorders | [140] |
| Pielkenrood et al./Netherlands/2020 | Prospective cohort study | 310 | Spinal metastases | Radiotherapy | 202 | Visceral fat area, subcutaneous fat area, total muscle area, skeletal muscle density | 48 | 86 | Sarcopenia can improve predictions of overall survival | [94] |
| Ferini et al./Italy/2021 | Prospective Study | 28 | Bladder cancer | Radiotherapy | 735 | Skeletal muscle index | NA | 28.6 | Sarcopenia cannot be considered a negative prognostic factor for elderly patients treated with external beam radiotherapy | [141] |
| Zhang et al./China/2016 | Prospective study | 113 | NA | Chemo-radiotherapy | NA | Total lumbar skeletal muscle cross-sectional area, total lumbar adipose tissue area | NA | 84.9 | Incidence of sarcopenia among patients with cancer is high, particularly for males | [142] |

NA — non-available
| Author/country/year | Study design | Sample size | Cancer type | Immunotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|---------------|------------------------------------|------------------------|-----------------------------|-----------------|-----|
| **Non-small cell lung cancer (NSCLC)** |
| Revel et al./France/2018 | Prospective study | 779 | Lung cancer | Anti-PD-1 antibody | 60 | Total muscle area, skeletal muscle index | NA | 70 | Sarcopenia is associated with higher risk of immunotherapy interruption | [113] |
| Cortellini et al./Italy/2019 | Retrospective observational study | 23 | NSCLC | Nivolumab | NA | Skeletal muscle index | NA | NA | Influence of nutritional status and sarcopenia on immune response, suggesting these factors could affect treatment with nivolumab | [118] |
| Nishioka et al./Japan/2019 | Retrospective study | 38 | NSCLC | Pembrolizumab, nivolumab | NA | Psoas major muscle area | NA | NA | Patients with sarcopenia are associated with poor outcomes for immunotherapy | [110] |
| Shiroyama et al./Japan/2019 | Retrospective study | 42 | NSCLC | Pembrolizumab, nivolumab | NA | Psoas muscle index | NA | 52.4 | Sarcopenia at baseline is a significant predictor of worse outcome | [119] |
| Magri et al./Italy/2019 | Retrospective study | 46 | NSCLC | Nivolumab | 720 | Body mass index, skeletal muscle mass index, fat-free mass index, fat mass index, weight change | NA | NA | Weight loss is significant negative prognostic factors for NSCLC patients on immunotherapy | [143] |
| Popinat et al./France/2019 | Retrospective study | 55 | NSCLC | Nivolumab | 365 | Lean body mass, fat body mass, muscle body mass, visceral fat mass, subcutaneous fat mass | NA | NA | Subcutaneous fat mass is a significant prognosis factor of stage IV NSCLC treated by nivolumab | [144] |
| Author/country/year | Study design | Sample size | Cancer type | Immunotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|-------------|-------------|-------------|---------------|------------------------------------|------------------------|---------------------------|---------------|-----|
| Cortellini et al./Italy/2020 | Retrospective study | 100 | NSCLC, Melanoma, Renal cell carcinoma, others | Pembrolizumab, nivolumab, atezolizumab, others | NA | Hounsfield Unit, skeletal mass index | 51 | Low skeletal muscle index is associated with shortened survival in advanced cancer patients treated with PD1/PDL1 checkpoint inhibitors | [145] |
| Roch et al./France/2020 | Retrospective study | 142 | NSCLC | Pembrolizumab, nivolumab | 165 | Skeletal mass index | 65.7 | Cachexia — sarcopenia syndrome negatively influences patients’ outcome during pembrolizumab, nivolumab therapy | [146] |
| Petrova et al./Bulgaria/2020 | Retrospective study | 167 | NSCLC | Pembrolizumab | NA | Psoas major muscle area | 30.3 | Presence of sarcopenia are potential risk factors for the development of disease progression | [147] |
| Ichihara et al./Japan/2020 | Retrospective study | 513 | NSCLC | Pembrolizumab, nivolumab, atezolizumab | NA | Body mass index | NA | BMI was significantly associated with the efficacy of immune checkpoint inhibitors | [148] |
| Minami et al. Japan/2020 | Retrospective study | 74 | NSCLC | Pembrolizumab, nivolumab, tezolizumab | NA | Psoas muscle index, intramuscular adipose tissue content, visceral to subcutaneous ratio, visceral fat area | NA | Neither sarcopenia nor visceral adiposity may be associated with the efficacy of immune checkpoint inhibitors therapy | [149] |
| Katayama et al./Japan/2020 | Retrospective study | 35 | NSCLC | Pembrolizumab, nivolumab, atezolizumab | NA | Body mass index | NA | Low BMI may be negative predictors for checkpoint inhibitors rechallenge treatment | [150] |
Table 4. cont. Summary of clinical cohort studies regarding the potential impact of cancer immunotherapy and sarcopenia

