Clinics of Oncology

Research Article

ISSN: 2640-1037 | Volume 7

Changes in the Local Therapy of Primary and Secondary Liver Tumors with Curative Intent - Single-Center Experience Over 20 Years

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Received: 03 Aug 2023
Accepted: 25 Sep 2023
Published: 02 Oct 2023
J Short Name: COO

Citation:

Öfner D, Changes in the Local Therapy of Primary and Secondary Liver Tumors with Curative Intent - Single-Center Experience Over 20 Years. Clin Onco. 2023; 7(2): 1-10

1. Abstract

1.1. Background: Malignant liver tumors encompass a wide range of primary malignancies, and the liver is a vital target organ for metastases from various cancers. Commonly accompanied by systemic therapy, surgical treatment is a well-established option. Numerous innovations made even complex liver resections with extensive tumor burden safe and effective. As a result, the last two decades have focused on expanding indications, including transplantation, parenchyma-sparing, and less invasive procedures. This study was designed to describe the advancement of local liver-directed interventions at a hepatobiliary and transplant center.

1.2. Methods: Data from consecutive patients treated locally with primary and secondary malignant liver tumors at the Department of Visceral, Transplant and Thoracic Surgery and the Department of Radiology at the Medical University of Innsbruck between 2002 and 2021 were analyzed. All patients were treated aggressively and with curative intent. Endpoints of the study were the distribution of liver resection and ablative procedures over time.

1.3. Results: Two thousand nineteen patients with 3,217 procedures were included in the study. Eight hundred twenty-seven surgical resections of the liver, 365 orthotopic liver transplants, 2,021 SRFAs, and conventional intraoperative ablations were performed. Over time, the main findings are a continuous increase with tripling (from 406 to 1,241) of procedures and a highly statistically significant (P<.001) inverse correlation between liver resection and SRFA treatment for primary and secondary liver tumors.

1.4. Conclusion: During the last 20 years, liver-directed local treatments of primary and secondary liver tumors with curative intent have become increasingly common and shifted towards more minimally invasive approaches. Further analysis is needed to determine the clinical benefit.

2. Introduction

Malignant liver tumors include a broad spectrum of primary and secondary tumors, with the latter being more than twenty times more common and incurable in most cases [1]. Well-established treatment options for patients with primary and secondary liver malignancies include surgical resection [2] and systemic chemotherapy [1,3]. Surgery remains the mainstay of curative treatment [4] and is combined with various neoadjuvant, intraoperative, and adjuvant strategies [5–10] that have led to significant improvements in survival [11]. It has been shown that oligometastatic disease can be treated curatively, which requires aggressive local treatment in appropriate patients [2,11–15]. Starting with hepatic metastases of colorectal carcinoma (CRLM), significant advances have been made in recent decades [16], which also make complex liver surgery safe and effective [17–19]. Extensive tumor burdens traditionally considered inoperable can now be treated curatively by systemic conversion chemotherapies [20] and complex surgery. Combination with a variety of measures such as augmentation of the healthy liver by portal vein occlusion to induce liver remnant hypertrophy [21], staged surgery [22], or ablation modalities [23] are available. Liver transplantation has been established in selected patients with hepatocellular carcinoma (HCC) [24–26]. Still, it is now becoming a promising option for many other tumor types such as perihilar cholangiocarcinoma (phCCA), neuroendocrine tumors (NET), or CRLM [27]. Surgical resection of CRLM is now a state-of-the-art treatment, usually in combination with systemic therapy [22], limited only by the function of the future remnant liver [28,29]. This determinant is still challenging to assess preoperatively. It is essential in extensive resections, especially in pre-damaged livers, such as in a cirrhotic liver or after systemic hepatotoxic pre-treatment [30]. With the widespread adoption of minimally invasive surgery (MIS) to further reduce postoperative morbidity, the use of laparoscopic and, eventually, robotic procedures in liver surgery has steadily increased [31]. Compared to open liver surgery, a faster recovery time is assured with MIS procedures. Due to these developments, in addition to the resection of metastases of mainly hormonally active neuroendocrine tumors (NELM) [32,33], metastases of other primary tumors (non-CRLM non-NELM) have increasingly been treated surgically [12,34–38]. Even though systemic therapy plays a prominent role in the latter [39,40], and despite the surgical success, the percentage of resectable patients ranges from 25% to less than 10%, depending on the primary tumor [41]. To save as much liver parenchyma as possible during surgery, so-called parenchyma-sparing liver resections and increasingly interventional methods, often used in combination with surgery, have been developed. Among these methods, radiofrequency ablation (RFA) and microwave ablation (MWA) [42,43] have become established. However, they can only be used for curative purposes in the case of small, locally limited disease. At our hospital, a 3D navigated method of RFA, multi-needle stereotactic RFA (SRFA) with intrainterventional image fusion, has been developed to verify the ablation margin. Even large (>5cm) and multiple tumors (>10 lesions) can be treated with this technique within a single session [44]. Due to the parenchyma-sparing approach and the conservation of anatomical structures (e.g., liver and portal veins), SRFA may be repeated in case of tumor recurrences.

