A retrospective study of hypofractionated radiotherapy for small cell lung cancer

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Research

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Abstract

Purpose: Hypofractionated radiotherapy (HypoRT) shows the superiority in cancer treatment because of its high biological equivalent dose. This retrospective study aims to evaluate the toxicity and efficacy of HypoRT on small cell lung cancer (SCLC).

Methods: Medical records of SCLC patients between July 2018 and October 2019 were collected. All patients treated with chemotherapy plus HypoRT (PTV: 30 Gy/10F, PGTV: 45 Gy/10F) were eligible for analysis. The chemotherapy was performed for a total of 4-6 cycles by using Etoposide plus Cisplatin or Carboplatin in peri-radiotherapy phase. Meanwhile, indexes including in-field recurrence rate (ifRR), in-field relapse-free survival (ifRFS) and overall survival (OS) were calculated.

Results: Medical data of 30 patients were eligible for analysis. Male to female ratio was 19: 11. The median age was 64 (range from 46 to 75 years old, 95% CI: 52.5-83.75). The median follow-up time was 15 months (range from 1 to 19 months). In follow-up period, either radiation esophagitis or radiation pneumonitis of grade 3 occurred in 6.7% of the patients (2/30). The incidences of severe hematologic toxicities (grade 3/4) including leukopenia, granulocytopenia, thrombocytopenia and anemia were 33.3%, 66.7%, 26.7% and 16.7%, respectively. The ifRR post-HypoRT was 6.7% (2/30) with a median ifRFS of 15 months (rang from 1 to 19 months, 95% CI: 11.25-18.75) and a median OS of 15 months (range from 1 to 19, 95% CI: 11.25-18.75).

Conclusion: HypoRT can be tolerated by most of enrolled patients, and HypoRT exhibits its efficacy in controlling SCLC tumors.

Introduction

Small cell lung cancer (SCLC) accounts for 15% ~ 17% of all lung cancers.(1) Comparing with non-small cell lung cancer (NSCLC), it has the characteristics of more rapid doubling time, higher growth rate and earlier metastasis.(2) The combined-modality treatment of chemotherapy and thoracic radiotherapy (TRT), especially concurrent chemoradiotherapy (CRT) for patients with good performance status, is the standard treatment for SCLC.(3) And prophylactic cranial irradiation (PCI) can prolong the survival of patients with limited stage small cell lung cancer (LS-SCLC) and extensive stage small cell lung cancer (ES-SCLC), who achieve a complete or partial remission after systemic therapy.(3) According to published data, the median overall survival time (OS) of LS-SCLC after standard therapy was calculated as 19.9 months,(4) and the median OS of ES-SCLC was about 12 months.(5)

Regarding to the dose-fraction regimen of TRT for SCLC, HARMARK INT0096 study showed that 45 Gy in 3 weeks (1.5 Gy per fraction, twice per day) can significantly improve the OS comparing to conventional mode (45 Gy/25F in 5 weeks).(6) In this situation, Hyperfractionated-accelerated radiotherapy (HyperRT) was recommended as the standard of care for controlling primary tumors of SCLC. But comparing to the conventional, although HyperRT showed a high biological equivalent dose (BED), it still had a high incidence of grade 3 or more severe esophagitis. Besides, a series of study in the Cancer and Leukemia

Group B (CALGB) showed that conventionally fractionated radiotherapy of a prescribed dose of 70 Gy with concurrent chemotherapy improved survival of LS-SCLC patients, and radiation-related toxicities were tolerable.(4, 7-10) On this basis, Phase III CONVERT study compared the efficacy and toxicity between HyperRT (45 Gy/30 F, twice-daily) and conventionally fractionated radiotherapy (66 Gy/33 F, once-daily) with concurrent chemotherapy on LS-SCLC, and relevant results showed similar survival and toxicity when performing these two regimens except for more severe neutropenia in HyperRT arm. This result supported the use of conventionally fractionated radiotherapy (66 Gy/33 F, once-daily) as the standard of care for LS-SCLC patients.(11)

