Published in final edited form as:

Clin Lung Cancer. 2019 March ; 20(2): 107–116. doi:10.1016/j.clcc.2018.10.010.

Stereotactic Body Radiation Therapy (SBRT) for Early-Stage Multiple Primary Lung Cancers

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Abstract

Background: Patients with multiple primary lung cancers (MPLC) increasingly receive multiple courses of stereotactic body radiation therapy (SBRT). We aimed to clarify the efficacy and safety of such treatments.

Patients and Methods: We reviewed a prospective lung SBRT database for patients treated for stage I non-small cell lung cancer between June 2004 and December 2015.

Results: 374 patients received a single course of SBRT, 14 received synchronous SBRT, 48 received metachronous SBRT alone, and 108 received surgery and metachronous SBRT. Median follow-up was 37.0 months for survivors. Patients that received a single course had a three-year overall survival (OS) of 54.2% (95% confidence interval [CI], 48.8–59.3%), three-year freedom from progression (FFP) of 67.3% (95% CI, 60.9–72.9), and grade 3 toxicity of 3.5%. Compared to single-course patients, patients receiving metachronous SBRT alone and patients receiving surgery and metachronous SBRT had improved OS (79.7% [95% CI, 64.4–88.9%], $P<0.0001$ and 95.4% [95% CI, 89.2–98.0%], $P<0.0001$, respectively) and FFP (85.8% [95% CI, 70.7–93.5], $P=0.03$ and 95.4% [95% CI, 89.2–98.0%], $P<0.0001$, respectively). Patients receiving synchronous SBRT had similar OS (46.4% [95% CI, 19.3–69.9%], $P=0.75$) and similar FFP (57.5% [95% CI, 25.3–80.0%], $P=0.17$) as single-course patients. There were no significant differences in rates of grade 3 or 1 toxicity between single-course patients and the other groups.

Conclusions: Patients that received either synchronous or metachronous SBRT had no significant detriment in OS or toxicity when compared to single-course patients. This supports the use of SBRT in patients with MPLC.

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Conflicts of Interest

None of the authors have conflicts of interest relevant to this study.

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MicroAbstract:

Outcomes of patients with early stage multiple primary lung cancer (MPLC) were reviewed from a prospective database at a high volume institution. Compared to patients receiving a single course of stereotactic body radiation therapy (SBRT), MPLC patients receiving multiple courses of SBRT or receiving surgery followed by SBRT had no significant detriment in survival, freedom from disease progression, or toxicity.

Introduction

Lung cancer remains the leading cause of cancer mortality, in the United States and abroad, with non-small cell lung cancer (NSCLC) comprising 85% of all cases.¹ As a result, there have been efforts supported by the U.S. Preventive Services Task Force to diagnose lung cancers at earlier and more treatable stages using annual, low-dose computed tomography (CT) for at-risk populations.² These screening efforts are part of the reason why up to 30% of lung cancer cases in the United States are now being diagnosed at an early stage, defined as either stage I or II.³ These early tumors can be successfully resected, with local control rates of up to 96% and overall survival (OS) rates of approximately 50–60% at 3 years.⁴ A significant obstacle to treating these patients is that many of them have underlying pulmonary or cardiac comorbidities that make them poor surgical candidates.⁵ Fortunately, stereotactic body radiation therapy (SBRT) has emerged as an effective treatment modality for medically inoperable, early-stage NSCLC patients, achieving local control rates similar to those of surgery.⁵

Current literature regarding disease control and treatment toxicity of SBRT has largely been limited to patients with a single early-stage NSCLC. However, medically inoperable patients who are diagnosed with multiple, simultaneous tumors may need to receive parallel courses of SBRT, (synchronous treatment). Likewise, medically inoperable patients who develop new primary tumors following initial treatment may need additional courses of SBRT (metachronous treatment). The efficacy and safety of SBRT for patients with synchronous and metachronous early-stage NSCLC is not well defined. Therefore, we retrospectively analyzed the clinical outcomes of this cohort of patients at our institution with high volumes of prior surgical patients. In contrast to other reports on MPLC, we compare these MPLC clinical outcomes to those of patients treated with SBRT for a single early-stage NSCLC at our institution.

