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Biochemical liver function markers after CT-guided brachytherapy for liver metastases

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SUMMARY

Next to thermoablation, radioembolization or chemoembolization, radiation therapy is one of non-surgical methods of local treatment for primary and secondary liver cancers. Brachytherapy is a radiotherapy technique which enables high-dose irradiation with relatively low doses delivered to the remaining, healthy liver parenchyma owing to appropriate arrangement and number of applicators. The aim of the study was to assess the impact of various doses in the healthy hepatic parenchyma on early biochemical toxicity in patients undergoing brachytherapy for liver tumors.

Material and methods. The analysis involved values of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (BIL) in 16 patients within the period of 6 months after brachytherapy. Six patients (37.5%) were administered 20 Gy, 7 (43.75%) 15 Gy (43.75%), and 3 (18.75%) 10 Gy. Toxicity was assessed based on the most common clinical liver function parameters: ALT, AST and BIL.

Results. None of the patients demonstrated statistically significant differences in biochemical liver function markers (ALT, AST and BIL) for the first, second and third time periods. A statistically significant correlation was found between the maximum dose delivered to the liver and ALT levels in the second ($p = 0.002$) and third time periods ($p = 0.014$). Also, a correlation existed between CTV with the AST value in the first time period at a borderline significance level ($p = 0.04$). There were no statistically significant correlations between other physical parameters (D_{max}, $D_{1/3}$, $D_{2/3}$, $D_{50\%}$, D_{10cm3}, D_{100cm3}, D_{500cm3}, $D_{100\%}$, $D_{90\%}$, liver volume) and levels of biochemical liver function markers in individual time periods ($p>0.05$).

Conclusions. Hepatotoxicity of brachytherapy depends on the volume of the irradiated tumor. This correlates with an increase in transaminases and indicates the existence of a certain tumor volume at which the toxicity of brachytherapy is not acceptable. Further studies are needed to assess the influence of brachytherapy conducted for the treatment of liver tumors on hepatotoxicity.

Key words: liver brachytherapy, alanine aminotransferase, aspartate aminotransferase, bilirubin

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INTRODUCTION

The liver is one of the most common sites for metastases from a number of cancers (colorectal cancer, breast cancer, cutaneous and ocular melanoma and neuroendocrine tumors) [1]. Surgery is the mainstay of secondary liver tumor therapy. Non-surgical local treatment methods include: radiofrequency ablation (RFA), transarterial radioembolization (TARE), transarterial chemoembolization (TACE) as well as cryo-, laser and radiation therapy [2]. Stereotactic radiotherapy and three-dimensional conformal radiotherapy are the prevailing radiation methods [3]. Image-guided brachytherapy has recently been gaining popularity [4,5]. This results from the possibility of delivering high doses to the tumor volume and low doses to the remaining normal liver parenchyma, which enables escalation of the radiation dose above the average dose for the whole liver.

This study presents the influence of various doses delivered to the healthy hepatic parenchyma on early biochemical toxicity in patients undergoing brachytherapy for liver tumors. Toxicity was assessed based on the most common clinical liver function markers: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (BIL).

MATERIAL AND METHODS

Patient characteristics

The preliminary analysis involved 46 patients undergoing brachytherapy for metastatic lesions in the liver in 2013–2014. Patients with disease progression within 9 months after treatment, those undergoing chemotherapy or surgery as well as those with active disease beyond the irradiated sites were excluded. Finally, 16 patients were included. The clinical

characteristics of the patients are presented in Tab. 1.

Technique of application

The patients included in the analysis underwent HDR brachytherapy using Ir 192 as a radiation source. Application was performed under constant image guidance (computed tomography). Intravenous iodine contrast agents were used in nearly all patients (15: 93.75%). Application was performed under general anesthesia or local paravertebral block. It consisted in percutaneous insertion of a needle followed by a sleeve with an angiostatic valve and an applicator into a tumor in the liver. Due to tumor size and shape, some patients had 2 or 3 applicators inserted. The applicators were introduced so that their arrangement was as parallel as possible to enable the prescribed dose to be delivered to the entire lesion.

