

O.O.Kolesnik, A.A.Burlaka, A.V.Lukashenko, V.V.Priymak, M.O.Volk,

Yu.O.Zhukov

Colorectal cancer with synchronous liver metastases: influence of surgical strategy on treatment results and costs

National Cancer Institute, Kyiv. Division of Tumors of Abdominal Cavity and Retroperitoneal Space. Corresponding author, surgeon-oncologist A.A.Burlaka, e-mail: nir.burlaka@gmail.com, tel.: 067-800-27-48

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Problem statement and analysis of recent research. Annually WHO registers worldwide more than 940 thousand new cases and about 500 thousand deaths due to colorectal cancer (CRC)^[6]. According to the data of National Cancer Register of Ukraine CRC holds third place in deaths distribution from malignant neoplasias^[3]. The most common target organs of metastatic disease in CRC in Ukraine and globally are liver and lungs^[1]. According to literature data about 50 % of patients with this oncologic pathology have distant metastases in liver, 25 % of them are diagnosed synchronously with primary tumor^[5], and synchronous metastases in lungs are diagnosed in 8–10 % of patients^[8]. Synchronous metastatic liver affection in colorectal cancer (smCRC) is an extremely unfavorable prognostic factor as the median of total survival in such patients without surgical treatment is 6–12 months, and with application of chemotherapy treatment alone this value rises up to 19 months.^[7]

Evolution of surgical and anaesthesiological technologies, development of more effective and safe targeted drugs facilitated the revision of standards for surgical treatment of smCRC. And although there are recommendations of leading international oncologic organizations related to determination of treatment strategy

for smCRC patients (NICE 2014, BSG 2008, SSAT 2014, ESMO 2014, SIGN 2011 ta NCCN v2 2015), consensus regarding personalized choice of optimal surgical algorithm of resection of primary colon tumor and resection of liver with synchronous metastases is absent. And data about feasibly acceptable volume of liver parenchyma resection at simultaneous resection of colon/rectal cancer with synchronous metastases in liver and/or lungs are absent or ambiguous [6]. Therefore, scientifically based algorithm of surgical treatment of smCRC patients is a disputable issue of modern oncology. And also high cost of oncologic patients' treatment requires a clear rationale for a treatment strategy choice. The aim of the study was to improve immediate and long-term results of smCRC patients' treatment by means of development of surgical treatment program with application of simultaneous and staged methods for resection of primary tumor and liver metastases.

Aim of the study: to improve immediate and long-term results of smCRC patients treatment by means of development of surgical treatment program with application of simultaneous and staged methods for resection of primary tumor and liver metastases.

Materials and methods. Materials of the study are based upon reviewing of treatment results for 125 patients with smCRC ($pT_{1-4}N_{0-2}M_1$ at colon cancer and $pT_{1-3}N_{0-2}M_1$ at rectal cancer) that underwent either simultaneous or staged surgical treatment in the period from 2008 till 2015 in the Division of Tumors of Abdominal Cavity and Retroperitoneal Space of the National Institute of Cancer. This work has a character of prospective single-center randomized study.

The patients received chemotherapy according to approved international and domestic standards and clinical protocols. In the group I adjuvant polychemotherapy (aPCT) was applied with the schemes FOLFOX-6/FOLFIRI (4-6 courses). In the group II the patients received 2–3 courses of PCT in neoadjuvant regimen (nPCT), FOLFOX-6/FOLFIRI after stage of primary smCRC tumor resection and 4-6 courses of aPCT with the same schemes after the stage of resection of liver with synchronous

metastatic foci. In the case of tumor progression on the background of PCT treatment the patients of the group II were not subjected to liver resection. Rectal cancer patients received pre-surgical radiotherapy onto the zone of primary rectum tumor (2.0 Gr x 15). Surgical treatment protocols in colon and liver were described by authors in previous publication ^[1,2].

Statistical analysis was provided with the software STATISTICA 6.0. Non-parametric values are presented by median and interquartile range, for comparison Mann-Whitney test was applied. Categorical values were compared using chi-square test. Comparing values, presented as Mean±SEM were considered statistically reliable at $p < 0.05$. Patient's survival rate was analyzed by Kaplan-Mayer method, survival difference – by Long-Rank criterion. Data were considered statistically reliable at $p < 0.05$.