Nowadays, conventionally fractionated radiotherapy remains the most common treatment for SCLC in most regions of China. Nonetheless，in previous study showed that once-daily HypoRT can both shorten the overall treatment time and optimize survival and tumor control.(12) In 1993, Murray *et al*. reported the therapeutic efficacy of HypoRT (40 Gy/15 F) on LS-SCLC, presenting a median OS and 5-year survival rates of 21.2 months and 22%, respectively.(13) In a subsequent phase II study, HypoRT (55 Gy/22F in 4.5 weeks) with concurrent chemotherapy achieved a median OS of 28.5 months and a two-year survival rate of 58.2%.(14) Beside, a retrospective study showed that HypoRT (55 Gy/22 F) had similar toxicity and efficacy as conventionally fractionated radiotherapy (56-66 Gy / 28-33F) did, presenting that HypoRT arm had a median OS of 27.2 months and a 2-year survival rate of 62.2%.(15) On this basis, we treated a portion of SCLC patients in our institution with HypoRT in the past 1.5 years. This retrospective study aimed to evaluate the toxicity and efficacy of HypoRT.

Materials And Methods

Patients

This study was approved by the Ethics Committee of the First Hospital of Jilin University.. All patients signed the informed consent form before receiving HypoRT. A database of 30 patients with SCLC confirmed by histology or cytology from July 2018 to October 2019 at the First Hospital of Jilin University. was retrospectively reviewed. Routine staging assessment for SCLC included a medical history and physical examination, blood count and comprehensive chemistry panel with renal and hepatic function tests, contrast-enhanced chest CT scan, contrast-enhanced abdomen CT scan, bone scan, and brain MRI. Whole-body PET-CT was not mandatory. The initial staging of SCLC was based on the two-stage classification of Veterans Administration Lung Study Group (VALSG) and the improved staging system proposed by the International Association for the Study of Lung Cancer (IASLC).(16) The ES-SCLC patients who successfully achieved to residual tumors in lung after multiple cycles of chemotherapy were eligible for analysis as well.

Treatment delivery

In peri-radiotherapy phase, all patients received chemotherapy, which was performed every 3 weeks for a total of 4 ~ 6 cycles. The regimens included etoposide (100 mg/m^2, day 1 ~ 3) plus cisplatin (25 mg/m^2,

day 1-3), or plus carboplatin (AUC 5-6, day 1). All the LS-SCLC cases received HypoRT immediately after 2 ~ 3 cycles of chemotherapy.

In radiotherapy phase, patients were placed in the supine position with a thermoplastic thoracic peritoneum with both arms over head. The enhance-contrast CT scan of simulation with a thickness of 5 mm was used. Target volumes were delineated refered to INT0096 document.(6) Gross target volume (GTV) was based on the restaging chest CT obtained after induction chemotherapy, including the residual primary tumor and lymph nodes >1 cm in short axis diameter observed on initial thoracic CT scans. The clinical target volume (CTV) included GTV and previously involved lymph node areas based on pre-chemotherapy CT scans. The planned target area volume (PTV) was was generated with a margin of 1.0-1.5 cm added to CTV. No selective nodule irradiation. The planned gross target volume (PGTV) expanded by a margin of 0.3 to 0.5 cm from GTV.

CT images were imported to the treatment planning system to create a treatment designation. Nineteen patients were treated by using step-shoot intensity-modulated radiotherapy (sIMRT) technique, and eleven patients were treated by using volumetric modulated arc therapy (VMAT) technique. patients with sIMRT used Pinnacle@9.10 planning system of Philips to make treatment plan, the others used Eclipse@13.6 planing system of Varian. Radiotherapy treatment used Varian linear accelerators. Herein, the prescribed doses of HypoRT were simultaneously performed as 45 Gy for PGTV and 30 Gy for PTV, which were arranged in 10 fractions in 2 weeks. According to UK consensus of SBRT (17), the doses of organs at risk were constrained as follows: V_{20} for whole lung < 20%; D_{5cc} for esophagus < 30 Gy, D_{max} for esophagus < 45 Gy; V_{15cc} for heart < 34.4 Gy, D_{max} for heart < 40 Gy; V_{5cc} for trachea < 50 Gy, D_{max} < 56 Gy; $V_{0.35cc}$ for spinal cord < 26.4 Gy, D_{max} for spinal cord < 33.6 Gy.