| Author/country/year | Study design | Sample size | Cancer type | Immunotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|---------------------|--------------|-------------|-------------|---------------|------------------------------------|------------------------|----------------------------|----------------|------|
| Tsukagoshi et al./Japan/2020 | Retrospective study | 30 | NSCLC | Nivolumab | NA | Skeletal mass index | NA | NA | Skeletal muscle loss may be a predictive factor of poor outcomes in NSCLS patients undergoing nivolumab therapy | [151] |
| Takada et al./Japan/2020 | Retrospective study | 103 | NSCLC | Pembrolizumab, nivolumab | 605 | Skeletal mass index | NA | NA | L3 muscle index Low is an independent predictor of worse outcomes in NSCLC patients treated with anti-PD-1 inhibitors | [152] |
| Kichenadasse et al./Australia/2020 | Pooled post hoc analysis | 1434 | NSCLC | Atezolizumab | 210 | Body mass index | NA | NA | Baseline BMI should be considered as a stratification factor in future immune checkpoint inhibitor therapy trials | [153] |
| Gastrointestinal | | | | | | | | | |
| Kano et al./Japan/2021 | Retrospective study | 31 | Gastric cancer | Nivolumab | NA | Psoas muscle mass index | NA | 29 | Psoas muscle mass index might help predict the response to nivolumab | [120] |
| Kim et al./Korea/2021 | Retrospective study | 149 | Gastric cancer | Pembrolizumab, nivolumab | NA | Skeletal mass index | NA | 53 | Sarcopenia is an independent prognostic factor for progression-free survival in patients treated with PD-1 inhibitors | [154] |
| Qayyum et al./USA/2021 | Retrospective study | 36 | Hepato-cellular carcinoma (HCC) | Pembrolizumab or nivolumab/ ipilimumab/ sorafenib | 180 | Skeletal mass index | NA | NA | Sarcopenia was associated with reduced survival and HCC necrosis | [155] |
| Alice et al./USA/2021 | Retrospective study | 57 | Hepato-cellular carcinoma | Anti-PD-1 antibody | 180 | Skeletal mass index | NA | 49.1 | Sex-specific sarcopenia does not predict overall survival | [156] |
| Author/ country/ year | Study design | Sample size | Cancer type | Immunotherapy | Duration (pre-post therapy in days) | Body composition marker | Rate of sarcopenia evaluation | Main outcomes | Ref. |
|----------------------|--------------|-------------|-------------|---------------|-----------------------------------|-------------------------|-----------------------------|----------------|-----|
| **Melanoma**         |              |             |             |               |                                   |                         |                             |                |     |
| Daly et al./ Ireland/ 2017 | Retrospective study | 84 | Metastatic melanoma | Ipilimumab | 100 | Muscle attenuation | 17 32 | Patients with sarcopenia and low muscle index are more likely to experience severe treatment-related toxicity. Loss of muscle during treatment was predictive of worse survival | [112] |
| Heidelberger et al./ France/ 2016 | Retrospective study | 71 | Melanoma | Pembrolizumab, nivolumab | NA | Body mass index | NA NA | Patients with sarcopenia experienced significantly more early severe toxicities | [114] |