Treatment planning and follow-up

Based on the fusion of images from computed tomography with implanted applicators and previous diagnostic computed tomography or magnetic resonance images, the tumor volume and critical organs were contoured. The basic critical organs were the healthy liver parenchyma and, depending on the site: the liver hilum, gallbladder, kidney, stomach and intestine. Three doses were applied depending on the tumor size and proximity of the critical organs: 10 Gy, 15 Gy and 20 Gy. The principle of treatment planning was to cover with the prescribed dose at least 90% isodose line ($D_{90\%}$). Also, the maximum dose and a dose in a 100% isodose were reported. Doses in the healthy liver were reported for 33%, 50% and 67% of the liver volume as well as for 10 cm^3, 100 cm^3 and 500 cm^3 of the liver volume.

After irradiation, applicators were removed and a follow-up computed tomography scan was performed to rule out complications, such as bleeding or pneumothorax.

Depending on the dose delivered to 1/3 (D1/3) and 2/3 (D2/3) of the liver volume, the patients were divided into 3 groups:

- Group 1: doses in 1/3 of the healthy liver (D1/3) < 2Gy and in 2/3 of the healthy liver (D2/3) <1Gy;
- Group 2: D1/3 2–4 Gy or D2/3 1–2 Gy;
- Group 3: D1/3 >4 Gy or D2/3 >2 Gy.

In these groups, we conducted a retrospective analysis of the dynamics of three basic biochemical liver function markers: alanine aminotransferase, aspartate aminotransferase and total bilirubin. Their baseline values were considered referential. Within a 6-month follow-up, 3 time periods were distinguished: from the day of treatment to 30 days after its conclusion, from day 31 to 90 after treatment and from day 91 to 180 after treatment. In patients who had ALT, AST and BIL determined more than once in a given time period, higher values were analyzed.

Tab. 1. Clinical characteristics of patients

Parameter	Number of patients / Range
Sex	
– Females	8 (50%)
– Males	8 (50%)
Age	Median 62 years (47–82)
Primary tumor site:	
– gastrointestinal tract	12 (75%)
– breast	2 (12,5%)
– pancreas	1 (6,25%)
– liver	1 (6,25%)
Previous treatment:	
– surgery (primary focus)	15 (93,75%)
– surgery (metastatic focus)	2 (12,5%)
– radiotherapy (primary or metastatic focus in other sites than brachytherapy)	9 (56,25%)
– radiotherapy (lesion treated with brachytherapy)	0 (0%)
– chemotherapy	16 (100%)
– hormonal therapy	1 (6,25%)
Number of hepatic foci	
– 1	14 (87,5%)
– 2	2 (12,5%)

Statistical analysis

1. The significance of differences between the groups in variables that did not present a parametric distribution was evaluated with the Kruskal-Wallis ANOVA test.
2. The analysis of monotonic relationships was performed using the Spearman's rank correlation module.

RESULTS

Liver function marker assessment depending on the dose

Six patients (37.5%) were administered 20 Gy, 7 (43.75%) 15 Gy (43.75%), and 3 (18.75%) 10 Gy. Median doses covering 90% and 100% of the tumor volume ($D_{90\%}$ and $D_{100\%}$) were 16.63 Gy (10.94–26.95 Gy) and 9.45 Gy (6.18–17.28 Gy), respectively. The median tumor volume was 46.9 cm^3(4.8–180.6cm^3). Five patients needed 1 applicator to cover the CTV (clinical target volume) area, 6 patients needed 2 and 5 needed 3 applicators. The median duration of irradiation was nearly 14 minutes: 838 s (358–2123 s). Tab. 2

Also, the analysis involved doses in various liver volumes. The median maximum dose (D_{max}) and average dose ($D_{50\%}$) were 1409.4 Gy (749.5–3174.2 Gy) and 3.23 Gy (0.85–6.69 Gy), respectively. Median doses for 10 cm^3, 100 cm^3 and 500 cm^3 (D_{10cm3}, D_{100cm3}, D_{500cm3}) were 22.35 Gy (12.1–35.1 Gy), 9.98 Gy (2.6–14.68 Gy) and 2.59 Gy (0.68–6.66 Gy), respectively. The median dose in 1/3 of the healthy liver was 2.97 Gy (0.58–6.93 Gy), and in 2/3 of the healthy liver: 1.22 Gy (0.22–3.82 Gy) – Tab 3.

Follow-up and statistical analysis

In the groups described above, ALT, AST and BIL were determined in given time periods and the differences from their baseline values were analyzed for individual groups. Tab. 4, 5 and 6.

Differences in the values of these parameters in the analyzed time periods are presented in plots (Fig. 1–3).