Results and discussion.

Patients' characteristics

Among 125 patients that were included into the study there was 71 (56.8%) males and 54 (43.2%) females. Average population age was 55 ± 0.43 years and it varied in a range from 27 to 73 years. The groups did not have statistically reliable difference in age characteristics ($p = 0.85$). The groups also did not differ in gender distribution, where the males comprised 36 (58.1%) and 35 (55.5%) persons, and females - 26 (41.9%) and 28 (44.4%) persons in the groups I and II, respectively ($p = 0.85$). Average age of the males was 55.5 ± 0.76 and 55.8 ± 0.77 , whereas among females this characteristic was in a range 58.5 ± 0.88 and 54 ± 0.119 for the groups I and II, respectively.

Comparison groups were representative by oncologic process dissemination. All smCRC patients had IV stage of the disease, in the majority of patients primary tumors infiltrated subserous membrane of large intestine wall without invasion into adjacent organs or structures (T_3) – 29 (46.7%) and 30 (44.7%), ($p = 0.87$) or spread beyond intestinal serous membrane (T_4) – 24 (38.7%) and 27 (42.8%) for the groups I

and II, respectively, ($p = 0.76$), whereas primary tumors T_{1-2} were determined in 9 (14.6%) and 6 (9.5%) clinical cases in the groups I and II, respectively, ($p = 0,77$). In the group I regional lymph nodes affection (pN_1 and pN_2) was registered in 24 (38.7%) and 6 (9.5%) patients, respectively. These characteristics do not differ statistically from the group II - 29 (46.7%) and 10 (15.8%) for pN_1 ($p = 0.55$) and pN_2 ($p = 0.72$), respectively.

Patients' distribution in the groups by primary tumor localization was homogeneous: in the group I there were registered 21 (33.9 %) and 41 (66.2 %) patients with rectal and colon cancer, respectively; in the group II rectal cancer was determined in 23 (36.5 %) patients, and primary tumors with colon localization were registered in 40 (63.5 %) patients ($p = 0.68$).

Immediate surgical treatment results

We registered disease progression in patients during undergoing PCT, therefore the part of the patients enrolled to the study failed to complete the scheduled treatment. In particular, in the group I in 19 (30.6 %) cases during aPCT, and in the group II in 15 (23.8 %) cases there was a trend towards disease progression in patients that were subjected to large intestine resection and obtained nPCP. Nevertheless, in the group II the progression on the background of aPCT was registered significantly rarer – in 2 (3.2 %) patients ($p < 0.001$).

Surgical treatment analysis revealed significant difference in a number of “major” liver resections (≥ 3 segments) – 23 (37.2 %) and 29 (60.4 %) in the groups I and II, respectively, ($p = 0.03$). In particular, in the group II there were more non-standard trisegmentectomies of liver - 5 (10.4 %) cases, and in the group I – 3 (4.8 %) cases, $p = 0.3$. Also in the group of staged surgical tactics there were 2 (4.2 %) resections of 2 central sections (mesohepatecomies), whereas in the group I such operative interventions were not provided, $p = 0.1$. Extended right-sided hemihepatectomies were performed in 10 (16.2 %) and 15 (31.3 %) cases in the groups I and II, respectively, $p = 0.06$. Immediate analysis of surgical stages demonstrated that complete scheduled surgical treatment was achieved in 110 (88 %)

patients, among them 62 (56.4 %) and 48 (43.6 %) with simultaneous and staged surgical approaches, respectively.

“Minor” resections (< 3 segments) of liver were performed in the group I significantly more frequently, in particular, atypical bisegmentectomies in 10 (16.1 %) cases, and in the group II in 2 (4.2 %) patients, $p = 0.045$.

Pairwise analysis did not find reliable differences within the groups in number and type of large intestine resections performed, including patients that received low anterior rectal resections – 3 (4.8 %) and 2 (3.2 %), $p = 0.64$; or low anterior rectal resections with ileostomy – 5 (8.1 %) and 9 (14.3 %) at $p = 0.27$ in the groups I and II, respectively.