Patients and Methods

Eligibility Criteria

An IRB-approved, prospective lung SBRT database was retrospectively analyzed for patients that were first treated with SBRT between June 2004 and December 2015 in the Department of Radiation Oncology at Washington University in St. Louis. All patients signed an informed consent document for inclusion in this database prior to receiving treatment.

The selection criteria for this study were as follows: 1) Patients must have American Joint Committee on Cancer 7th edition stage IA or IB NSCLC that has been confirmed by

pathology or clinically diagnosed by virtue of positron emission tomography (PET) and CT findings, if biopsy was deemed unsafe. 2) Patients must be free of any other malignancies or metastases at the time of SBRT administration. 3) Patients must have received definitive intent treatment. 4) Patients must have at least three months of follow-up after SBRT that includes at least one imaging study (either PET or CT scan) to assess response to therapy. 5) Patients must have not received prior conventionally fractionated thoracic radiation.

Eligible patients were then separated based on whether they received SBRT alone or first surgery and then SBRT. Patients that received SBRT alone were then separated based on whether they were treated with a single course, a synchronous course, or a metachronous course of SBRT. Metachronous SBRT courses were defined as treatments more than 3 months apart (Figure 1).

Treatment Methods

SBRT planning was performed as previously described.⁶ Patients were immobilized either by Elekta Stereotactic Body Frame (SBF) (Elekta, Crawley, England), BodyFix system (Medical Intelligence, Munich, Germany), or Alpha Cradle (Smithers Medical Products, North Canton, OH). To characterize tumor motion, patients underwent simulation using four-dimensional CT (4DCT), performed using a 16-slice CT (Somatom Sensation 16, Philips Medical, Cleveland, OH). If 4DCT showed tumor movement greater than 10 mm in any direction, abdominal compression was used in addition to the above immobilization techniques. Patients immobilized by BodyFix system additionally received two thoracic CT scans and a helical CT scan. Patients immobilized with SBF additionally received a helical CT of the thorax.

SBRT delivery was performed as previously described.^{6,7} Maximum intensity projections (MIP) were used to set the internal target volume (ITV) for the tumor and its path of motion. Planning target volume (PTV) was set as 5 mm around the border of the ITV. Radiation therapy was generally delivered using a 7–11 non-coplanar beam arrangement. Superposition/convolution algorithms were used to correct for heterogeneity. Dose was delivered to 95% of the PTV and was most commonly set to the 75 to 85% isodose line (range, 60 and 90% isodose line). Patients either received 5400 cGy in 3 fractions for peripheral lesions or 5000–5500 cGy in 5 fractions for tumors that were within 2 cm of the proximal bronchial tree or were adjacent to the mediastinal or pericardial pleura. The standards set in RTOG 0813⁸ and RTOG 0236⁹ were used for normal tissue dose limits.

Follow-up

Follow up consisted of physical examination and volumetric imaging with CT or PET/CT every 3 to 4 months after completion of therapy for the first two years and then every 6 months thereafter. If there was clinical suspicion for local, regional, or metastatic disease, patients underwent repeat assessment and evaluation similar to that at initial diagnosis.

Evaluation

Overall survival (OS) was calculated starting from the diagnosis date of the first NSCLC. The diagnosis dates were defined as the earliest conclusive biopsies or PET scans. Freedom

from progression (FFP) and local control were calculated starting from the date of the first surgery or SBRT fraction. Progression was defined as any primary tumor site, regional, or distant progression, identified either through CT or PET scan, that occurred after the completion of SBRT. If only one new lesion in the lungs was seen on CT imaging at a follow-up, it was defined as a new primary. If more than one lesion in the lungs was seen, it was defined as metastatic disease. Patients were censored if deceased but not counted as failure. Local failure was defined as any in-field progression that occurred after the completion of SBRT, identified by PET scan. It was assessed for each individual tumor that was treated with SBRT. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, versions 4.0.¹⁰ This assessment was generally performed prospectively by the treating physician. In cases where no grade was assigned, this was done by retrospectively interpreting the physician notes. Severe toxicity was defined as adverse events that were grade 3.

