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Survival impact and risk factors of skeletal muscle loss during first-line EGFR-TKIs therapy in advanced lung adenocarcinoma patients

Xin Nie[1†], Mingzhu Zou[2†], Chenhui Song[3†], Ping Zhang[1], Di Ma[1], Di Cui[4], Gang Cheng[1] and Lin Li[1*]

Abstract

Purpose The impact of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) on muscle mass in individuals with advanced lung cancer has yet to be fully delineated. This study aimed to examine the dynamics of skeletal muscle mass during EGFR-TKIs targeted therapy, elucidate its clinical relevance, and explore the potential mechanisms.

Methods We retrospectively recruited 104 patients with EGFR-mutant advanced lung adenocarcinoma who received icotinib or afatinib as first-line treatment. Skeletal muscle changes were assessed by abdominal CT obtained before and during treatment with EGFR-TKIs. The mean interval (± SD) between two CT scans was 109 days (± 16 days). Targeted panel sequencing of tumor tissue was used to detect genetic alterations. Functional enrichment analysis of genes interacting with EGFR-TKIs and muscle loss was performed to elucidate the potential toxicological mechanisms.

Results A total of 42 (40.4%) patients experienced muscle loss during targeted therapy. Genetic analysis indicated muscle loss group had a higher proportion of MDM2 amplification and PIK3CA alterations ($p = 0.011$ & $p = 0.045$, respectively).Patients with baseline low muscle density and experienced ≥ Grade 2 diarrhea had higher rate of muscle loss ($p = 0.005$ & $p < 0.001$, respectively). Multivariate analysis revealed that muscle loss was independently associated with shorter PFS (hazard ratio [HR] 1.86, 95% confidence interval [CI]: 1.09 ~ 3.18; $p = 0.023$). Besides, we found genes associated with icotinib, afatinib and muscle loss were significantly enriched in MAPK signaling pathway and calcium signaling pathway.

Conclusions This study highlights the high prevalence and detrimental impact of muscle loss during EGFR-TKIs treatment.

Keywords Epidermal growth factor receptor tyrosine kinase inhibitors, Skeletal muscle mass, Lung adenocarcinoma

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Introduction

Sarcopenia is highly prevalent in cancer patients and independently associated with poor survival and treatment tolerance [1, 2]. Furthermore, sarcopenia negatively affects physical function and global quality of life in non-small cell lung cancer (NSCLC) patients [3]. Consequently, alleviating sarcopenia during treatment is also important for cancer patients. However, skeletal muscle loss during anti-cancer treatment is under-recognized and poorly managed in routine clinical practice. Body weight loss and body mass index (BMI) do not adequately capture changes in body composition that may occur much earlier [4, 5]. Therefore, enhancing the evaluation of skeletal muscle mass in lung cancer patients is warranted [6].

Significant skeletal muscle loss was prevalent during chemotherapy in advanced lung cancer patients [7, 8]. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) had shown higher response rate, longer survival and lower toxicity profiles compared with traditional platinum doublets chemotherapy in patients with EGFR mutation-positive advanced NSCLC [9–12]. Given the extended progression-free survival (PFS) associated with EGFR-TKIs therapy, there may exist a window of opportunity to alleviate sarcopenia in patients with advanced NSCLC.

Currently, there is limited knowledge about changes in skeletal muscle mass during first-line treatment with EGFR-TKIs in advanced NSCLC patients. This study aimed to examine the dynamics of skeletal muscle mass during EGFR-TKIs targeted therapy, clarify its clinical significance, and explore the potential mechanisms.

Methods

Patient selection

We retrospectively collected data on 104 consecutive advanced lung adenocarcinoma patients with EGFR mutations who underwent abdominal CT scans before and during first-line treatment with EGFR-TKIs (first-generation EGFR-TKI icotinib or second-generation EGFR-TKI afatinib) between December 2016 and December 2020 at Beijing Hospital/National Center of Gerontology. The patients initially received either icotinib 125 mg three times daily or afatinib 40 mg once daily orally. EGFR mutation detection was performed using either the amplification refractory mutation system (ARMS) method or next-generation sequencing (NGS) approach.

Patients' medical records were reviewed to collect baseline characteristics, tolerance, and efficacy of EGFR-TKIs. The tumor response was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The incidence and severity of adverse events were evaluated based on Common Terminology Criteria for Adverse Events (CTCAE; version 5.0). The performance status was assessed using the Eastern Cooperative Oncology Group performance status (ECOG PS). The Charlson Comorbidity Index (CCI), which incorporates 19 chronic diseases weighted according to their association with mortality, was calculated for each patient. BMI was calculated using the formula weight/height^2 (kg/m^2) obtained from the patients' data at diagnosis. The patients were categorized into underweight (BMI < 18.5 kg/m^2), normal range (BMI: 18.5 ~ 22.9 kg/m^2), and overweight (BMI ≥ 23 kg/m^2) according to the World Health Organization (WHO) classification of weight by BMI for adult Asians. Nutritional risk screening 2002(NRS 2002) was used to evaluate nutritional risk. Patients were classified into the nutritional risk group (NRS 2002 score ≥ 3) and the non-nutritional risk group (NRS 2002 score < 3).

Skeletal muscle measurement

Skeletal muscle mass was calculated from routine abdominal CT scans performed for diagnosis and response evaluation using OsiriX software (Lite version 12.0.1, Pixmeo, Geneva, Switzerland) (Fig. 1) [13]. This study utilized CT scans at two distinct time points: (1) at baseline, which was 30 days prior to the initiation of EGFR-TKI treatment, and (2) during the course of EGFR-TKI therapy. The mean interval (± standard deviation [SD]) between the two CT scans was 109 days (± 16 days). The CT imaging parameters included contrast-enhanced or unenhanced scans with a 5-mm slice thickness and 120 kVp.