Table 1

Clinical data characteristics

Characteristics	Group I (Median \pm SD)	Group II (Median \pm SD)	p
Intra-operative blood loss (ml)	200.0 \pm 95.3	240.0 \pm 156.8	0.11
Duration of operative interventions (min.)	367.0 \pm 71.8	515.0 \pm 119.1	< 0.001
Bed-day (n)	18.0 \pm 9.5	31.0 \pm 7.8	< 0.001

The examined groups also did not differ in aggregate level of intra-operative blood loss (200.0 \pm 95.3) ml and (240.0 \pm 156.8) ml in the groups I and II, respectively, ($p=0.11$). In the group II the total volume of blood loss during resection of large intestine with primary tumor and second surgical stage for synchronous liver metastases removal was exaluated.

Statistical reliable differences in duration of in-patient patients’ rehabilitation between studied patients groups were registered. In that way, total bed-day comprised 18.0 \pm 9.5 and 31.0 \pm 7.8 for the groups I and II, respectively, $p < 0.001$. Also we determined the advantage of simultaneous surgical tactics by operative interventions

duration that comprised 367.0 ± 71.8 min. for simultaneous resections group and 515.0 ± 119.1 min. for staged surgical interventions group, $p < 0.001$ (Tabl.1).

Studied groups did not differ in total level of post-operative complications and lethality in 30-days post-operative period. Analysis of immediate surgical results determined that in the majority of cases R0-resections were performed in 59 (95.2 %) and 47 (95.6 %) cases in the groups I and II, respectively.

Table 2

Characteristics of the surgical treatment results for studied patients
(categorical variables are presented with appropriate percentage meanings)

Characteristics	Patients. total (n = 110)		Group I (n = 62)		Group II (n = 48) ¹		p
	n	%	n	%	n	%	
Status of liver resection margins							
R0	106	96.4	59	95.2	47	97.9	0.45
R1	4	3.6	3	4.8	1	2.1	0.45
All post-operative complications	31	28.2	19	30.6	12	25.0	0.51
Abscess of abdominal cavity or small pelvis	4	3.6	2	3.2	2	4.2	0.8
Colonic anastomosis insufficiency	3	2.7	3	4.8	-	-	0.12
Acute liver insufficiency	10	9.1	7	11.3	3	6.3	0.36
Cardiac	11	10	5	8.1	6	12.5	0.44
Other	3	2.7	2	3.2	1	2.1	0.7
Post-operative lethality	4	3.6	3	4.8	1	2.1	0.45
Post-operative complications rate according to Calvien-Dindo scale							
Grade II	5	4.5	3	4.8	2	4.2	0.8
GradeIIIa	15	13.6	7	11.3	8	16.7	0.4
GradeIIIb	5	4.5	4	6.5	1	2.1	0.3
GradeIVa	6	5.5	5	8.1	1	2.1	0.2

Grade V (death)	4	3.6	3	4.8	1	2.1	0.4
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Note. In the group II the results of treatment of 48 patients that completed both surgical staged were taken into account.

The most common complications were acute liver insufficiency – (7 (11.3 %) and 3 (6.3 %) cases, $p = 0.36$) and abscesses of abdominal cavity and small pelvis (5 (8.1 %) and 6 (12.5 %) cases, $p = 0.44$). Complications of severity grade IIIa were in both patients groups with similar frequency – 7 (11.3 %) and 8 (16.7 %) cases, $p = 0.4$, in the groups I and II, respectively, (Tabl. 2). Surgical strategy with application of simultaneous resections led to higher level of post-operative lethality – 3 (4.8 %) cases comparing with staged operations – 1 (2.1 %) case, although this difference was not statistically significant ($p = 0.4$), (Fig. 1).