Assessment of liver function markers in individual time periods

Changes in the values of individual liver function parameters were analyzed in all groups for all time periods. In the case of ALT values, there were no statistically significant differences for the first, second and third time period (Kruskal-Wallis test: H [2, N= 16]: 0–1 months after treatment – test value 3.710, p =0.156, 2–3 months after treatment – test value = 0.546, p = 0.761 and 4–6 months after treatment – test value 2.175, p = 0.337 [Fig. 4]).

Tab. 2. $D_{100\%}$, $D_{90\%}$, tumor volume, number of applicators and duration of treatment in individual patients or in groups

Patient No	Planned dose (Gy)	D100% (Gy)	D90% (Gy)	Tumor volume (cm^3)	Number of applicators	Irradiation time (s)
			Group I D1/3 < 2, D2/3 <1			
1	15	10,08	17,24	12,4	1	400
2	20	10,025	20,46	14,4	1	442,2
3	10	8,825	13,77	27,9	1	581,3
4	20	17,275	26,95	4,8	1	358,4
5	20	10,175	20,601	16,5	2	551
			Group II D1/3 =2- 4, D2/3=1-2			
6	10	6,575	10,94	45	2	598,8
7	15	9,38	17,06	39,9	1	749,2
8	20	12,226	20,11	52,6	2	972,4
9	20	14,825	22,27	29,8	2	759,5
10	15	9,776	15,14	48,8	2	945,9
11	15	7,775	15,06	176,1	3	1645,8
			Group III D1/3 >4, D2/3>2			
12	10	6,175	11,93	163,7	3	1493
13	15	8,275	16,19	180,6	3	2122,7
14	20	9,525	20,62	51	2	916,4
15	15	7,025	15,42	130,7	3	1577,3
16	15	8,725	15,02	49,6	3	1422,1

D100% – a dose in an isodose for 100% tumor volume, D90% – dose in an isodose for 90% tumor volume

As for AST, there were no statistically significant differences for the first, second and third time period, either (Kruskal-Wallis test: H [2, N= 16]: 0–1 months after treatment – test value 4.740, p =0.093, 2–3 months after treatment – test value = 0.497, p = 0.780 and 4–6 months after treatment – test value 1.394, p = 0.498 [Fig. 5]).

Also, there were no statistically significant differences in the analyzed time periods for total bilirubin (Kruskal-Wallis test: H [2, N= 16]: 0–1 months after treatment – test value 4.058, p =0.132, 2–3 months after treatment – test value = 0.652, p = 0.722 and 4–6 months after treatment – test value 1.874, p = 0.392 [Fig. 6]).

Tab. 3. Maximum and average doses as well as doses in 1/3, 2/3 and 10 cm^3, 100 cm^3 and 500 cm^3 in the study group

Patient No	D_{max} (Gy)	$D_{50\%}$ (Gy)	$D_{1/3}$ (Gy)	$D_{2/3}$ (Gy)	D_{10cm3} (Gy)	D_{100cm3} (Gy)	D_{500cm3} (Gy)	Liver volume (cm^3)
Group I D1/3 < 2, D2/3<1								
1	749,5	1,82	1,44	0,69	17,4	4,95	1,43	1507,8
2	2137,4	1,535	1,11	0,478	17,69	5,67	1,51	2008,3
3	1069,1	1,967	1,59	0,71	18,2	5,9	1,73	1659,2
4	1379,8	0,848	0,58	0,22	12,1	2,6	0,68	1737,6
5	1438,9	2,407	1,84	0,76	21,95	6,55	1,63	1348,4
Group II D1/3 =2- 4, D2/3=1-2								
6	1897,7	2,312	2,04	0,788	18	7,22	2,37	1779,1
7	1845,8	3,037	2,79	1,02	19,79	7,77	2,23	1262,4
8	1261	3,929	3,4	1,6	24	10,37	2,82	1290,1
9	1562	2,89	2,13	0,81	25,24	9,6	2,18	1544,9
10	1192	4,23	3,6	1,63	29,8	10,8	3,02	1323,2
11	1043,3	3,423	3,14	1,41	22,75	12,47	4,97	2698,8
Group III D1/3 >4, D2/3>2								
12	1332,4	4,66	4,74	2,23	24,5	13	5,86	2099,3
13	2160,3	5,856	6,08	2,59	29,6	15,06	6,31	1737,9
14	1061	4,35	4,3	1,73	21,9	10,5	2,9	1127,8
15	1639,1	5,309	5,39	2,67	26,4	12,69	4,93	1468,1
16	3174,2	6,69	6,93	3,82	35,1	14,68	6,66	1459,9