| Heidelberger et al./ France/ 2017 | Monocentric, retrospective study | 68 | Melanoma | Pembrolizumab, nivolumab | NA | Body mass index, skeletal muscle index | NA 19 | Sarcopenic overweight is associated with more early acute limiting toxicity of anti-PD1 in melanoma patients | [111] |
| Hu et al./ USA/ 2020 | Retrospective chart review | 156 | Melanoma | Pembrolizumab | 165 | Psoas muscle index | NA 34 | Sarcopenia did not appear to predict clinically relevant outcomes. Obesity, however, represents a readily available predictor of pembrolizumab toxicity | [157] |
| **Urothelial carcinoma (UC)** |              |             |             |               |                                   |                         |                             |                |     |
| Shimizu et al./ Japan/ 2020 | Retrospective study | 27 | UC | Pembrolizumab | 360 | Psoas major muscle area | NA 56 | Evaluation of sarcopenia may help in the management of UC with pembrolizumab | [158] |
| Fukushima et al./ Japan/ 2020 | Retrospective study | 28 | UC | Pembrolizumab | NA | Skeletal muscle index | NA 68 | Patients with advanced UC who received pembrolizumab had sarcopenia, which was significantly associated with poor therapeutic efficacy | [159] |
| Author/country/year | Study design                        | Sample size | Cancer type                      | Immuno-therapy | Duration (pre-post therapy in days) | Body composition marker                                                                 | Rate of sarcopenia evaluation | Main outcomes                                                                 | Ref.       |
|---------------------|-------------------------------------|-------------|----------------------------------|----------------|-------------------------------------|------------------------------------------------------------------------------------------|-------------------------------|---------------------------------------------------------------------------------|-----------|
| Massicotte et al./France/2013 | International, double-blind-ed, placebo-controlled, phase III trial | 23          | medullary thyroid carcinoma       | Vandetanib     | 90                                  | Visceral adipose tissue, skeletal muscle index                                           | NA                            | Patients with low muscle mass had high vandetanib serum concentration and high incidence of toxicities | [115]     |
| Veasey-Rodrigues et al./USA/2013 | Prospective Trial                  | 16          | Advanced solid tumors            | Temsirolimus   | 63                                  | Skeletal muscle index                                                                  | 44                            | Patients with higher grade toxicities tended to lose more body fat, suggesting a possible end-organ metabolic effect of temsirolimus               | [116]     |
| Gyawali et al./Japan/2016 | Retrospective study                | 20          | Breast/Pancreatic Cancer         | Everolimus/Temsirolimus | 180                                 | Body mass index, subcutaneous adipose tissue, visceral adipose tissue, skeletal muscle tissue | 60                            | Long-term use of mTOR inhibitors induces a marked loss of muscle mass             | [160]     |