The skeletal muscle area (SMA) at the L3 region, which includes the psoas, paraspinal, and abdominal wall muscles with both transverse processes visible, was measured as it has been shown to correlate best with whole-body skeletal muscle mass [14]. The structures of these specific muscles were quantified using a pre-established Hounsfield Unit (HU) range of -29 to 150 HU [15]. Any structures other than the skeletal muscles that were automatically marked were eliminated through manual corrections. The SMA was normalized for height (m^2) and reported as the skeletal muscle index (SMI; cm^2/m^2). Low skeletal muscle mass was defined as SMI < 38.5 cm^2/m^2 for women and < 52.4 cm^2/m^2 for men based on previous studies [16]. The mean muscle attenuation (HU) is reported for the entire skeletal muscle area at L3. Low muscle density was defined as muscle attenuation < 41 HU for patients with BMI < 25 kg/m^2 and muscle attenuation < 33 HU for patients with BMI ≥ 25 kg/m^2 [5]. A previous study has indicated that the technical error associated with patient positioning and slice selection can be seen in the variation of 1.5 to 2.5% between adjacent abdominal slices in the same individual [17]. In this study, changes in skeletal muscle mass were categorized as muscle loss (SMA decrease > 2%) or muscle

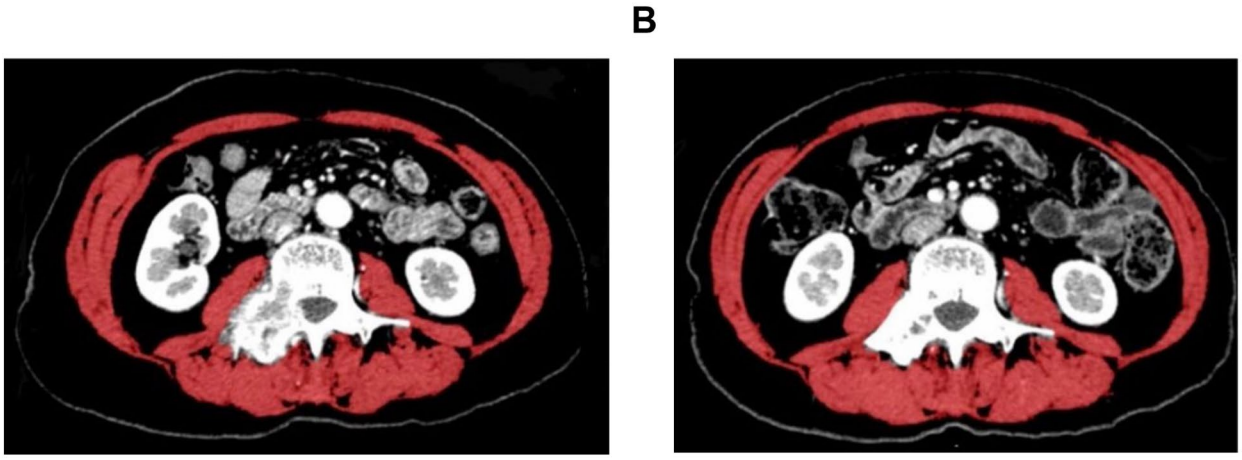

Fig. 1 Axial abdominal CT images of L3 region for a 64-year-old female. (**A**) Baseline CT, L3 skeletal muscle area is 97.1 cm^2; (**B**) CT after 3 months of afatinib treatment, L3 skeletal muscle area decreased to 89.1 cm^2 even though partial response was achieved. Red highlights the region with skeletal muscle. CT: computed tomography, L3: the third lumbar vertebra

stability (SMA decrease ≤ 2%). All muscle measurements were performed by a single trained radiologist who was blinded to the clinical information. Figure 1 demonstrated the changes of skeletal muscles in L3 region before and during afatinib treatment in a female patient.

Targeted panel sequencing of tumor tissue sample

All tumor tissue specimens were reviewed by pathologists to determine the percentage of viable tumor tissue and its adequacy for sequencing. Custom-designed probes, which covered 1.6 Mb regions for 1021 cancer-related genes, were used for DNA capture from baseline tumor tissue samples. A list of all the genes and their coordinates in the selected regions was provided in Table S1. DNA sequencing was performed using the GeneSeq2000 sequencing system with 2 × 100 bp paired end reads. Single nucleotide variants (SNVs), small insertions and deletions were called using MuTect (version 1.1.4) [18].

Pathway enrichment analysis of drug-associated genes

We utilized DGIdb (https://www.dgidb.org) [19], Pharm GKB (https://www.pharmgkb.org) [20], SwissTargetPrediction (http://www.swisstargetprediction.ch) [21] and SuperPred (https://prediction.charite.de) [22] to identify genes linked with afatinib or icotinib. Genes associated with skeletal muscle loss were extracted from GeneCards (https://www.genecards.org) [23] database using "skeletal muscle loss" as the keyword. Next, we used R package "clusterProfiler (version 4.6.2)" to perform the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis (pvalueCutoff = 0.05 and qvalueCutoff = 0.05).

Statistical analysis

Descriptive statistics (count [percent], mean±[SD] and median [P25, P75] as appropriate) were used to describe the study sample. PFS was defined as the time from initiation of EGFR-TKIs to progressive disease (PD) or death from any causes. Overall survival (OS) was measured from the date of diagnosis of metastatic disease to death or the last follow-up. The cut-off follow-up time for this study was 31 Dec 2022. Chi-square test or Fisher's exact test was used to compare categorical variables. PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards analysis for OS and PFS was performed to test associations between survival and muscle measurements, and adjustments were made with multivariate analysis. A two-tailed p value of less than 0.05 was statistically significant. Statistical analysis was performed using R software V.3.6.3.