D_{max} – maximum dose, $D_{50\%}$ – average dose, $D_{1/3}$ – dose for 1/3 of the healthy liver parenchyma, $D_{2/3}$ – dose for 2/3 of the healthy liver parenchyma, D_{10cm3} – dose in 10 cm^3 of the healthy liver parenchyma, D_{100cm3} – dose in 100 cm^3 of the healthy liver parenchyma, D_{500cm3} – dose in 500 cm^3 of the healthy liver parenchyma

Tab. 4. ALT levels in different time periods in individual patients.

Patient No	Baseline (u/l)	0-1 month	2-3 months	4-6 months
Group I D1/3 < 2, D2/3<1				
1	27	36	41	34
2	49	23	23	21
3	53	44	46	44
4	29	30	30	47
5	24	18	18	18
Group II D1/3 =2- 4, D2/3=1-2				
6	19	76	22	23
7	65	32	32	30
8	56	68	71	71
9	28	46	28	28
10	31	37	36	28
11	70	49	56	56
Group III D1/3 >4, D2/3>2				
12	16	36	40	39
13	22	36	13	22
14	48	55	41	46
15	35	93	147	147
16	13	11	12	12

ALT – alanine aminotransferase

Impact of individual physical parameters on biochemical liver function markers

A statistically significant correlation was found between the maximum dose delivered to the liver and the ALT level in the second (Spearman's rank correlation p = 0.002) and third time periods (Spearman's rank correlation p = 0.014). Also, a correlation existed between CTV and the AST value in the first time period at a borderline significance level (Spearman's rank correlation p = 0.04).

There were no statistically significant correlations between other physical parameters (D_{max}, $D_{1/3}$, $D_{2/3}$, $D_{50\%}$, D_{10cm3}, D_{100cm3}, D_{500cm3}, $D_{100\%}$, $D_{90\%}$, liver volume) and levels of biochemical liver function markers in individual time periods (p>0.05).

Tab. 5. AST levels in different time periods in individual patients

Patient No	Baseline (u/l)	0-1 month	2-3 months	4-6 months
Group I D1/3 < 2, D2/3<1				
1	22	24	22	25
2	23	19	19	21
3	40	21	34	35
4	21	27	27	48
5	14	14	14	14
Group II D1/3 =2- 4, D2/3=1-2				
6	20	219	20	32
7	59	62	62	56
8	39	67	49	49
9	23	33	23	23
10	22	21	18	20
11	47	40	32	32
Group III D1/3 >4, D2/3>2				
12	38	66	77	100
13	26	41	21	28
14	53	65	45	46
15	20	65	63	63
16	10	11	13	13

AST – aspartate aminotransferase

Tab. 6. BIL levels in different time periods in individual patients

Patient No	Baseline (mg/dl)	0-1 month	2-3 months	4-6 months
Group I D1/3 < 2, D2/3<1				
1	0,51	0,53	0,72	0,82
2	0,36	0,54	0,54	0,32
3	0,98	1,4	0,95	0,71
4	0,58	0,62	0,62	0,55
5	0,42	0,44	0,44	0,44
Group II D1/3 =2- 4, D2/3=1-2				
6	0,7	0,97	0,57	0,71
7	0,58	0,6	0,6	0,6
8	2,98	3,09	3,01	3,01
9	0,55	0,86	0,9	0,9
10	0,96	1,36	1,06	0,89
11	0,97	1,37	0,59	0,59
Group III D1/3 >4, D2/3>2				
12	0,34	0,38	0,47	0,75
13	0,52	0,56	0,32	0,25
14	0,51	0,64	0,53	0,63
15	0,47	0,4	0,76	0,76
16	0,33	0,33	0,62	0,62

BIL – Total bilirubin

DISCUSSION

The hepatic parenchyma is parallel in structure, which enables exposure of its individual parts to high doses of radiation until the average dose for the whole liver is exceeded. Using conventionally fractionated radiotherapy, a 5% risk of complications for 2/3 and 1/3 of the liver is observed with doses of 35 Gy and 50 Gy, respectively. Doses causing a 50% risk of liver damage for 2/3 and 1/3 of the liver volume are 45 Gy and 55 Gy, respectively [6]. Other studies indicate that a tolerance dose for the liver in conventional fractionation is 45 Gy [7]. Other authors indicate that the risk of focal liver damage with a dose exceeding 48 Gy is 73% and with a dose greater than 72.8 Gy – 86% [8].