Radiation pneumonitis, radiation esophagitis and hematologic toxicity were assessed by using RTOG criteria. Tumor response was assessed according to RECIST version 1.1. All patients underwent complete blood count, comprehensive chemistry panel with renal and hepatic function tests, and CT of the chest at 1 month after the completion of therapy. Patients with objective response (stable disease, partial response and complete response) were considered for PCI. The follow-up times were typically 3 months for the first 2 years. During the follow-up period, chest CT and abdominal CT or ultrasound were performed routinely. Brain MRI and bone imaging were performed at the onset of symptoms.

Statistical analysis

OS was defined as time from HypoRT to death. ifRFS was defined as time from the end of HypoRT to relapse in field or death. Time to locoregional recurrence was defined as time from the initiation of treatment until the date of locoregional failure as a first event. Time to distant metastasis was defined as time from the radiotherapy until the date of distant metastasis failure. The Statistical Package for Social Sciences (SPSS version 20.0, IBM, USA) software was used for statistical analyses. Comparisons of categorical variables were performed using the χ 2 test. Statistical significance was defined as a p-value less than 0.05. The Kaplan-Meier method was used to estimate OS and ifRFS.

Results

A total of 30 patients treated with HypoRT plus chemotherapy were eligible for analysis. All the medical data of patients can be evaluated. At initial diagnosis, there were 25 limited-stage cases and 5 extensive-stage cases, which had successfully achieved to residual tumors in lung after multiple cycles of chemotherapy. **Table 1** summarized the baseline characteristics of the patients.

Table 1 Patient demographics and clinical characteristics

Characteristics	HypoRT group (n=30)
Gender	
Male	19
Female	11
Age (yr)	
Median	64
Range	46-75
Smoking	
Yes	19
No	11
Performance status(ECOG)	
0-1	28
2	2
Stage	
Limited-stage	25
Extensive-stage	5
Cycles of chemotherapy	
<4 cycles	3
≥4 cycles	27
PCI	
Yes	9
No	21

Toxicity

Table 2 listed acute toxicities by site and grade. The most common radiation-associated acute complication was radiation esophagitis, which presented swallow pain and/or poststernal burning sensation commonly at 7 to 10 days post-HypoRT with the incidence of 16.7% (5/30) at Grade 2 and 6.7% (2/30) at Grade 3. All these patients were manageable by using the treatment including acid suppression, anti-inflammation, relieving pain and nutrition support. Besides, 10% of patients (3/30) had Grade 2 radiation pneumonitis, and 6.7% of patients (2/30) had Grade 3 radiation pneumonitis. No Grade 4 or pneumonitis-related death were observed. Of note, all the cases of radiation pneumonitis were diagnosed at 3 to 6 months post-HypoRT, with a similar time window of radiation pneumonitis occurrence as that observed in conventional radiotherapy. Besides, radiation-induced cardiac injury with atrial fibrillation occurred in one patient. The incidences of Grade 3 and 4 hematologic toxicities including leukopenia, granulocytopenia, thrombocytopenia and anemia were 33.3% (10/30), 66.7% (20/30), 26.7%

(8/30) and 16.7% (5/30), respectively. No death from HypoRT-related toxicity was observed. In addition, we observed that the rates of Grade 3 radiation pneumonitis and radiation esophagitis were both 5.3% (1/19) versus 9.1% (1/11) for the sIMRT and VMAT arms, respectively (p=0.685). **Table 3** lists severe radiation pneumonitis and radiation esophagitis.

Table 2 Acute toxicities

Acute toxicities		HypoRT group (n=30)		
Grade	1	2	3	4
Esophagitis	0	5(16.7%)	2(6.7%)	0
Pneumonitis	0	3(10%)	2(6.7%)	0
leukopenia	1(3.3%)	13(43.3%)	7(23.3%)	3(10%)
Granulocytopenia	0	8(26.7%)	13(43.3%)	7(23.3%)
Thrombocytopenia	4(13.3%)	3(10%)	5(16.7%)	3(10%)
Anemia	9(30%)	8(26.7%)	5(16.7%)	0

Table 3 Severe radiation pneumonitis and radiation esophagitis in the sIMRT and VMAT groups

Acute toxicities	sIMRT group(n= 19)		VMAT geoup(n= 11)		*P*
Grade	3	4	3	4	
Pneumonitis	1(15.3%)	0	1(15.3%)	0	0.685
Esophagitis	1(15.3%)	0	1(15.3%)	0	0.685

Response evaluation

At 1 month post-HypoRT, primary tumor remission was assessed by using chest CT scan among all patients. According to the RECIST version 1.1, the overall objective response rate was 100%, presenting that 5 patients (16.7%) achieved to complete remission in their primary tumors, and 22 patients (73.3%) exhibited partial remission in their primary tumors. Other 3 patients (10%) achieved to stable disease. **Figure 1** shows the best percentage change from baseline in target lesion size.