Results

Baseline patient characteristics and skeletal muscle status

The mean(± SD) age at the time of diagnosis was 65.0 ± 11.9 years. The EGFR exon 19 deletion and exon 21 L858R mutation comprised 43.3% and 48.1% of the cases respectively, while the remaining 8.6% were attributed to uncommon mutations. The median (P25, P75) SMI and muscle attenuation were 40.5 (35.2, 46.6) cm^2/m^2 and 39.5 (32.9, 46.2) HU respectively. At baseline, 62 (59.6%) patients were found to have low skeletal muscle mass, a condition that was significantly associated with advanced age ($p < 0.001$), nutritional risk ($p = 0.007$) and comorbidity ($p = 0.034$). Additionally, 47 (45.2%) patients exhibited low muscle density, which was significantly associated with advanced age ($p < 0.001$), poor PS ($p = 0.012$), notable weight loss ($p = 0.027$), nutritional risk ($p < 0.001$) and comorbidity ($p = 0.010$). The baseline characteristics of

the patients categorized by muscle status are detailed in Table 1.

The association between clinical features and skeletal muscle loss

The median SMA (P25, P75) in the L3 region before and during EGFR-TKIs treatment was 106.3 (88.9, 129.5) cm^2 and 103.7 (87.3, 128.8) cm^2 respectively. The median muscle attenuation (P25, P75) was 39.7 (30.7, 44.9) HU during EGFR-TKIs treatment. The changes in SMA and muscle attenuation after EGFR-TKIs treatment are demonstrated in Fig. 2. A total of 42 (40.4%) patients experienced skeletal muscle loss during EGFR-TKIs treatment, and the median reduction rate (P25, P75) was 5.3% (2.9%, 7.6%). Patients with baseline low muscle density and those who experienced ≥ Grade 2 diarrhea during EGFR-TKIs treatment had significantly higher rates of muscle loss (55.3% vs. 28.1%, $p = 0.005$; 79.3% vs. 25.3%, $p < 0.001$, respectively; see Table 2). Genetic analysis from 37 baseline tumor tissue revealed that muscle loss group had a higher proportion of MDM2 amplification (33.3% vs. 0%, $p = 0.011$) and PIK3CA alterations (44.4% vs. 10.7%, $p = 0.045$) compared with the muscle stable group (Fig. 3).

Table 1 Baseline clinical characteristics of the study subjects($n = 104$)

Characteristic	Low SMI		Low muscle density	
	($n = 62$)	P value	($n = 47$)	P value
Age(years), n (%)		< 0.001		< 0.001
≥ 70	38(90.5)		30(71.4)	
< 70	24(38.7)		17(27.4)	
Gender, n (%)		0.080		0.111
Male	25(71.4)		12(34.3)	
Female	37(53.6)		35(50.7)	
Targeted therapy, n (%)		0.507		0.664
Icotinib	42(57.5)		34(46.6)	
Afatinib	20(64.5)		13(41.9)	
EGFR mutation, n (%)		0.052		0.185
Exon19 Del	22(48.9)		17(37.8)	
Non-exon19 Del	40(67.8)		30(50.8)	
ECOG PS, n (%)		0.356		0.012
0 ~ 1	56(58.3)		40(41.7)	
≥ 2	6(75.0)		7(87.5)	
Weight loss, n (%)		0.083		0.027
≥ 5%	16(76.2)		14(66.7)	
< 5%	46(55.4)		33(39.8)	
BMI (kg/m^2), n (%)		< 0.001		0.161
< 18.5	7(100)		3(42.9)	
18.5 ~ 22.9	28(80.0)		20(57.1)	
≥ 23	27(43.5) *#		24(38.7)	
CCI, n (%)		0.034		0.010
0	33(51.6)		22(34.4)	
≥ 1	29(72.5)		25(62.5)	
Metastases, n (%)		0.939		0.156
Mono-organ	30(60.0)		19(38.0)	
Multi-organ	32(59.3)		28(51.9)	
Nutritional risk, n (%)		0.007		< 0.001
Without	31(49.2)		19(30.2)	
With	31(75.6)		28(68.3)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, Epidermal growth factor receptor; SMI, skeletal muscle index. *Compared with underweight group (BMI < 18.5 kg/m^2), statistically significance existed. # Compared with normal range group (BMI:18.5 ~ 22.9 kg/m^2), statistically significance existed

The impact of skeletal muscle loss on clinical outcomes

At the time of evaluating muscle changes during EGFR-TKIs treatment, 54 (51.9%) patients achieved partial response (PR), 47(45.2%) patients had stable disease (SD), and 3(2.8%) patients experienced progressive disease (PD). Baseline low muscle mass (51.6% vs. 52.4%, $p = 0.939$) and muscle density (42.6% vs. 59.6%, $p = 0.082$), as well as muscle loss during EGFR-TKIs treatment (50.0% vs. 53.2%, $p = 0.747$), were not associated with objective response rate (ORR).

During the study period, a total of 100 (96.1%) patients progressed after first-line EGFR-TKIs. The median PFS was statistically shorter in patients experiencing muscle loss during EGFR-TKI treatment (9.3 vs. 12.0 months, $p = 0.036$) (Fig. 4A). Further analysis revealed that muscle loss during targeted therapy (hazard ratio [HR] 1.86, 95% confidence interval [CI]: 1.09 ~ 3.18, $p = 0.023$) was independently associated with PFS, after adjusting for ECOG PS, treatment efficacy, metastases, baseline muscle density and diarrhea (Table S2). This was in contrast to baseline low muscle mass (HR 1.27, 95% CI: 0.85 ~ 1.89, $p = 0.242$) and low muscle density (HR 1.32, 95% CI: 0.89 ~ 1.96, $p = 0.173$), which were not associated with PFS.

After progression on first-line EGFR-TKIs, 23.0% of patients received only palliative care, 60.0% were treated with osimertinib, and 42.0% underwent subsequent chemotherapy. The rate of chemotherapy was lower in the muscle loss group compared with the muscle stable group (22.0% vs. 55.9%, $p = 0.001$). However, the incidence of osimertinib treatment was similar between the muscle loss and muscle stable groups (53.7% vs. 64.4%, $p = 0.306$).