Brachytherapy is a technique of high conformality whereby only one high fractionated dose is used, and the healthy liver volume exposed to a high radiation dose is considerably lower. More recent studies, conducted in patients undergoing brachytherapy have demonstrated toxicity of radiotherapy with significantly lower doses than those previously quoted [9, 10].

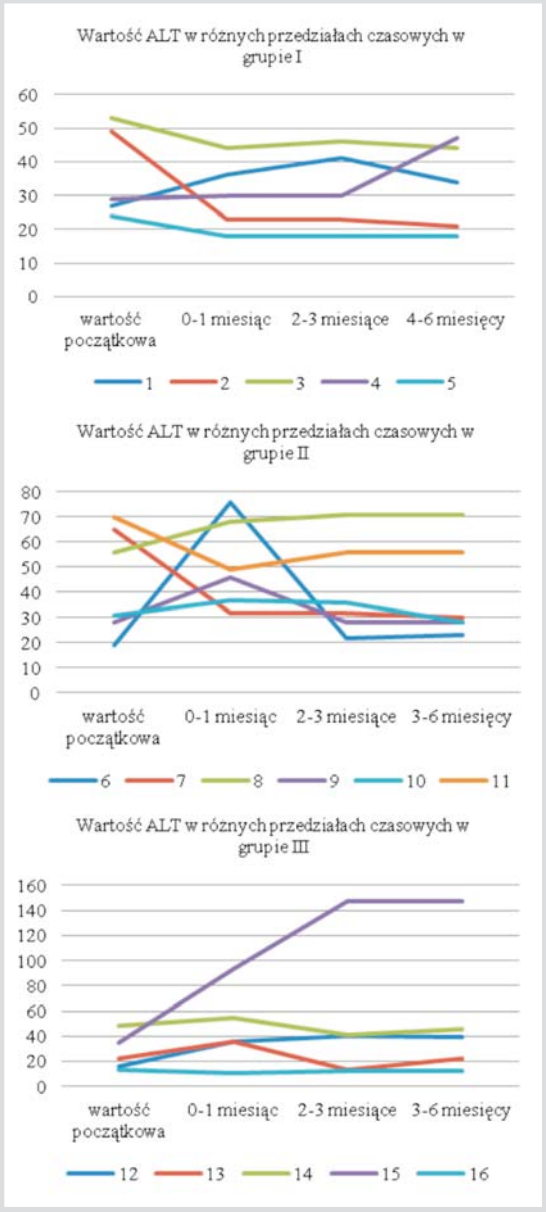

Fig. 1. Dynamics of ALT in individual time periods (1–16: numbers of consecutive patients from all groups)