Statistical Analysis

All statistical comparisons were made between the group of patients that received a single course of SBRT and each of the other three treatment groups. Differences in baseline patient characteristics were assessed by Fisher's exact test for gender, Eastern Cooperative Oncology Group (ECOG) performance status, percentage of patients that have ever smoked, and percentage of tumors that were biopsied. The Wilcoxon Rank-Sum Test was used for the other patient characteristics. Cumulative rates of OS, FFP, local control, and toxicity were calculated using Kaplan-Meier survival analysis. Significance was calculated using a Wilcoxon test. The differences in severe toxicity and overall toxicity were assessed by two-tailed Fisher's exact tests. Values of $P < 0.05$ were considered statistically significant. The PHREG procedure was used for the multivariate analysis of the differences in OS and FFP intervals seen between the groups. All statistical analyses were performed by IBM SPSS Statistics, version 24 (IBM Corp., Armonk, N.Y., USA) and SAS, version 9.4 (SAS Institute Inc., Cary, N.C., USA).

Results

Characteristics

Table 1 shows the characteristics of the 544 eligible patients. 374 patients were treated with a single course of SBRT, 14 patients were treated with synchronous courses of SBRT, 48 patients were treated with metachronous courses of SBRT alone, and 108 patients were treated first with surgery for at least one tumor and then with metachronous SBRT for at least another tumor (Figure 1). Median follow-up time for the entire cohort was 26.7 months (range, 3–152 months), and 37 months for survivors (range 3–153). Women were 54% of the patients. Median age at the time of first diagnosis was 73 (interquartile range (IQR), 67–79), and median age-adjusted Charlson Comorbidity Score was 5 (IQR 4–7). Compared to patients that received SBRT for a single lesion, patients treated with metachronous SBRT alone ($P=0.04$) or both surgery and metachronous SBRT ($P=0.02$) had significantly better ECOG Performance Scores. Meanwhile, there was no statistical difference in performance scores between single treatment or synchronous SBRT patients ($P=0.15$).

Clinical Outcomes

Three-year OS, FFP, and local control rates and their 95% confidence intervals (95% CI) are listed in Table 2. Compared to patients that received a single course of SBRT, patients that received metachronous courses of SBRT alone ($P<0.0001$) and patients that received both surgery and metachronous SBRT ($P<0.0001$) had significantly higher OS. There was no significant decrease in OS for patients that received synchronous courses of SBRT ($P=0.75$, Figure 2). Patients that received synchronous courses of SBRT had no significant difference in FFP compared to patients that received a single course of SBRT ($P=0.17$). However, there was a significant increase in FFP in patients that received both surgery and metachronous SBRT ($P<0.0001$) and in patients that received metachronous courses of SBRT alone ($P=0.03$, Figure 3). Compared to patients that received a single course of SBRT, there appeared to be a decrease in local control for patients that received synchronous SBRT treatments ($P=0.06$). However, there was an increase in patients that received metachronous SBRT ($P=0.10$) and a statistically significant increase in patients that received both surgery and SBRT ($P=0.007$, Figure 4).

When only patients with at least 1 year of follow-up were included in the analysis, patients that received a metachronous course of SBRT ($P=0.006$) or both surgery and metachronous SBRT ($P<0.001$) continued to have significantly higher OS, while synchronous patients still did not have significantly decreased OS ($P=0.30$). For FFP, the only significant change was that the higher FFP in the metachronous group was no longer statistically significant ($P=0.17$) when compared to the single treatment group. For local control, the only significant change was that the decrease seen in the synchronous group became statistically significant ($P<0.001$) despite the three-year local control rate staying at 75.0%.

Multivariate analysis was performed to look for the patient characteristics that predicted OS and FFP interval lengths. The statistically significant patient attributes in order of decreasing significance were type of tumor (i.e. single, synchronous, metachronous) ($P<0.0001$), ECOG ($P<0.0001$), gender ($P=0.008$), and central location ($P=0.03$). For FFP, the only statistically significant attribute was type of tumor ($P<0.0001$).