At the time of the last follow-up, 88(84.9%) patients had died, and the median OS was 25.5 months (95%CI: 20.3 ~ 30.7 months). The median OS was statistically shorter in the muscle loss group compared with the muscle stable group (20.5 vs. 30.3 months, $p = 0.019$) (Fig. 4B). However, the development of muscle loss during EGFR-TKI treatment was not independently associated with OS after adjusting for ECOG PS, metastases, post-progression osimertinib treatment, baseline muscle density and

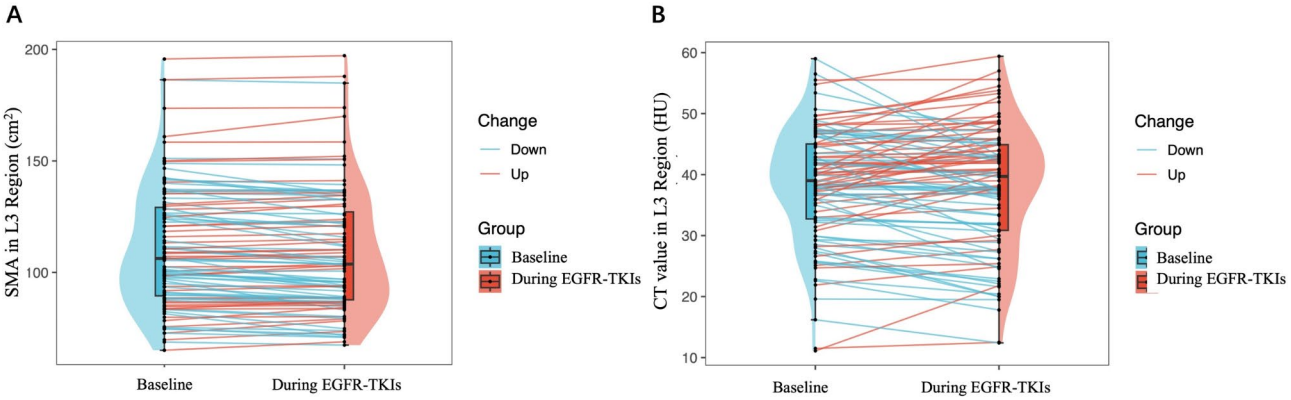

Fig. 2 (**A**) The changes of skeletal muscle area in L3 region before and during EGFR-TKIs. (**B**) The changes of mean CT value of skeletal muscle in L3 region before and during EGFR-TKIs

diarrhea (HR 1.44, 95%CI: 0.80 ~ 2.58, $p = 0.221$) (Table S3).

Analysis of genes interacting with EGFR-TKIs

After deduplicating the database, we identified 254 genes associated with afatinib, 234 genes associated with icotinib and 21,350 genes related to skeletal muscle loss (Table S4-6). The majority of genes associated with afatinib or icotinib were associated with skeletal muscle loss (Fig. 5A). To better understand the potential molecular mechanism of afatinib or icotinib inducing muscle loss, we conducted KEGG pathway enrichment analysis and focused on the top 20 pathways (Fig. 5B-D). The genes interacting with afatinib and icotinib were enriched in MAPK signaling pathway and calcium signaling pathway, which muscle loss-related genes were also significantly enriched in. The genes interacting with icotinib and muscle loss were enriched in PI3K-AKT signaling pathway.

Discussion

Skeletal muscle loss is an emerging concern in oncology. Chemotherapy is known to accelerate muscle loss in cancer patients [24]. A previous study indicated that the mean muscle area reduced by 4.6 cm^2 ($p < 0.002$) after first-line chemotherapy in advanced NSCLC patients, corresponding to a 1.4 kg loss of whole-body muscle mass [7]. EGFR-TKIs are considered less toxic and more effective than chemotherapy. Nevertheless, our study highlights that patients can experience muscle loss after targeted therapy. It is noteworthy that, although the disease control rate exceeded 90% during the first 3 months of targeted therapy, 40% of patients still experienced muscle loss, which was considered as early muscle loss during treatment in our study. Another retrospective study ($n = 45$) also showed that 42.2% of patients had skeletal muscle loss during EGFR-TKI therapy [25]. Our study demonstrated that early muscle loss during targeted therapy, rather than baseline muscle status, was independently associated with PFS. A previous study has also supported that baseline low muscle mass is not associated with PFS of EGFR-TKI [26]. Therefore, the dynamic changes in muscle mass compared to baseline muscle status may have a better correlation with the prognosis of patients receiving targeted therapy. Moreover, a previous study supported that skeletal muscle depletion had a significant impact on physical function and quality of life [27]. Therefore, physicians should not only focus on the efficacy of treatment but also consider preserving muscle mass in the management of advanced lung cancer.

The etiologies of muscle loss are multifactorial. A previous clinical study indicated that EGFR-TKIs could ameliorate cancer-associated cachexia by inhibiting cachexia mediator parathyroid hormone-related protein expression in tumor-bearing mice [28]. However, our study suggests that the effect of EGFR-TKIs on maintaining muscle mass is only modest for advanced lung cancer patients in real clinical practice. Our study indicated the majority of genes associated with afatinib or icotinib were correlated with skeletal muscle loss. Further pathway enrichment analysis indicated that these genes are enriched in MAPK signaling pathway, calcium signaling pathway and PI3K-AKT signaling pathway. EGFR-TKIs affect cancer cell growth and proliferation through these pathways, which may also have an impact on muscle growth. The relationship between EGFR-TKIs and muscle loss needs to be further investigated using clinical and experimental studies. Diarrhea is one of the most common adverse events of EGFR-TKIs. In this study, 27.9% patients suffered from Grade ≥ 2 diarrhea. Our study suggests that patients suffering from Grade ≥ 2 diarrhea had a significantly higher rate of muscle loss (79.3% vs. 25.3%, $p < 0.001$). Therefore, timely management of diarrhea during EGFR-TKI treatment might contribute to maintaining muscle mass. Despite an overall improved tolerance, about 15% of patients treated with osimertinib still experienced