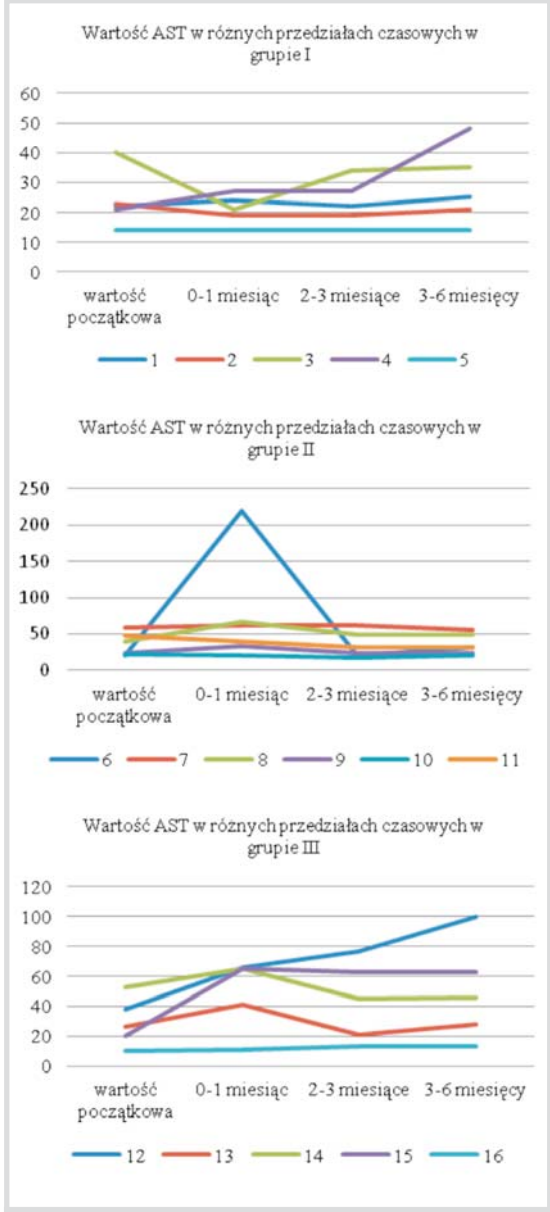

Fig. 2. Dynamics of AST in individual time periods (1-16: numbers of consecutive patients from all groups)

The methods enabling liver function assessment after irradiation include imaging and biochemical tests. The usage of MRI involving assessment of the dynamics of liver tissue edema in patients after brachytherapy has demonstrated that irradiation affects hepatocyte function. It has been shown that in the period of 3 days to 6 weeks after brachytherapy, parenchymal edema was present in the region covered by an isodose of 9.9±2.3 Gy. This image remained stable up to week 12 after brachytherapy and then began to reduce and covered an isodose of 14.7±4.2 Gy 24 weeks after treatment. The authors of this study suggested that the minimum tolerance dose in most cases (95%) was 7.6–12.2 Gy [9]. Herfarth et al. [10], in turn, have demonstrated in computed tomography that focal liver damage occurs at a dose of 13.7 Gy (8.9–19.2 Gy).

According to other authors, threshold doses in brachytherapy for the healthy parenchyma are 14, 16 and 18 Gy for 500 cm^3, 100 cm^3 and 10 cm^3, respectively [11].

The aforementioned threshold doses for 100 cm3 and 500 cm^3 were not exceeded in any of the patients from our study group

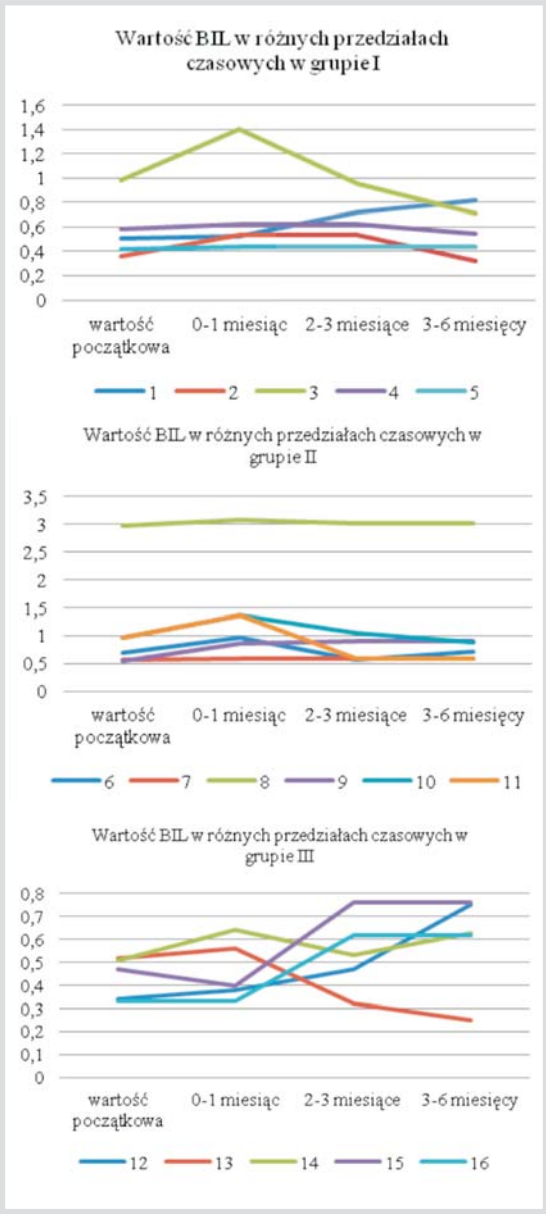

Fig. 3. Dynamics of AST in individual time periods (1-16: numbers of consecutive patients from all groups)