Toxicity

The severe (grade 3) toxicity rate for patients treated with SBRT for single lesions was 3.5% and the overall (any grade) toxicity rate was 29.4%. There was no significant difference in severe or overall toxicity rates for patients treated with synchronous SBRT, who had rates of 14.3% ($P=0.10$) and 50% ($P=0.14$), respectively. Likewise, there was no significant difference in severe or overall toxicity rates for patients treated with metachronous SBRT alone, who had rates of 4.2% ($P=0.68$) and 37.5% ($P=0.24$), respectively, or for patients treated with surgery and metachronous SBRT, who had rates of 5.6% ($P=0.40$) and 33.3% ($P=0.48$), respectively. There were 2 total cases of grade 5 toxicities, which consisted of 1 case of hemoptysis in a patient treated with SBRT for a single lesion and 1 case of pneumonitis in a patient treated with SBRT alone for metachronous lesions (Table 3). When Kaplan-Meier analysis was performed for the separate incidences of radiation pneumonitis or chest wall toxicity, there were no significant

differences between the single treatment group and the other three groups (Figure 5A and 5B).

Discussion

For patients with a single stage I NSCLC lesion, SBRT and surgery appear to achieve similar OS rates.^{4,11–14} However, for patients that have either synchronous or metachronous multiple primary lung cancers (MPLC), the results have been less encouraging for SBRT. Chang et al. studied a sample of 39 synchronous MPLC patients and 62 metachronous MPLC patients and found that synchronous SBRT achieved a significantly lower four-year OS rate compared to metachronous SBRT (39.7% vs 52.7%) and a significantly lower four-year progression free survival (PFS) rate (30.4% vs 75.6%).¹⁵ Although Chang et al. did not define PFS, it is likely similar to our use of FFP. The PFS rate was numerically larger than the OS rate in their synchronous cohort, which means that they also censored patients who were deceased in their PFS analysis. These authors also called 7 fractions of 10 Gy each SBRT, while we have limited SBRT to 5 fractions. Likewise, a study by Creach et al. used a sample of 15 synchronous patients and 48 metachronous patients and found that the two-year OS rate was significantly lower for the synchronous group than for the metachronous group (27.5% vs 68.1%), as was the two-year PFS rate (0% vs 53.3%).⁷ This current reports defines synchronous as treatment within 3 months, while the report of Creach et al. defined synchronous for any patient where two pulmonary nodules existed simultaneously. These earlier studies by Chang et al. and Creach et al. demonstrate that while SBRT is effective for treating metachronous primary lung cancers, it is less effective for treating synchronous cancers, posing a therapeutic challenge. In contrast to Chang et al. and Creach et al., our results support the idea that SBRT can be effective for treating synchronous lung lesions. We found that our small synchronous SBRT had no significant difference in three-year OS (46% vs 54%, $P=0.75$) and only had a modest decrease in three-year local control (75% vs 89%, $P=0.18$) when compared to the single treatment group.

There have been a few studies that combined synchronous primary lung cancer patients that received SBRT with those that received a combination of surgery and SBRT to achieve a higher sample size. However, they did not compare these two subgroups to each other to assess their relative efficacy. Shintani et al. studied 18 patients and found a three-year OS rate of 69.1% and a PFS rate of 43.2%.¹⁸ Griffioen et al. sampled 62 patients and found a two-year OS rate of 56% and a PFS rate of 87%.¹⁹ Griffioen et al. likewise did not explicitly define PFS, but as it is larger than their OS rate, it is likely comparable to our definition of FFP. Both sets of authors concluded that synchronous treatments of SBRT were effective which supports our conclusion that SBRT serves as an effective treatment for synchronous primary lung cancers.

A few studies have instead chosen to combine synchronous and metachronous SBRT patients into a single group and they have shown more favorable results for treating synchronous or metachronous MPLC. Using a sample of 63 MPLC patients, Owen et al. found that SBRT achieved a one-year OS rate of 85% and a one-year PFS rate of 91.9%.¹⁶ As their PFS is larger than OS, it is more comparable to our definition of FFP. Matthiesen et al. had a sample of 10 patients and found that 6/10 patients were alive and 20/21 tumors

were locally controlled at a median follow-up time of 15.5 months.¹⁷ However, a limitation of these studies is that most of their patients received metachronous SBRT. Therefore, these survival statistics likely represent the metachronous and not the synchronous group. Taking this into consideration, these two studies confirm our findings about metachronous primary lung cancers. Our study showed that metachronous SBRT treatment had significantly higher three-year OS (79.7% vs 54.2%, $P<0.0001$) and a similar three-year local control rate (94.5% vs 89.4%, $P=0.24$) compared to single SBRT treatments.