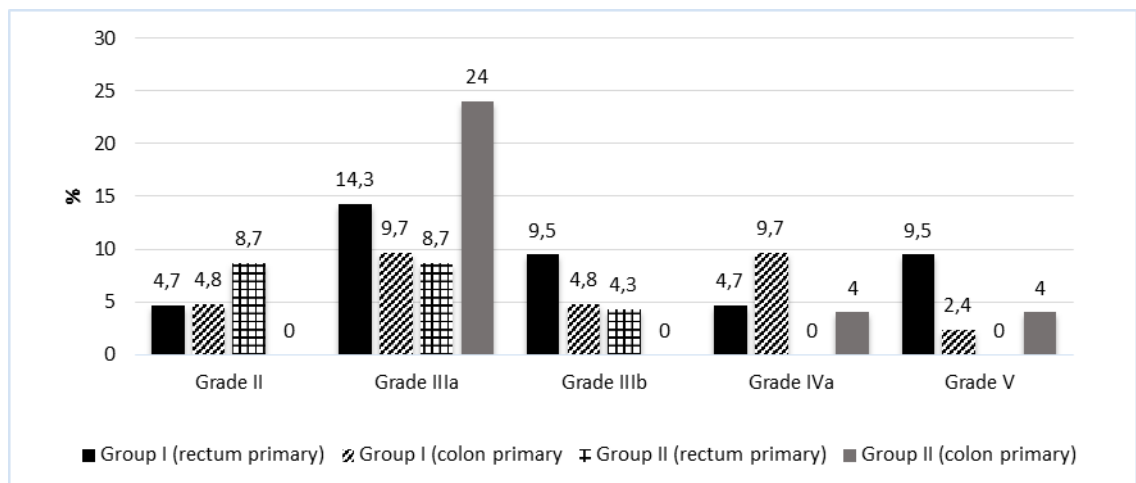


Fig. 1. Post-operative complications distribution (Clavien-Dindo scale) in groups of smCRC patients according to the group and primary tumor localization.

As it is seen from the Table 3 the majority of serious complications (of grade IIIa and higher according to Clavien-Dindo scale) were registered in the cohort of patients that underwent “large resection” of liver, in particular, in the group I, $n = 13$ (21.0 %), whereas in “small resections” there were 3 (4.8 %) cases, $p = 0.007$. In the group II this trend was not determined – 4 (8.3 %) and 6 (12.5 %) cases at “major” and “minor liver resections”, respectively, ($p = 0.5$). Besides this in resections of ≥ 3 liver segments in the group I high rates of acute liver insufficiency were determined ($n = 7$, (11.3 %), whereas at “minor” this complication was not registered ($p = 0.016$).

Table 3

Comparative characteristics of liver surgery in studied patients
(categorical variables are presented with appropriate percentage meanings)

Characteristics	Group I (n = 62)		Group II (n = 48) ³		P value
	n	%	n	%	
Major resections of liver¹					
Total complications rate	14	22.6	7	14.6	0.3
Complication of grade III and higher (according to Clavien-Dindo)	13	21.0	4	8.3	0.07
Acute liver insufficiency	7	11.3	2	4.2	0.2
Colonic anastomosis insufficiency	3	4.8	-	-	0.1
Lethality	3	4.8	-	-	0.1
Minor resections of liver²					
Total complications rate	5	8.1	5	10.4	0.6
Complication of grade III and higher (according to Clavien-Dindo)	3	4.8	6	12.5	0.2
Acute liver insufficiency	-	-	1	2.1	0.4
Colonic anastomosis insufficiency	-	-	-	-	
Lethality	-	-	1	2.1	0.4

Notes:

1. Resection of ≥ 3 liver segments.

2. Resection of <3 liver segments.

3. In the group II the results of treatment of 48 patients that completed both surgical staged were taken into account.

Also, all 3 (4.8 %) cases of post-operative lethality and development of sutures insufficiency of colonic anastomosis of the group I were specifically in patients with extended hemihepatectomies and rectal resection ($p = 0.08$). As result, it is possible

to claim about proved effect of large resections of liver on post-operative complications rate and lethality in group I patients (Fig. 2).