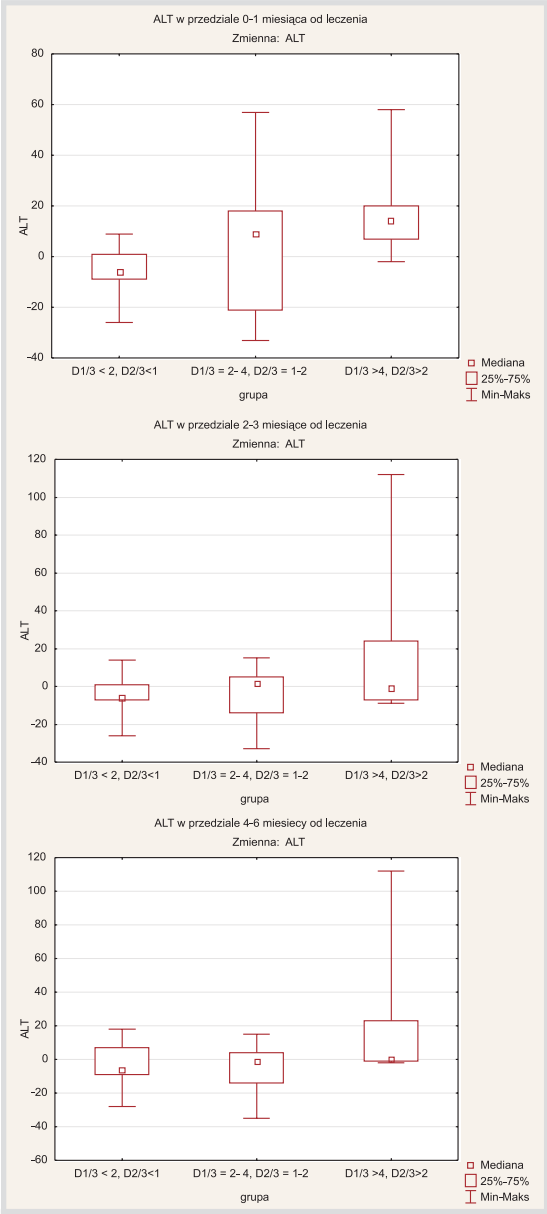

Fig. 4. Median, quartiles and ranges for alanine aminotransferase (ALT) in individual groups in different time periods

(median 9.98 Gy [2.6–14.68 Gy] and 2.59 Gy [0.68–6.66], respectively). However, due to considerable sizes of the treated lesions and relatively small number of applicators, the maximum dose of 18 Gy in 10 cm^3 was difficult to obtain (median 22.35 Gy [12.1–35.1]).

Studies show that the rate of hepatic complications in patients undergoing brachytherapy is very low. A German center with so far the greatest experience follows the principle that a dose of 5 Gy in 2/3 of the liver volume cannot be exceeded. This dose was not exceeded in our patients either. Moreover, there were no other significant hepatic complications in this group of patients.

We analyzed the impact of brachytherapy on the values of three most popular biochemical liver function markers obtained in the period of 6 months after treatment. There are no studies presenting changes in the levels of these parameters depending on the dose delivered to the liver. This study also assessed liver function for 2/3 and 1/3 of the liver parenchyma. These doses were significantly lower after the application of brachytherapy. The median dose in 1/