Survival

The last follow-up date was March 31th, 2020. The median follow-up was 15 months, with the longest of 1 month and the longest of 19 months. Among all enrolled patients, the ifRR post-HypoRT was calculated as 6.7% (2/30) with the median ifRFS of 15 months (rang from 1 to 19 months, 95% CI:11.25-18.75) and the median OS of 15 months (range from 1 to 19, 95% CI: 11.25-18.75). The Kaplan-Meier ifRFS and OS curves are shown in **Figure 2 a** and **Figure 2 b**. When this paper was written, a total of 10 patients died. Most of them died from distant metastasis rather than HypoRT related toxicity.

Patterns of failure

Table 4 showed the failure patterns for all patients. Three patients (10%) developed locoregional failure during follow-up. The locoregional failure included in-field failure and recurrence outside PTV but within the ipsilateral hilar, bilateral mediastinal and bilateral supraclavicular nodal basin regions. Distant

metastasis was the main failure pattern. Nine patients (30%) developed distant metastasis. Herein, the brain was the most frequent site with an incidence of 16.7%, followed by bone (10%) and liver (10%).

Table 4 Failure patterns

	HypoRT group (n=30)
Failure rates	13(43.3%)
Initial failure pattern	
Locoregional failure	4(23.3%)
In field	1(3.3%)
Out of field	2(6.7%)
Both	1(3.3%)
Distant	9(30%)
Liver only	2(6.7%)
Bone only	1(3.3%)
Brain only	4(23.3%)
Multiple sites	2(6.7%)
Both locoregional and distant failure	0

Discussion

Radiotherapy and chemotherapy remain the mainstay of treatment for SCLC patients. Regarding to LS-SCLC, a meta-analysis indicates that integration of radiotherapy into etoposide/platinum chemotherapy gives rise to a reduction of 14% in mortality and an improvement of 5.4% in 3-year survival of LS-SCLC patients.(18) At a certain extent, powerful locoregional control by thoracic radiotherapy contributes to this process. As documented, the local control rate of thoracic radiation achieves to 25.3%, thus benefiting the survival of LS-SCLC patients.(19) This case can be translated into ES-SCLC as well. A meta-analysis of two randomized trials indicates that thoracic radiation can improve OS and progression-free survival of ES-SCLC patients.(20) As mentioned above, HyperRT of 45 Gy and conventionally fractionated radiotherapy of 66 Gy perform well in controlling primary tumors of SCLC. Besides, although HypoRT regimens for SCLC were rarely investigated in past years, but an existing evidence still revealed the therapeutic efficacy of HypoRT on SCLC as well. (14) As advancing in radiation technology and our insights into the radiobiology related to malignant tumors, HypoRT is increasingly being used to treat early-staged tumors or metastatic tumors. In fact, HypoRT commonly gives rise to higher BED than conventional RT. In theory, it is widely accepted that a high BED will give rise to increased tumor control rate across cancers. In addition, shortening RT period is another benefit of HypoRT, and a previous study found that shortening RT period will cause increased local control and survival of SCLC patients.(21) On this basis, we carried out this study, and retrospectively analyzed the toxicity and efficacy of HypoRT in the treatment of SCLC.