The present study describes the development of locoregional, liver-directed methods for primary and secondary liver malignancies at a tertiary university center over 20 years. The treatment of primary liver malignancies comprises HCC and cholangiocellular carcinoma (CCA), hepatoblastomas, cystadenocarcinoma, and sarcomas. The origins of liver metastases included colorectal, breast, pancreatic, renal cell, and lung carcinomas, NET, gastrointestinal stromal tumors (GIST), uveal melanomas, and a variety of other orphan tumors. Locoregional therapies discussed involve surgical treatment and ablative techniques, focusing on SRFA.

3. Materials and Methods

3.1. Patient Cohort

The clinical records of all consecutive patients treated with curative intent at the Department of Visceral, Transplant, and Thoracic Surgery at the Medical University of Innsbruck between 2002 and 2021 were included in the analysis using a prospectively managed, quality-controlled internal registry. Written informed consent for treatment decisions was obtained in multidisciplinary tumor board meetings. The study period was divided isochronously into four periods of 5 years each. Group A, B, C, and D covered 2002 to 2006, 2007 to 2011, 2012 to 2016, and 2017 to 2021.

3.2. Operative Procedures

Major hepatectomy was defined as a resection of 3 or more segments. Resections were performed either anatomically, non-anatomically, or as a combination. Anatomical resections were classified according to Brisbane 2000 terminology [45]. In the case of major hepatectomy, liver function and calculation of future residual liver volume (FLRV) were assessed by CT scans. As previously recommended, an FLRV of at least 20% was required in patients without underlying liver disease, 30% with steatosis, and 40% with cirrhosis (Child A) [46].

3.3. Multi-probe Stereotactic Radiofrequency Ablation (SRFA)

The method of SRFA has already been described in detail [47,48]. Briefly, the entire procedure is performed in a CT procedure room. The intubated patient is immobilized on the CT table with a vacuum mattress. 10-15 fiducials (X-SPOT, Beekley Corporation, Bristol, USA) are attached to the skin of the upper abdomen, and a contrast-enhanced CT in the arterial and portal venous phases is acquired. To create reproducible stereotactic conditions, the endotracheal tube is temporarily disconnected during the planning CT, at each needle advance, and during the final CT check. Needle trajectories and overlapping ablation zones are planned on multiplanar reconstructions of the three-dimensional CT data set using the frameless stereotactic navigation system (Stealth Station Treon plus, Medtronic Inc., Louisville, USA). After registration using the skin markers, 15G x 17.2 cm coaxial needles (Bard Inc., Covington, USA) are advanced sequentially through the rigid targeting device to the depth calculated by the planning software. To check the placement of the coaxial needles, a native control CT with needles in place is superimposed on the planning CT using the image fusion software of the navigation system. Biopsies can be taken through coaxial needles. Three 17 G RF probes with 3 cm tips (Cool-tip, Medtronic, Mansfield, USA) are inserted through the coaxial needles for serial tumor ablation. RFA is performed using a unipolar ablation device with a switching generator (Cool-tip, Medtronic, Mansfield, USA). After ablation, a contrast-enhanced

CT in the arterial and portal venous phase is obtained after the probe has been withdrawn. The respective three-dimensional data sets are superimposed on the planning CT to verify complete coverage of the tumor by the ablation zone.

3.4. Statistical Analysis

Nominal variables are expressed as frequencies and percentages, and continuous variables as means with standard deviation (SD). Differences in nominal variables were analyzed with the chi-square test or Fisher's exact test. Two-tailed p-values < 0.05 were considered significant. Data analysis was conducted using SPSS 24.0 (IBM Inc., USA). Time-trends are depicted as simple moving average.