NA — non-available
was the high-ranked marker among the reviewed studies (63.7%), as following: chemotherapy (44.6%) and equal proportion for chemo-radiotherapy and immunotherapy (27.7%). The present study also showed that lower than half of the reviewed studies revealed a significant increase in the rate of sarcopenia (47%) following all cancer therapies (chemo-radio-and immunotherapy).

The direct toxic effects of chemotherapy on skeletal muscle metabolism and loss of muscle mass were reported in 13.7% of the studies, while studies that reported the impact of sarcopenia on a reduction in chemotherapy dosage or a delay in the administration of chemotherapeutic cycles was 10.8% and 7.8% for the administration of immunotherapy. A total of 11.8% of studies showed lowered overall survival by the coinciding impact of chemotherapy and sarcopenia and 14.7% by the coinciding impact of radiotherapy and sarcopenia (Tab. 1). Moreover, the outcomes of the reviewed studies derived from their findings which showed that 93.1% reported a significant negative correlation and prognosis related to the co-occurrence of sarcopenia and cancer therapy (chemo-radio-and immunotherapy) (Tab. 1).

**Discussion**

Cancer chemotherapy and sarcopenia

In this study, most of the reviewed studies were about the potential impact of cancer chemotherapy and sarcopenia. Chemotherapy immensely strains the body of malignancy patients, causing a more prominent consumption of energy and thus an expansion on the whole-cell catabolic cycles that, subsequently, sabotage tissue creation [16]. Malignancy is conceivably the most remarkable obsessive condition that advances muscle atrophy, especially in elderly patients. On the other hand, sarcopenia is prevalent in patients with various malignancies and the rate of its occurrence in cancer patients varies between 11–74%. It has been recognized that cancer patients with sarcopenia have a poor prognosis regarding various malignancies, such as lung, stomach, pancreas, and colorectal cancers alongside different complications associated with cancer treatment [17, 18]. In addition, long-term outcomes and overall survival are significantly shorter while death rates are more frequently observed in cancer patients with sarcopenia submitted to oncological therapy [19], as reported in studies by Blauwhoff-Buskermolen et al. [20], Liu et al. [21], Ma et al. [22], Paireder et al. [23], Järvinen et al. [24], Choi et al. [25], Jung et al. [26], Miyamoto et al. [27], Derksen et al. [28], Go et al. [29], Prado et al. [30] and Rutten et al. [31].

There is also a direct toxic effect of chemotherapy on skeletal muscle metabolism and loss of muscle mass. This was reported in studies by Blauwhoff-Buskermolen et al. [20], Awad et al. [32], Yip et al. [33], Daly et al. [34], Guinan et al. [35], Cooper et al. [36], Benjamin et al. [37], Sandini et al. [38], Poterucha et al. [39], Eriksson et al. [40], Nattenmüller et al. [41], Goncalves et al. [42], Zargar et al. [43] and Rimar et al. [44].

During cancer chemotherapy, there is a progressive loss of skeletal muscle mass by 1.4 kg after 9 weeks of chemotherapy. In patients receiving systemic chemotherapy for colorectal cancer, deficiency of ≥ 9 % muscle mass during 3 months was freely prescient of lower survival at 6 months. This might be related to uncontrolled muscle protein catabolism that is exaggerated as the tumour growth progresses [20, 45, 46]. As the amount of stored protein diminishes due to sarcopenia, the metabolism and immunity decline relatively to this, prompting an abatement in antitumor response and an increase in mortality [47].

Other possible contributing factors to aggressive loss of muscle mass secondary to low food intake are nausea, vomiting, diarrhea, anorexia, and fatigue. This is induced by many chemotherapeutic agents particularly by platinum compounds, such as cisplatin, carboplatin, and oxipaltin [48], as also reported by the findings of the present study where platinum-based compounds represented the most common chemotherapeutic agents administered among the reviewed studies within the scope of chemotherapy and sarcopenia. Neuropathy and myalgia secondary to complications by taxanes chemotherapy might induce sarcopenia and skeletal muscle loss [49]. Moreover, cancer chemotherapy may also induce oxidative stress in skeletal muscle tissues through increase production of reactive oxygen species [50, 51], causing a reduction in muscle microvasculature through antiangiogenesis [52] and increase muscle catabolism secondary to the overproduction of tumour growth factors [50, 53].

Lower content of muscular fibres alongside a concomitant decrease of some metabolizing enzymes available in the skeletal muscle tissue could decrease the capability to metabolize some chemotherapeutic agents. An example of these enzymes is dihydropyrimidine dehydrogenase (DPD), which plays an important role in the catabolism of 5-Fluorouracil and capetitabine by converting fluoropyrimidines to inactive metabolites. On the other hand, patients with low lean body mass have poor tolerability and show more toxic adverse effects from anticancer drugs. This is related to a decreased volume of distribution of these agents which may lower the capacity for metabolizing anticancer [54]. Such patients are more prone to a reduction in chemotherapy dosage or a delay in the administration of chemotherapeutic cycles, as reported in studies by Ali et al. [54], Palmela et al. [55], Prado et al. [56], Barret et al. [57], Jung et al. [26], Kurk et al. [58], Go et al. [29], Prado et al. [30], Prado et al. [59], Mazzuca et al. [60], and Zargar et al. [43].
Skeletal muscle mass also decreases during neoadjuvant chemotherapy which might impair the prognosis for adjuvant therapy. Accordingly, maintaining muscle mass during chemotherapy administration is independently associated with disease stabilization and mortality reduction [21, 22, 61].