We believe that our metachronous SBRT treatment group achieved significantly higher OS than our single SBRT treatment group due to the immortal time bias. Patients who have a shorter life expectancy with more comorbid diseases are less likely to manifest metachronous disease. Therefore, patients who do manifest metachronous disease will tend to have a longer expected life-span. Similarly, we found that patients that received both surgery and metachronous SBRT also had a higher OS rate. This likely occurred because patients eligible for surgery, as opposed to SBRT, tend to be healthier and have fewer comorbidities, which gives them a longer life expectancy. The baseline patient characteristics of this study support this hypothesis, with both of these groups having significantly better ECOG performance status scores compared to the single treatment group (Table 1). Our multivariate analysis supports this, since the type of treatment group the patients were part of was the most important predictor of both OS and FFP. Being able to receive metachronous SBRT or qualifying for surgery appears to confer certain survival and FFP benefits, even more important than age at diagnosis, ECOG performance status, or location of the tumor.

As for the safety of multiple courses of SBRT, we found that for both severe adverse events (grade 3) and all adverse events, there was no significant difference in the toxicity rates between the single treatment group and the other three MPLC groups. Repeating the statistical tests with Kaplan-Meier survival analysis also failed to show statistically significant differences between the single treatment group and any of the other three groups. This suggests that multiple courses of radiation therapy are well-tolerated by patients, without worrisome increases in radiation pneumonitis, dermatitis, or chest wall toxicity.

There are some limitations with this study. The first, as was previously mentioned, is the smaller sample size for the synchronous treatment group. Another limitation is that not all patients underwent a biopsy. This was generally due to an increased risk for complications due to pulmonary comorbidities. A third limitation was that the toxicity data used in this study was physician-reported and in some cases assessed retrospectively. A more robust means of toxicity assessment would include consistent use of validated instruments as well as patient reported outcomes. A final limitation is that the study is retrospective in nature and subject to inherent bias. However, despite these limitations, our results confirm previously published reports and serve as a basis for future, larger multi-institutional studies.

In conclusion, SBRT appears effective and safe for patients with for synchronous and metachronous MPLC. However, despite these results, further study and validation against other institutional experiences merit examination.

Clinical Practice Points

Smaller retrospective series of patients with multiple, early stage lung cancers (MPLC) receiving stereotactic body radiation therapy (SBRT) have been published with differing outcomes. This is the first study to compare outcomes of these patients with MPLC directly with those receiving SBRT for a single, early stage lung cancer. It did so from a prospective database at a high-volume institution. This study is also notable as one of the largest series of previous thoracic surgery, followed by SBRT for a second cancer published to date. Most importantly, this comparative study with single course SBRT showed no statistically significant increases in toxicity in patients who receive SBRT after previous lung surgery or who receive multiple courses of SBRT, even courses of SBRT within 3 months of each other. This supports as safe the repeated use of SBRT in this population. This study suggests improved disease and survival outcomes in patients receiving both surgery and SBRT as well as multiple courses of SBRT alone for MPLC, though this could be due to selection bias. In contrast to other studies, it showed that the use of SBRT for synchronous MPLC had similar disease outcomes as the use of SBRT for a single lung cancer. Together, this supports the use of SBRT for any type of MPLC as both safe and effective.

Acknowledgments

Research reported in this publication was supported by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002344. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure 1:
Consort diagram.

Figure 2: Overall survival for each group.

Kaplan-Meier survival analysis was performed followed by Wilcoxon tests comparing each group to the single SBRT treatment group (n.s.; not significant, **** $P < 0.0001$).

Figure 3: Freedom from progression for each group.

Kaplan-Meier survival analysis was performed followed by Wilcoxon tests comparing each group to the single SBRT treatment group (n.s.; not significant, * $P < 0.05$, **** $P < 0.0001$).

Figure 4: Local control for tumors treated with SBRT in each group.

Kaplan-Meier survival analysis was performed followed by Wilcoxon tests comparing each group to the single SBRT treatment group (n.s.; not significant, ****P<0.01**).