4. Results and Discussion

Three thousand two hundred seventeen local procedures were performed on 2,099 patients from 2002 to 2021 for primary and secondary malignancies of the liver. 674 (31.1%) were female, 1,425 (67.9%) male. Gender was homogeneously distributed over time. The mean age of the patients was 62.0 ± 12.34 years and constant over periods. One thousand seven hundred four were primary tumors, 1,513 metastases. Eight hundred twenty-seven surgical resections of the liver, 365 orthotopic liver transplants, 2,021 SRFAs, and four conventional RFAs performed intraoperatively were carried out. Out of 1,125 patients in whom a surgical measure was taken, 791 (93.7%) received purely surgical treatment only once and in 53 (6.3%) cases repeatedly. Among the 1,253 patients treated by SRFA, 974 (77,7%) patients were treated with intervention alone, and of these, 350 (35.9%) patients were treated more than once (up to 9 times). In the remaining 281 (13,4%) patients, a combination of surgery and RFA (i.e., SRFA or intraoperative RFA (iRFA)) was observed during the disease course. None of the three patients with iRFA were treated exclusively with this method. One patient underwent iRFA twice during the disease. The distribution of surgeries among Groups A, B, C, and D is 276 (23.1%), 301 (25.3%), 294 (24.7%), 321 (26.9%), respectively. A statistically significant ($\chi 2=32.89$; P < .001) increase in MIS surgery from 3 (1.1%) to 11 (3.7%), 12 (4.1%) and 36 (11.2%) cases was observed. An increasing number of SRFA interventions were performed over the timeframes with 129 (6.4%), 363 (18.0%), 611 (30.2%), and 918 (45.4%) cases, respectively. The distribution of surgical cases among the periods and the data on SRFA, as well as the remaining local therapy measures, are summarized in (Table 1).

Table 1: Numbers of different local procedures of liver malignancies (N=3,217) with regard to the periods

	GROUP A				GROUP B				GROUP C				GROUP D			
	2002 - 2006				2007-2011				2012-2016				2017-2021			
	HT	OLT	SRFA	iRFA	HT	OLT	SRFA	iRFA	HT	OLT	SRFA	iRFA	HT	OLT	SRFA	iRFA
iCCA	19	0	5	0	17	2	26	0	22	0	57	0	35	1	39	0
extrahepatic CCA	20	2	0	0	28	1	0	0	19	2	0	0	34	2	0	0
hepatoblastoma	31	80	66	0	29	77	134	0	28	98	294	0	41	93	385	0
cystadenocarcinoma	4	0	0	0	0	0	0	0	1	3	0	0	3	1	0	0
sarcoma	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HCC	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
CRLM	81	0	36	1	97	0	103	1	72	0	132	0	65	0	338	2
NELM	7	0	1	0	6	0	13	0	11	0	27	0	15	3	26	0
non-CRLM non-NELM	29	0	21	0	42	0	87	0	38	0	101	0	28	0	130	0
Total	194	82	129	1	221	80	363	1	191	103	611	0	221	100	918	2

Abbreviations: CCA: Cholangiocellular Carcinoma; iCCA: Intrahepatic Cholangiocellular Carcinoma; HCC: Hepatocellular Carcinoma; CRLM: Colorectal Liver Metastases; NELM: Neuroendocrine Liver Metastases; nonCRLM: Non NELM: Metastases other than CRLM or NELM; HT: Hepatectomy; OLT: Orthotopic Liver Transplantation; SRFA: Stereotactic Radiofrequency Ablation; iRFA: Intraoperative Radiofrequency Ablation

4.1. Primary Liver Tumors

Out of 1,704 primary liver tumors, 698 (41.0%) were treated surgically and 1,006 (59.0%) by SRFA. The numbers of Groups A, B, C, and D were 230 (13.5%), 316 (18.5%), 524 (30.8%), 634 (37.2%). The most common indications for surgical treatment were HCC (N=477; 68.3%), followed by extrahepatic (N=108; 15.5%) and intrahepatic CCA (iCCA; N=96; 13.8%), respectively. Over the periods, there was a statistically significant ($\chi 2=25.70$; DF=9; P = .002) decrease in surgically treated gallbladder carcinoma and an increase in iCCA, phCCA, and distal CCAs (dCCA; Table 2a). In addition, CCAs were increasingly statistically significant ($\chi 2=19.7$; DF=6; P < .01) more frequently treated by major (N=148 vs 45 minor) resections. HCCs were resected 128 times, half with a major resection. Three hundred forty-eight of all HCC patients (73.0%), 7 (5.5%) out of 74 phCCAs, and three of the 96 iCCA underwent orthotopic liver transplantation (OLT). The surgical cases also included 12 (1.7%) hepatoblastomas, four of which were treated by OLT, three (.4%) primary sarcomas, and two (.3%) primary cystadenocarcinomas of the liver that were resected. All data are depicted in (Table 2a). One thousand six patients with primary liver tumors were treated by SRFA. HCC with 879 (87.4%) cases, iCCA with 127 (12.6%). The distribution over periods is shown in (Table 2b).