Table 2 Skeletal muscle mass changes during EGFR-TKIs therapy($n=104$)

Characteristic	Muscle loss($n=42$)	Muscle stable($n=62$)	*P* value
Age(years), n (%)			0.216
≥ 70	20(47.6)	22(52.4)	
< 70	22(35.5)	40(64.5)	
Gender, n (%)			0.185
Male	11(31.4)	24(68.6)	
Female	31(44.9)	38(55.1)	
Baseline muscle mass, n (%)			0.228
Low	28(45.2)	34(54.8)	
Normal	14(33.3)	28(66.7)	
Baseline muscle density			0.005
Low	26(55.3)	21(44.7)	
Normal	16(28.1)	41(71.9)	
Targeted therapy, n (%)			0.278
icotinib	27(37.0)	46(63.0)	
afatinib	15(48.4)	16(51.6)	
EGFR mutation status, n (%)			0.636
Exon 19 del	17(37.8)	28(62.2)	
Exon 21 L858R	25(42.4)	34(57.6)	
Response evaluation, n (%)			0.747
PR	21(38.9)	33(61.1)	
Non-PR	21(42.0)	29(58.0)	
Baseline Weight loss, n (%)			0.449
≥ 5%	10(47.6)	11(52.4)	
< 5%	32(38.6)	51(61.4)	
ECOG PS, n (%)			0.263
0 ~ 1	37(38.5)	59(61.5)	
≥ 2	5(62.5)	3(37.5)	
CCI, n (%)			0.242
0	23(35.9)	41(61.4)	
≥ 1	19(47.5)	21(52.5)	
Metastases, n (%)			0.633
Mono-organ	19(38.0)	31(62.0)	
Multi-organs	23(42.6)	31(57.4)	
Diarrhea, n (%)			< 0.001
≤Grade1	19(25.3)	56(74.7)	
≥Grade2	23(79.3)	6(20.7)	
Nutritional Risk			0.555
without	24(38.1)	39(61.9)	
with	18(43.9)	23(56.1)	
BMI (kg/m^2), n (%)			0.406
< 23	19(45.2)	23(54.8)	
≥ 23	23(37.1)	39(62.9)	

Abbreviations CCI, Charlson comorbidity index; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, Epidermal growth factor receptor tyrosine kinase inhibitors; L3, the third lumbar vertebra; PR, partial response; SD, stable disease

Grade ≥ 2 diarrhea according to the result from FLAURAL study. Thus, it is also essential to focus on diarrhea management and the surveillance of muscle mass during osimertinib therapy. In addition, the approved doses of EGFR-TKIs are fixed currently, without adjustment for physical size and reserves. Afatinib 40 mg/day has been approved as a first-line treatment for EGFR mutation-positive NSCLC. Diarrhea is the primary reason for dose reduction and treatment discontinuation. It is noteworthy that dose reduction occurred in 53.3% of patients in the LUX-Lung 3 study with the initiation of afatinib 40 mg/day [11]. Our previous study suggested that baseline sarcopenic patients had a higher rate of ≥ Grade 2 diarrhea (75.0 vs. 27.3%, $p=0.011$) and toxicity-related dose reduction (75.0 vs. 9.1%, $p=0.001$) when treated with afatinib 40 mg/day initially [29]. Therefore, sarcopenic patients might begin treatment with a lower initial administration dose of afatinib according to their tolerance.

Given that muscle loss is prevalent among patients receiving EGFR-TKIs, oncologists should monitor muscle mass during treatment and consider additional interventions such as nutritional support and exercise programs, especially for high-risk patients. Our study indicated that patients with baseline low muscle density had a higher rate of muscle loss during targeted therapy (55.3% vs. 28.1%, $p=0.005$). The revised European consensus on the definition and diagnosis of sarcopenia emphasizes that low muscle strength is a key characteristic of sarcopenia [30]. A previous study showed that muscle density, rather than muscle size, correlates well with muscle strength and physical performance [13]. Therefore, routine evaluation of muscle density might contribute to the early intervention of muscle loss for lung cancer patients.

A recent study suggests that patients with cancer-associated cachexia have distinct tumor genomic and transcriptomic profiles [31]. Genetic analysis from our study indicated muscle loss group had a higher proportion of MDM2 amplification and PIK3CA alterations. Previous studies have revealed that concurrent genetic alterations could play an important role in the response and resistance to EGFR-TKIs in EGFR-mutant NSCLC [32]. PIK3CA mutations are found in about 2–5% of NSCLC patients and are considered rare oncogenic drivers in NSCLC. A previous study found that patients with concurrent PIK3CA mutations had shorter median PFS (7.8 vs. 10.9 months, $p=0.001$) to EGFR-TKI [33]. Additionally, MDM2 is a primary negative regulatory factor of the tumor suppressor protein P53. A study showed that MDM2 amplification was independently associated with worse PFS (HR 2.46, 95% CI:1.02 ~ 5.94, $p=0.046$) to third-generation EGFR-TKI [34]. Promotion of epithelial mesenchymal transformation, angiogenesis, and activation of bypass signaling pathways such as nuclear factor-κB are possible mechanisms of EGFR-TKI resistance in lung cancer with MDM2 amplification [35]. Therefore, the limited survival benefits from EGFR-TKIs for the muscle loss group might be related to the above genetic alterations. Early muscle loss might serve as a