In the present study, we assessed the toxicity of patients after receiving HypoRT in the first place. Herein, we observed that the most common grade 3 or more acute toxicity was myelosuppression. Besides,

radiation pneumonitis and radiation esophagitis were also presented in a portion of enrolled patients. Comparing to the published data, HyperRT was reported to cause a high risk of leukopenia and esophagitis.(6) Moreover, patients treated with conventional RT of 70 Gy also developed severe leukopenia and esophagitis as well.(4) In our study, one-third of patients experienced severe leukopenia, and incidence of Grade 3 radiation esophagitis was 6.67%. Intriguingly, most of patients developed their radiation esophagitis at 7-10 days post-HypoRT. Another toxicity that we paid close attention was radiation pneumonitis. In INT0096 study, the incidence of severe pneumonitis with HyperRT was reported as 4%.(6) In our study, two patients were diagnosed as grade 3 radiation pneumonitis at 3-6 months post-HypoRT, and no grade 4 or pneumonitis-related deaths were observed. In addition, a retrospective study reported that the incidences of severe radiation esophagitis and radiation pneumonitis related to conventional RT was 24.0% and 6.0%, respectively, and the incidence by HyperRT was 20.0% and 4.0%, respectively. (22) Additionally, no significant difference was found in the incidence of severe radiation pneumonitis and radiation esophagitis between sIMRT and VMAT groups. Thus, most of enrolled patients in our study can tolerate HypoRT. We believe several reasons can be attributed to this notion. Foremost, in this study, all LS-SCLC patients received 3-4 cycles of induction chemotherapy, and all ES-SCLC patients received 6 cycles of chemotherapy. The reduction in tumor size due to induced chemotherapy may result in a smaller radiation range and radiation dose to surrounding normal tissues, potentially reducing the incidence of acute toxicity.(23) A study also showed that the incidence of radiation pneumonitis is related to the volume of high-dose radiation in the lungs.(24) Another study showed a significant correlation between acute esophageal toxicity and esophageal D5cc and Dmax.(25) A Dmax of 56 Gy EQD_2^{10} and a D 5cc of 35.5 Gy EQD_2^{10} were observed without severe radiation esophagitis.(25) In this study, dose limit of D5cc<30 Gy and Dmax<45 Gy may explain the esophageal tolerance. Moreover, the duration of HypoRT was only 2 weeks and could be completed in the interim between 2 cycles of chemotherapy, which was also considered to contribute to fewer toxicities.

The preliminary results showed that this new HypoRT regimen achieved a ifRR of 6.67% (2/30), which was better than the results in the literature. In this study, the locoregional failure rate of 10% was observed, which was lower than that of daily RT of 70 Gy over 7 weeks in the CALGB studies (28%),(4) confirmed that the prolonged total radiotherapy time may be one of the reasons for the local treatment failure. In Radiation Therapy Oncology Group protocol 0239, the local failure rate was observed to be lower of 20%. And in that study, the accelerated RT with a relatively shorter total radiation time was used. (26) Although the median follow-up time was only 6 months and the median ifRFS of 15 months currently, the local control rate was very high, with only 6.67% of patients failing in the field of HypoRT.

In our study, the adverse reactions are acceptable, indicating that the regimen is well tolerable and clinically feasible. Notablely, the local control of HpoRT is very high. Additionally, such a RT schedule slashes the total duration of treatment. We are continuing to collect eligible SCLC patients and continue to follow current patients. Based on these results, a multicenter prospective trial is being conceived. Limitations of this study include retrospective studies, insufficient sample size, and differences in the total cycles of chemotherapy, which may affect the objectivity of the results. Approximately 70% (21/30)

of patients did not receive PCI, possibly due to the compliance of patients (most patients lived out of city). In addition, previous study showed that the use of PET/CT improves the accuracy of SCLC staging, which has a potential impact on the delineation of targets and the assessment of isolated nodule failure and distant failure.(27)However, only a few of patients in this study underwent PET/CT staging, which also caused limitations.

Conclusions

The incidence of HypoRT-related severe toxicity is not that high than we expect. Most of patients can tolerate the HypoRT plus chemotherapy, and the toxicities can be manageable by using symptomatic treatment. Besides, HypoRT exhibit therapeutic efficacies on SCLC patients.

Abbreviations

BED: biological equivalent dose, CRT: concurrent chemoradiotherapy , ES-SCLC: extensive stage small cell lung cancer , HyperRT: Hyperfractionated-accelerated radiotherapy, HypoRT: Hypofractionated radiotherapy , ifRFS: in-field relapse-free survival , ifRR: in-field recurrence rate, LS-SCLC: limited stage small cell lung cancer, NSCLC: non-small cell lung cancer, OS: overall survival, PCI: prophylactic cranial irradiation, SCLC: small cell lung cancer, TRT: thoracic radiotherapy.