Literature reported that several molecular pathways have been recognized for muscle protein degradation and skeletal muscle depletion after cancer chemotherapy administration, such as dysregulation in energy metabolism, mitochondrion biogenesis, and dysregulation in muscle fibre metabolism following mitochondrial damage and reduced cytochrome C synthesis needed for oxidative phosphorylation and peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) [26]. Mammalian Target Of Rapamycin (mTOR) inhibitors, such as everolimus and temsirolimus, involved insulin-like growth factor 1/phosphatidylinositol-3-kinase/PKB–protein kinase B)/mamalian target of rapamycin pathway in activating skeletal muscle synthesis [62].

Platinum compounds induced sarcopenia to include several pathways, such as ubiquitin-proteasome pathway (UPP) in the degradation of myofibrillar proteins; the autophagy-lysosome pathway (ALP) in the elimination of mitochondria, over-expression of pro-inflammatory cytokines (TNF-α) leading to the activation of the NF-κB pathway, activation of the myostatin pathway, phosphorylation of SMAD2, silences the IGF-1/PI3K/Akt/mTOR anabolic pathway through the decreased phosphorylation of Akt and mTOR [63]. Doxorubicin and etoposide cause skeletal muscle depletion and muscle protein degradation and direct muscle loss through the activation of the NF-κB molecular pathway. This leads to up-regulation of ubiquitin and proteasomes, increasing the process of proteolysis and production of inflammatory cytokines (IL-1β, IL-6, and TNF-α) which in turn increase E3 ligases (atrogin-1), and the ubiquitin-protein binding for proteolysis [64–66].

Cancer radiotherapy and sarcopenia

Radiation restrains recovery and muscle hypertrophy by harming satellite cells. Radiation is thought to forestall satellite cell mitosis by causing breaks in strands of the cell’s DNA. If a break happens just on a single strand, the harm can be fixed by polymerases utilizing the correlative strand as a layout. If harm happens at a similar point on the two strands, the deletion may be irreparable which can prompt mitotic failure and cell death [67].

It has been reported that muscle damage and fibrosis are common and irreversible late effects of radiation on skeletal muscle tissue [68]. Radiotherapy is associated with a wide range of toxic effects that could further deteriorate the nutritional status of cancer patients, such as xerostomia, dysphagia, oral mucositis, oral pain, and sticky saliva [69–71]. Simultaneous chemotherapy and radiation are related to significant toxicities including mucositis, dysphagia, odynophagia, nausea, vomiting, anorexia, fatigue, and dysgeusia bringing about eating difficulty [72–74]. Lower content of muscular fibres, mass and strength are more likely to require radiation treatment breaks and suffer chemotherapy toxicity. These findings were reported in studies by Ganju et al. [73], Li et al. [75] and Panje et al. [76].

Moreover, numerous patients present with symptomatic tumours that lead to eating difficulty preceding the inception of treatment. Patients with HNC going through concurrent chemo-radiotherapy are regularly losing more than 5% of their body weight in the 6 months around this therapy [77, 78]. To some extent, this has been exacerbated by a change in resting energy consumption, which assists the loss of lean body mass seen during and following treatment. Accordingly, malnutrition might be present nearly in 35-60%, weight loss in 10%, and sarcopenia in up to 70% among patients undergoing radiotherapy for HNC. Therefore, sarcopenia is associated with poor overall and disease-free survival [79], as presented in studies by Cho et al. [80], Mallet et al. [81], van Rijn-Dekker et al. [82], Thureau et al. [83], Sanders et al. [84], Shen et al. [85], Olson et al. [86], Ma et al. [87], Yoon et al. [88], Liang et al. [89], Lee et al. [90], Lin et al. [91], Park et al. [92], Ki-yotoki et al. [93], and Pielkenrood et al. [94].