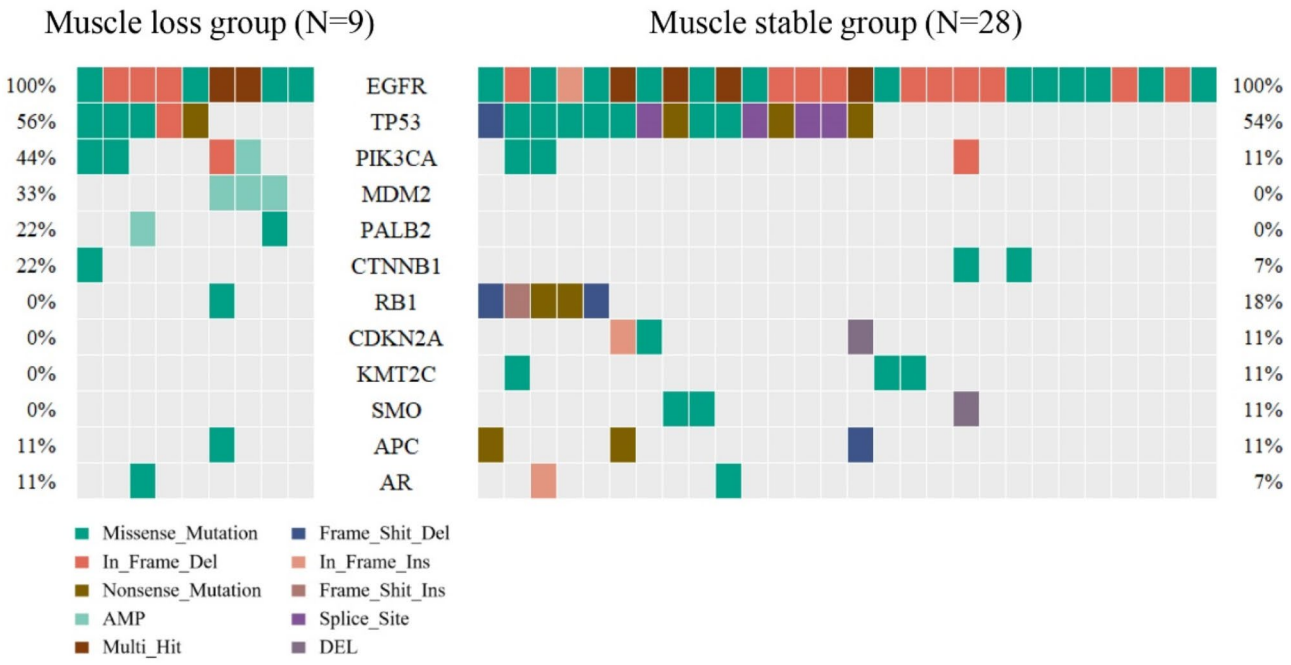

Fig. 3 Landscape of genetic alterations in muscle loss group and muscle stable group

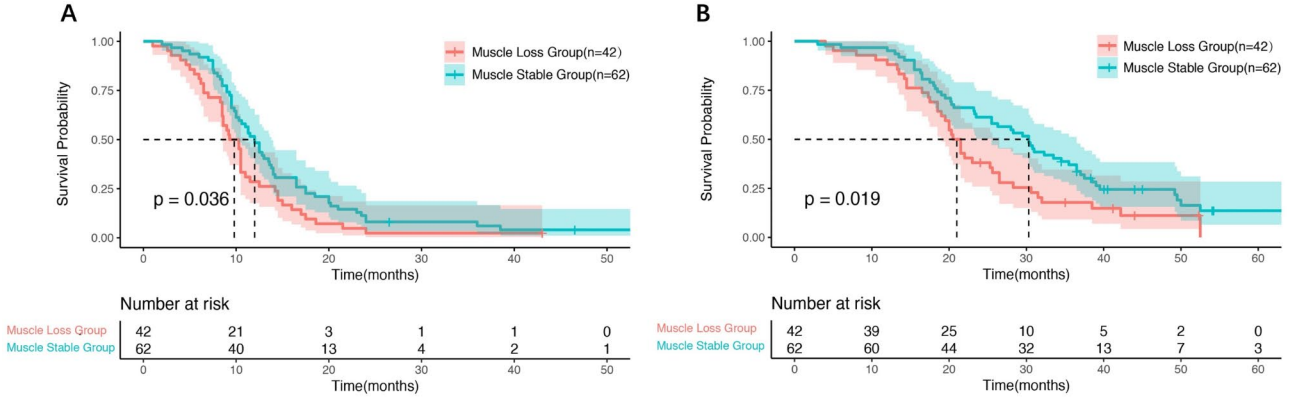

Fig. 4 Kaplan–Meier survival curves. (**A**) Progression free survival comparison between muscle loss group and muscle stable group. (**B**) Overall survival comparison between muscle loss group and muscle stable group

surrogate marker for disease aggressiveness and treatment resistance. Further studies are warranted to evaluate whether more aggressive treatment strategies, such as EGFR-TKI combined with chemotherapy or bevacizumab, can contribute to maintaining muscle mass for advanced NSCLC patients with EGFR co-mutations.

Our study had several limitations. Firstly, although this study indicates that patients experiencing early muscle loss have a reduced PFS compared to those in the muscle-stable group, the observational design of the study lacks the capacity to establish a definitive causal link between muscle loss and unfavorable prognosis. Additional prospective research is essential to investigate the prognostic impact of early muscle mass depletion. Secondly, data regarding physical activity and detailed nutritional status were not included in this retrospective study. Muscle loss causes should be studied more in depth to identify rational interventions in future research. Thirdly, while the study revealed an increased prevalence of MDM2 amplification and PIK3CA mutations within the muscle loss group, the retrospective design and limited sample size of the study preclude the establishment of concrete links between genetic mutations and muscle wasting. Additional investigations are essential to elucidate the precise connection between particular genetic alterations and the occurrence of muscle mass depletion. Finally, considering that osimertinib is associated with lower incidence of diarrhea compared with first and second-generation EGFR-TKIs, further study was warranted to evaluate skeletal muscle change during osimertinib treatment.