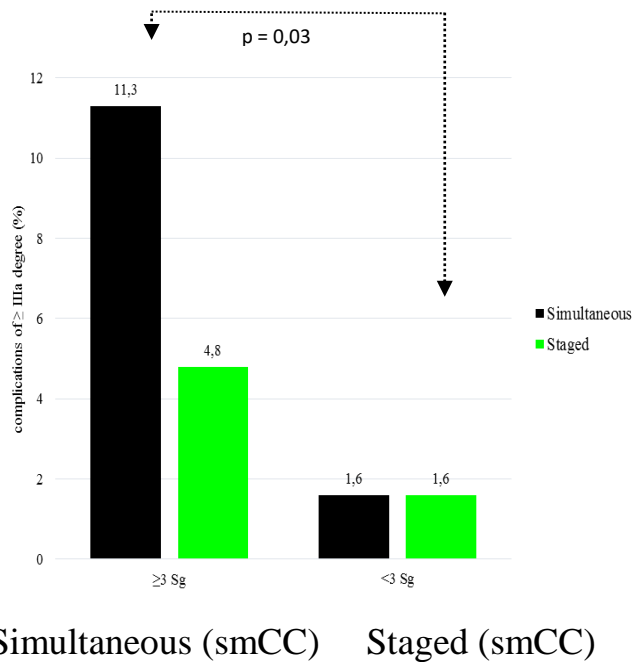


Fig. 2. 30-days complications of grade IIIa and higher (Clavien-Dindo scale) in simultaneous resections group in smCC.

Long-term treatment results

At the time of analysis total 5-years cumulative survival rate of smCRC patients that underwent R0-resection of primary tumor and synchronous liver metastases was 42% and 35% for the groups I and II, respectively, $p=0.73$, (Fig. 3).

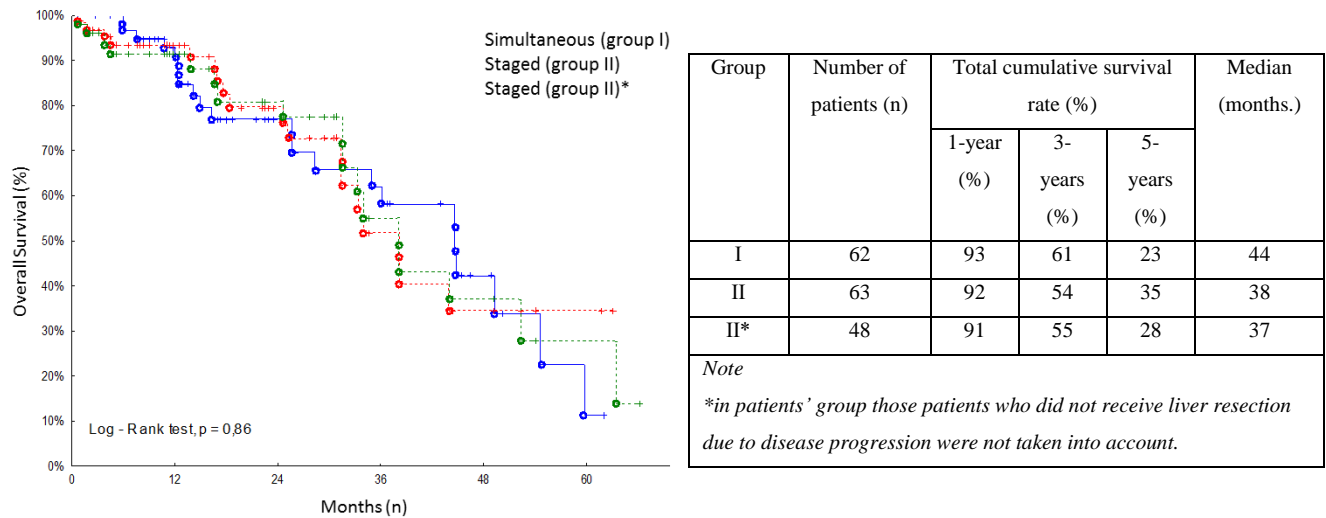


Fig. 3. Total cumulative survival rate of sCRC patients in the groups I and II (Log-RankTest, $p = 0.86$).

Treatment costs

Total costs of treatment provided for one patient of group I was 19597.2 ± 956 hrn. whereas in the group II this value was significantly higher – 31287.9 hrn. Difference in average expenses between studied groups was 12820.8 hrn. ($p < 0.001$). Average costs of treatment of one smCRC patient with application of staged resection exceeded those in the group of patients with application of simultaneous surgical treatment of this pathology by 40.9% ($p < 0.001$).