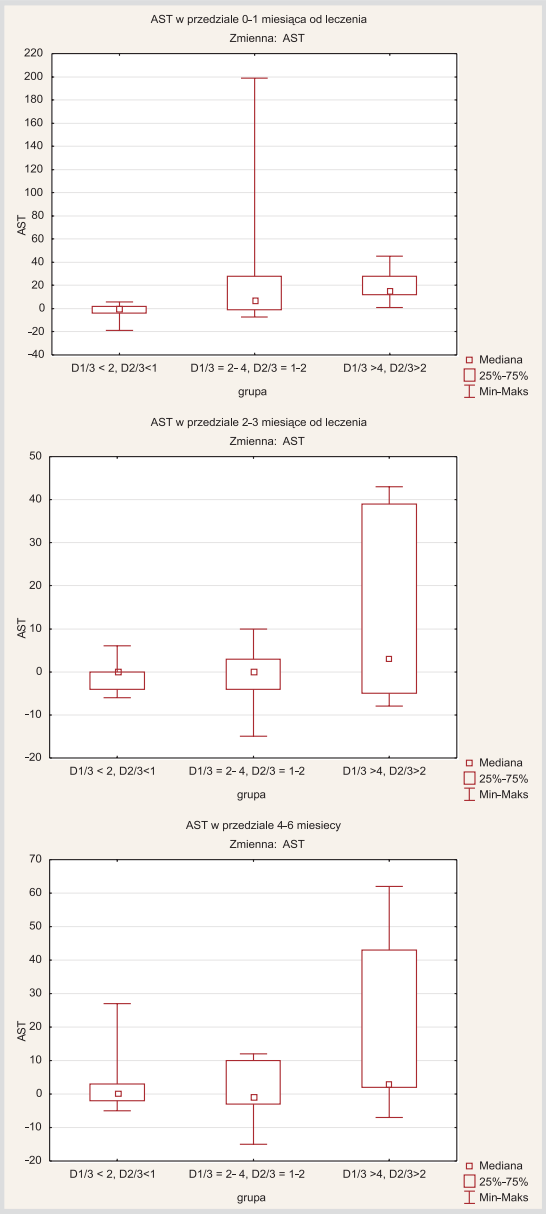

Fig. 5. Median, quartiles and ranges for aspartate aminotransferase (AST) in individual groups in different time periods

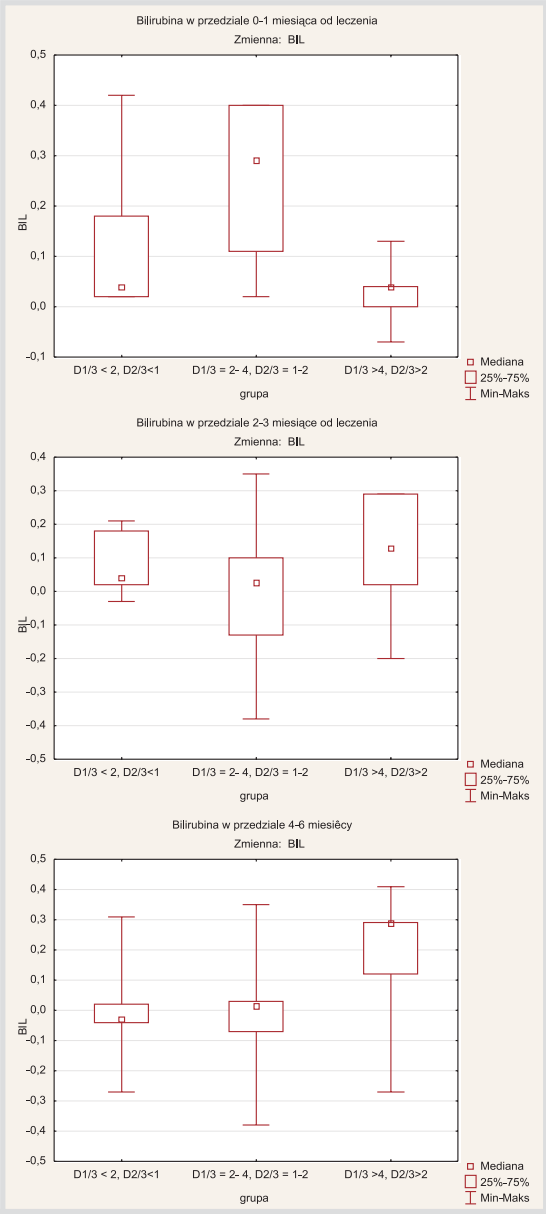

Fig. 6. Median, quartiles and ranges for total bilirubin (BIL) in individual groups in different time periods

3 of the healthy liver was 2.97 Gy (0.58–6.93 Gy) and in 2/3 of the healthy liver 1.22 Gy (0.22–3.82 Gy). As could have been expected, no biochemical hepatotoxicity was noted. However, a tendency for ALT and AST to rise with an increase in doses for 2/3 and 1/3 of the liver volume was observed (for AST, this was noticed in the first time period after treatment $p=0.09$).

The correlation of CTV, i.e. the volume of the irradiated lesion, with an increase in ALT and AST values indicates direct influence of irradiated volume on the level of transaminases, which might suggest a risk of toxicity in patients with large tumors.

CONCLUSIONS

Hepatotoxicity of brachytherapy depends on the volume of the irradiated tumor. This correlates with an increase in transaminases and indicates the existence of a certain tumor volume at which the toxicity of brachytherapy is not acceptable. Further studies are needed to assess the influence of brachytherapy conducted for the treatment of liver tumors on hepatotoxicity.

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