This expanded radiation-induced toxicity in sarcopenic patients contrarily impacts their quality of life since dysphagia altogether impacts the quality of life [95]. Furthermore, an earlier literature review showed that sarcopenia itself was related to an undeniable decrease in quality of life [96]. A recent study reported that sarcopenia is a powerful independent prognostic factor, related to an ascent of the general mortality in patients treated solely by radio-chemotherapy for locally advanced oesophageal cancer. Along these lines, the quality of life in this patient population may be influenced by both radiation-induced toxicities and sarcopenia [81].

Cancer immunotherapy and sarcopenia

The advancement of immune senescence with age is likely a result of many associating cytokine and hormonal adjustments. Increased age, muscle loss, and immune senescence are believed to be interlinked. Skeletal muscle is known to modulate the immune system by producing cytokines (myokines) such as interleukin (IL)-15 and IL-6, and it has been proposed that sarcopenia causes a change in cytokine signalling which modifies immune cells to induce immune dysregulation and cre-
ate pro-inflammatory conditions [97–99]. Changes in other immune cell populations, such as expanded myeloid-derived suppressor cells (MDSCs), that have been accounted for with increasing age may likewise be connected to skeletal muscle loss through changes production of myokines [100, 101]. Chronic inflammation within malignancy also adds to sarcopenia. For instance, a high serum level of IL-6, a pro-inflammatory cytokine adding to muscle catabolism, following instance, a high serum level of IL-6, a pro-inflammatory cytokine that additionally adds to sarcopenia [105, 106]. On the other hand, peroxisome proliferator-initiated receptor-gamma coactivator (PGC)-1α is a key factor created in the muscle that has fundamental negative impacts on the anti-tumour immune response. Along these lines, skeletal muscle loss may prompt expanded creation of TGF-β and IL-6, and diminished creation of PGC-1α and other myokines [107, 108], which might be related to poor response to PD-L1 blockade. Hence, sarcopenia has been related to poor outcomes or toxicity to tyrosine kinase inhibition, and to immune checkpoint inhibitors (ICIs), including programmed cells death 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab [109, 110]. This was evidenced in earlier studies by Heidelberger et al. [111], Daly et al. [112], Revel et al. [113], Heidelberger et al. [114], Massicotte et al. [115], and Veasey-Rodrigues et al. [116].

Sorafenib through multiple steps causes inhibition of PI3K, Akt, and mTOR which are directly involved in the activation of amino acid transporters and synthesis of muscle protein alongside inhibition of the physiologically activated pathways following the physical exercise involving RAF, MEK, and MAPK/ERK kinase. Moreover, it causes a reduction in muscle blood supply and substrates delivery to the muscle through antiangiogenesis properties [117]. The PD-1 inhibitors, such as nivolumab or pembrolizumab, block the PD-1/programmed death-ligand 1 (PD-L1) pathway by which malignancy cells escape immune recognition. Sarcopenic patients treated with nivolumab for non-small cell lung carcinoma (NSCLC) had more limited progression-free survival and overall survival [118]. Moreover, earlier studies found a significant relationship between sarcopenia, shorter progression-free survival, and lower response rate in NSCLC patients treated with PD-1 checkpoint inhibitors [110, 119]. A higher incidence of adverse events was also reported in sarcopenic melanoma patients treated with PD-1 inhibitors [111, 120] and ipilimumab [112].

Conclusions

Despite the high proportion of the reviewed studies that were retrospectively conducted, it was observed that the dual impact from coinciding potential complications of cancer therapy and sarcopenia are highlighted. Consequently, the evaluation of sarcopenia in cancer patients should be considered as a primary part of oncology care in cancer patients receiving diverse lines of cancer therapy.

Conflict of interest

All authors declare no conflicts of interest.

Funding

No funding was received for performing this research.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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