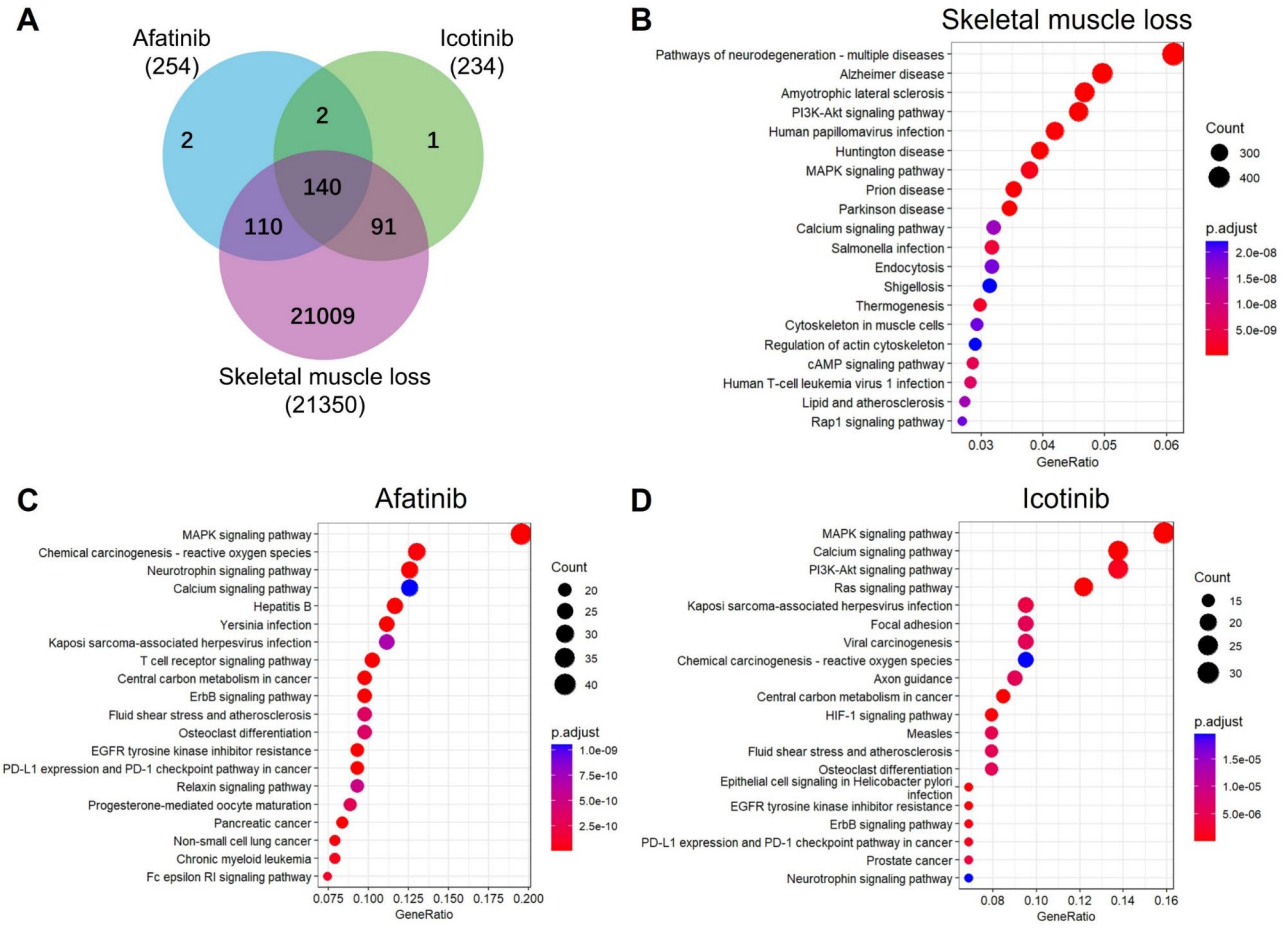

Fig. 5 KEGG pathway analysis of genes associated with skeletal muscle loss, afatinib and icotinib. **A**. Venn diagram showing the number of shared and unique genes. KEGG pathway enrichment analysis of genes associated with skeletal muscle loss (**B**), afatinib (**C**) and icotinib (**D**)

Despite these limitations, our results underscore the importance of monitoring muscle mass status using routine CT scans in clinical practice for advanced lung cancer patients.

Conclusion

This study highlighted that patients could experience skeletal muscle loss during EGFR-TKI targeted therapy and identified the potential high-risk patients for skeletal muscle loss. Additionally, early skeletal muscle loss during EGFR-TKI therapy may be associated with a worse PFS in advanced lung adenocarcinoma patients. Further studies are warranted to investigate the management of muscle mass loss during targeted therapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13775-z.

Supplementary Material 1: Supplementary Information Table S1. Targeted regions of pan-cancer panel sequencing. Table S2-3. Univariate and multivariate analysis of PFS and OS in patients receiving first-line EGFR-TKIs. Table S4-6. Lists of genes associated with afatinib, icotinib, and muscle loss.

Supplementary Material 2

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Author contributions
Study concept: Xin Nie, Lin Li. Muscle measurements: Mingzhu Zou, Di Ma. Data acquisition: Xin Nie, Ping Zhang, Di Cui. Statistical analysis: Xin Nie, Gang Cheng. Manuscript preparation: Xin Nie, Chenhui Song.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethical approval
This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review boards of Beijing Hospital (2020BJYYEC-106-01).

Informed consent
Patient consent was waived because of the retrospective nature of the study and the analysis of anonymous clinical data.

Competing interests
The authors declare no competing interests.