Declarations

This study was approved by the Ethics Committee of the First Hospital of Jilin University. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. This work was supported by National Natural Science Foundation of China (No.81874254), and partially by Scientific research planning project of the 13th five year plan of Jilin Provincial Department of Education (JJKH20201043KJ). Authors' contributions: Pengyu Chang and Lihua Dong developed and planned this retrospective study. Man Li and Chao Ge were responsible for data collection and statistical analysis, and drafted the manuscript. Kunzhi Chen involved in the data collection. Libo Wang reviewed and commented on the results of the study.

Competing interests

The authors declare that they have no competing interests.

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Figures

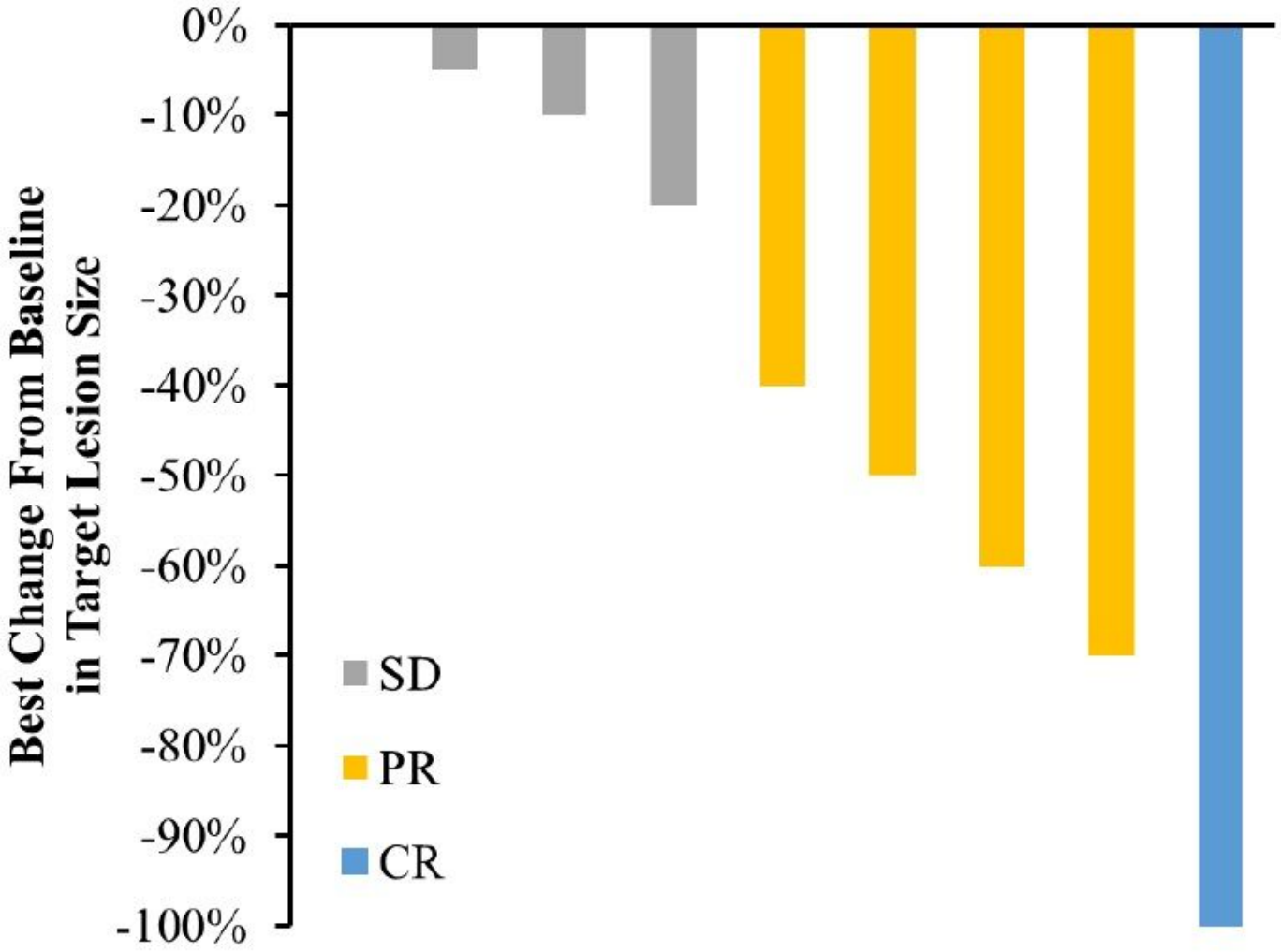

Figure 1

Best percentage change from baseline in target lesion size.