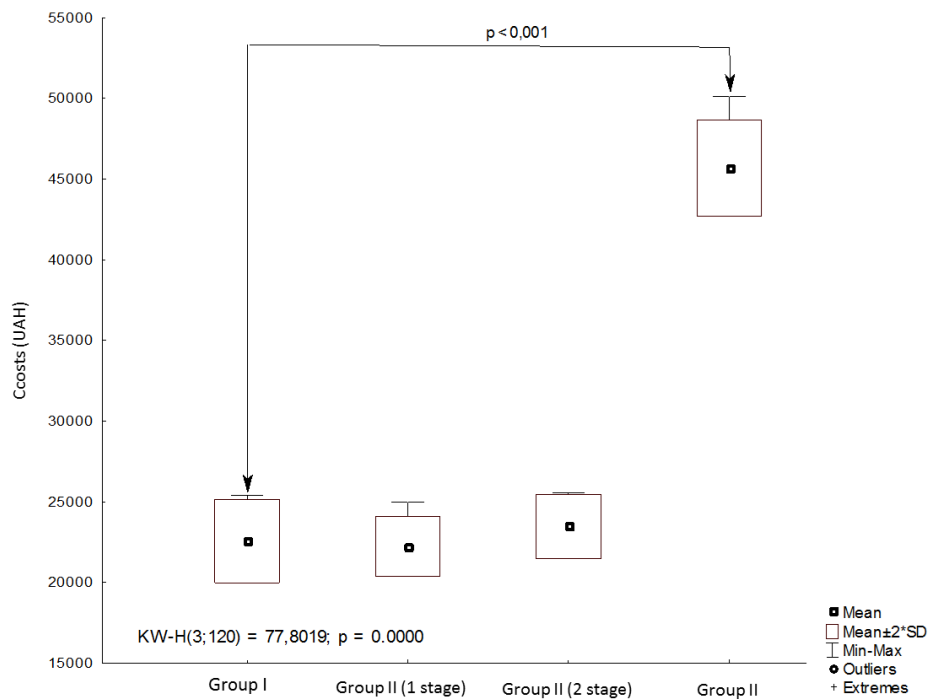


Fig. 2. Comparison of costs of simultaneous and staged surgical strategies of smCRC patients treatment.

Application of simultaneous surgical operative interventions in smCRC patients in settings of the National Cancer Institute provides with statistically reliable reduction of state funds expenses at the stages of out-patient examination and consulting, in pre-operative in-patient period, during patients' preparation for operative intervention, narcosis supply, intensive therapy in resuscitation unit conditions, post-operative in-patient treatment and hospital stay.

Conclusions

Liver resection in smCRC remains the only method that allows to improve reliably total 5-years patients' survival rate independently of surgical tactics – by 42 % and 35 % at simultaneous and staged resections, respectively, $p=0.73$. Simultaneous resections of ≤ 3 segments of liver with metastases and colon with primary tumor in smCRC is a safety surgical tactics – complications of \geq IIIa degree constitute 4.8 %. Simultaneous resections of > 3 segments of liver with metastases and rectum with primary tumor in smCRC statistically significantly increase complications of \geq IIIa degree – by 20.9 %, $p = 0.007$. Average cost of one smCRC

patient treatment with application of staged resections exceeds those in the group of patients with application of simultaneous surgical treatments by 40.9%.

List of literature:

1. I.B. Schepotin, E.A. Kolesnik, A.V. Lukashenko, A.A. Burlaka, V.V. Priymak. Surgical treatment colorectal cancer with synchronous liver metastases. Clin. oncology. – 2014; 13: 6-11.
2. I.B. Schepotin, O.O. Kolesnik, A.V. Lukashenko, A.A. Burlaka V.V. Pryymak, A.V. Hanich. Combination of in-situ separation of the liver and portal vein ligation in patients with metastatic colorectal cancer liver. Clinical Surgery. – 2014; 11: 8-13.
3. Cancer in Ukraine. Morbidity, mortality, cancer service performance. Bulletin of the National Cancer Registry of Ukraine. – 2013; 1-14: 124.
4. Kelly M.E. et al., Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. // J. Surg. Oncol. – 2015 №3. – P. 341-351.
5. Veereman G. et al., Pooled analysis of the surgical treatment for colorectal cancer liver metastases. // Crit. Rev. Oncol. Hematol. – 2015. №1. – P. 122-135.
6. Woubet T. Kassahun. Unresolved issues and controversies surrounding the management of colorectal cancer liver metastasis. // World Journal of Surgical Oncology. -2015. - №13. – P. 61.
7. Zisis C. et al., The management of the advanced colorectal cancer: management of the pulmonary metastases. // J. Thorac. Dis. – 2013. - №4. - P. 383-388.