Figure 5: Freedom from pneumonitis (A) and chest wall toxicity (B).

Kaplan-Meier survival analysis was performed followed by Wilcoxon tests comparing each group to the single SBRT treatment group (n.s.; not significant).

Table 1:

Patient characteristics at diagnosis.

Type of Treatment	Single	Synchronous		Metachronous		Surgery + SBRT	
			<i>P</i> -value		<i>P</i> -value		<i>P</i> -value
<i>Sample Size (n), patients</i>	374	14	-	48	-	108	-
Age at diagnosis (years),	73.7	73.4	0.85	72.9	0.44	70.6	<0.01
Gender							
Male	49.0%	14.3%	0.01	56.3%	0.36	34.3%	0.01
Female	51.0%	85.7%		43.7%		65.7%	
Smoking history (pack years), mean	52.4	58.0	0.53	51.0	0.94	57.3	0.18
Have ever smoked?							
Yes	93.6%	100%	1.00	97.9%	0.34	94.4%	1.00
No	6.4%	0%		2.1%		5.6%	
ECOG Performance Status							
0	24.6%	7.7%	0.15	41.3%	0.04	36.5%	0.02
1	55.0%	84.6%		47.8%		51.4%	
2	20.4%	7.7%		10.9%		12.2%	
Age-adjusted Charlson Comorbidity Score, mean	5.4	5.8	0.35	5.3	0.68	5.8	<0.01
Follow-up duration (months), mean	27.7	22.7	0.37	44.3	<0.0001	38.7	<0.0001
Tumor Location							
Central	16.8%	14.3%	1.00	12.5%	0.54	19.4%	0.57
Peripheral	83.2%	85.7%		87.5%		80.6%	
Biopsy Performed							
Yes	85.6%	100%	0.23	89.6%	0.66	62.0%	<0.0001
No	14.4%	0%		10.4%		38.0%	

Pairwise comparisons were made between the single SBRT treatment group and each of the other three groups using either Fisher's exact test or a twosided Wilcoxon test. ECOG=Eastern Cooperative Oncology Group. Bold *P*-values are significant according to the threshold *P*<0.05.

Table 2:

Clinical Outcomes.

	Single SBRT	95% CI	Synchronous SBRT	95% CI	Metachronous SBRT	95% CI	Surgery + SBRT	95% CI
3-Year OS Rate	54.2%	48.8–59.3%	46.4%	19.3–69.9%	79.7% *	64.4–88.9%	95.4% *	89.2–98.0%
3-Year FFP Rate	67.3%	60.9–72.9%	57.5%	25.3–80.0%	85.8%	70.7–93.5%	95.4% *	89.2–98.0%
3-Year Local Control Rate	89.4%	85.3–93.5%	75.0%	53.8–96.2%	96.0%	90.3–100%	98.2% *	95.8%–100%

* means a statistical difference when compared to the single SBRT cohort.

Table 3:

SBRT-related toxicity in each group.

Type of Toxicity	Singlen=374 patients					Synchronous=14 patients					Metachronousn=48 patients					SBRT + Surgery n=108 patients				
Grade*	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Chest Wall	39	36	2	1		1	3				11	3				15	3	1		
Pneumonitis	7	12	4				1	1				1	1		1		10	4		
Brachial Plexopathy	2											1					1			
Bronchial obstruction	3																		1	
Dermatitis	5	4	1			1						1				2			1	
Esophagitis		1						1				1	2							
Hemoptysis					1			1				1	2							
Pleural Effusion			2									1								
Other	1	3									1									
Severe (Grade 3					14					2					2					6
% of patients					3.5%					4.3%					4.2%					5.6%
Significance					-					n.s.					n.s.					n.s.
P-value					-					0.10					0.68					0.40
Overall					124					8					24					38
% of patients					29.4%					50%					37.5%					33.3%
Significance					-					n.s.					n.s.					n.s.
P-value					-					0.14					0.24					0.48

* Toxicities were graded according to the Common Terminology Criteria for Adverse Events. Analysis was performed using two-sided Fisher's exact tests between the single treatment group and each of the other three groups (n.s.; not significant).