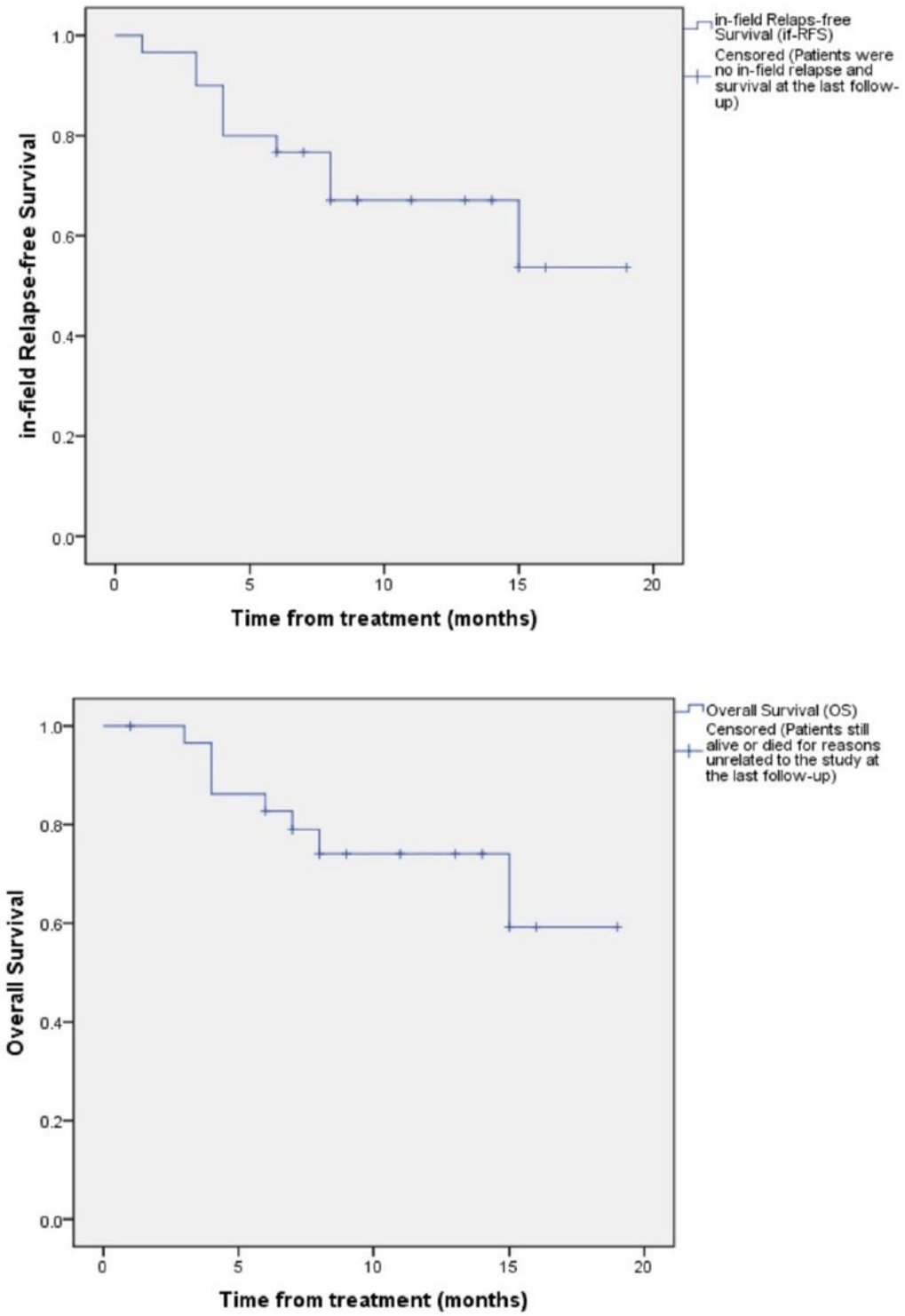

Figure 2

a In-field relapse-free survival for patients. b Overall survival for patients.