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References

1. Yang M, Shen Y, Tan L, Li W. Prognostic value of sarcopenia in lung cancer: A systematic review and meta-analysis. Chest. 2019;156(1):101–11.
2. Cortellini A, Palumbo P, Porzio G, Verna L, Giordano AV, Masciocchi C, et al. Single-institution study of correlations between skeletal muscle mass, its density, and clinical outcomes in non-small cell lung cancer patients treated with first-line chemotherapy. Thorac Cancer. 2018;9(12):1623–30.
3. Bye A, Sjøblom B, Wentzel-Larsen T, Grønberg BH, Baracos VE, Hjermstad MJ, et al. Muscle mass and association to quality of life in non-small cell lung cancer patients. J Cachexia Sarcopenia Muscle. 2017;8(5):759–67.
4. Roeland EJ, Ma JD, Nelson SH, Seibert T, Heavey S, Revta C, et al. Weight loss versus muscle loss: Re-evaluating inclusion criteria for future cancer cachexia interventional trials. Support Care Cancer. 2017;25(2):365–9.
5. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, Mccargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539–47.
6. Recio-Boiles A, Galeas JN, Goldwasser B, Sanchez K, Man L, Gentzler RD, et al. Enhancing evaluation of sarcopenia in patients with non-small cell lung cancer (NSCLC) by assessing skeletal muscle index (SMI) at the first lumbar (L1) level on routine chest computed tomography (CT). Support Care Cancer. 2018;26(7):2353–9.
7. Stene GB, Helbostad JL, Amundsen T, Sørhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol. 2015;54(3):340–8.
8. Kakinuma K, Tsuruoka H, Morikawa K, Furuya N, Inoue T, Miyazawa T, et al. Differences in skeletal muscle loss caused by cytotoxic chemotherapy and molecular targeted therapy in patients with advanced non-small cell lung cancer. Thorac Cancer. 2018;9(1):99–104.
9. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–57.
10. Shi YK, Wang L, Han BH, Li W, Yu P, Liu YP, et al. First-line Icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): A phase 3, open-label, randomized study. Ann Oncol. 2017;28(10):2443–50.
11. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of Afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327–34.
12. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213–22.
13. Wang L, Yin L, Zhao Y, Su Y, Sun W, Chen S, et al. Muscle density, but not size, correlates well with muscle strength and physical performance. J Am Med Dir Assoc. 2021;22(4):751–9.
14. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, Mccargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.
15. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85(1):115–22.
16. Prado CM, Lieffers JR, Mccargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and Gastrointestinal tracts: A population-based study. Lancet Oncol. 2008;9(7):629–35.
17. Macdonald AJ, Greig CA, Baracos V. The advantages and limitations of cross-sectional body composition analysis. Curr Opin Support Palliat Care. 2011;5(4):342–9.
18. Cibulskis K, Lawrence MS, Carter SL, Sivachenko A, Jaffe D, Sougnez C, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol. 2013;31(3):213–9.
19. Drug-Gene Interaction Database. https://www.dgidb.org. Accessed 14 October 2024.
20. Pharmacogenomics Knowledge Base. https://www.pharmgkb.org. Accessed 14 October 2024.
21. SwissTargetPrediction. http://www.swisstargetprediction.ch. Accessed 14 October 2024.
22. SuperPred. https://prediction.charite.de. Accessed 14 October 2024.
23. GeneCards.– the human gene database. https://www.genecards.org. Accessed 18 October 2024.
24. Jang MK, Park C, Hong S, Li H, Rhee E, Doorenbos AZ. Skeletal muscle mass change during chemotherapy: A systematic review and meta-analysis. Anticancer Res. 2020;40(5):2409–18.
25. Kucukarda A, Gokyer A, Gokmen I, Bekir HM, Kostek O, Kurt N, et al. Skeletal muscle loss during anti-epidermal growth factor receptor therapy is an independent prognostic factor on non-small cell lung cancer patients survival. J Buon. 2021;26(3):853–60.
26. Minami S, Ihara S, Nishimatsu K, Komuta K. Low body mass index is an independent prognostic factor in patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitor. World J Oncol. 2019;10(6):187–98.
27. Naito T, Okayama T, Aoyama T, Ohashi T, Masuda Y, Kimura M, et al. Skeletal muscle depletion during chemotherapy has a large impact on physical function in elderly Japanese patients with advanced non-small-cell lung cancer. BMC Cancer. 2017;17(1):571.
28. Weber B, Agca S, Domaniku A, Bilgic SN, Arabaci DH, Kir S. Inhibition of epidermal growth factor receptor suppresses parathyroid hormone-related protein expression in tumours and ameliorates cancer-associated cachexia. J Cachexia Sarcopenia Muscle. 2022;13(3):1582–94.
29. Nie X, Zhang P, Gao JY, Cheng G, Liu W, Li L. Sarcopenia as a predictor of initial administration dose of Afatinib in patients with advanced non-small cell lung cancer. Thorac Cancer. 2021;12(12):1824–30.
30. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.
31. Al-Sawaf O, Weiss J, Skrzypski M, Lam JM, Karasaki T, Zambrana F, et al. Body composition and lung cancer-associated cachexia in tracerx. Nat Med. 2023;29(4):846–58.
32. Guo Y, Song J, Wang Y, Huang L, Sun L, Zhao J, et al. Concurrent genetic alterations and other biomarkers predict treatment efficacy of EGFR-TKIs in EGFR-Mutant Non-Small cell lung cancer: A review. Front Oncol. 2020;10:610923.
33. Qiu X, Wang Y, Liu F, Peng L, Fang C, Qian X, et al. Survival and prognosis analyses of concurrent PIK3CA mutations in EGFR mutant non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors. Am J Cancer Res. 2021;11(6):3189–200.
34. Kim Y, Lee B, Shim JH, Lee SH, Park WY, Choi YL, et al. Concurrent genetic alterations predict the progression to target therapy in EGFR-Mutated advanced NSCLC. J Thorac Oncol. 2019;14(2):193–202.
35. Hou H, Sun D, Zhang X. The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. Cancer Cell Int. 2019;19:216.

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