4.2. Liver Metastases

Out of 1,513 liver metastases, 498 (32.9%) were treated surgically, comprising 4 cases with iRFA in CRLM and 3 OLT in NELM, and 1,015 (67.1%) by SRFA. The numbers in Groups A, B, C, and D were 176 (11.6%), 349 (23.1%), 381 (25.2%), and 607 (40.1%), respectively (see Table 1). Four hundred ninety-four cases with metastases to the liver treated surgically were distributed among colorectal carcinoma 315 times (63.8%), NET 42 times (8.4%), and non-CRLM non-NELM 137 (27.8%) times. Details are given in (Table 3a and Table 3b). Surgically, CRLM were more frequently treated with minor (N=192; 39.9%) than with major (N=127; 25.7%) resections. Furthermore, a statistically significant shift (χ2=19.63; DF=6; P < .01) of the primary towards the right-sided colon was observed over the periods. iRFA was combined with surgery in only four patients. In NELM (N=42), the majority of primary tumors were located in the pancreas (pNET; N=19; 45.2%), followed by the small bowel (siNET; N=13; 31.0%). Minor resections were more frequent (N=27; 64.3%) than major resections (N=12; 28.6%). Three transplantations for metastases limited to the liver were performed in the last five years, all NELM. Statistically significant increasing frequencies (χ2=40.62; DF=30 P<.05) of liver metastases from the small bowel (N=11; 8.0%), mainly gastrointestinal stromal tumors (GIST; N=7; 5.1%) and reproductive organs, primarily ovarian carcinoma (N=23; 16.8%) were treated surgically. Minor resections (N=110; 80,3%) predominated in the surgical treatment of non-CRLM non-NELM. Detailed data are given in (Table 3a). SRFA was performed in 609 CRLM patients with 609 (60.0%) sessions, 42 NELM patients with 67 (6.6%) sessions, and 230 non-CRLM non-NELM patients with 339 (33.4%) sessions with curative intent. Over time, a statistically significant (χ2=36.86; DF=6 P<.001) increase was observed primarily in SRFA procedures for CRLM (see Table 3b) (Table 4-6).

4.3. Surgery and SRFA

Over time, a highly statistically significant inverse correlation (χ2=161.35; DF=3; P<.001) between surgical and interventional (SRFA) therapy was found for both primary (χ2=114.49; DF=3; P<.001) and secondary (χ2=162.18; DF=3; P<.001) liver tumors. In the first period, surgical procedures predominated with a ratio of 2:1, and from the third period onwards, more SRFAs were performed than hepatectomies. This relationship is particularly powerful in CRLM (χ2=140.78 DF=3 P<.001). All data are shown in (Figure 1).

Table 2a: Surgery only of primary tumors of the liver (N=698) with regard to the periods

SURGERY (N=698)	GROUP A 2002 - 2006	GROUP B 2007-2011	GROUP C 2012-2016	GROUP D 2017-2021	P	total
CCA (N=204)	**41 (5.9%)**	**48 (6.9%)**	**43 (6.2%)**	**72 (10.3%)**		**204 (29.2%)**
iCCA	19 (2.7%)	19 (2.7%)	22 (3.2%)	36 (5.2%)	χ2=25.70 DF=9 P = .002	96 (13.8%)
phCAA	10 (1.4%)	18 (2.6%)	20 (2.9%)	26 (3.7%)		74 (10.6%)
dCCA	0 (0%)	1 (.1%)	0 (0%)	5 (.7%)		6 (.5%)
gallbladder	12 (1.7%)	10 (1.4%)	1 (.1%)	5 (.7%)		28 (2.3%)
minor resections	19 (2.7%)	9 (1.3%)	4 (.6%)	13 (1.9%)	χ2=19.70 DF=6 P < .01	45 (6.4%)
major resections	20 (2.9%)	36 (5.2%)	36 (5.2%)	56 (8.0%)		148 (21.2%)
OLT	2 (.3%)	3 (.4%)	2 (.3%)	3 (.4%)		10 (1.4%)
HCC (N=477)	**111 (15.9%)**	**106 (15.2%)**	**126 (18.1%)**	**134 (19.2%)**		**477 (68.3%)**
minor resections	17 (2.4%)	17 (2.4%)	15 (2.1%)	15 (2.1%)	χ2=7.40 DF=6 n.s.	64 (9.2%)
major resections	14 (2.0%)	12 (1.7%)	12 (1.7%)	26 (3.7%)		64 (9.2%)
OLT	80 (11.5%)	77 (11.0%)	98 (14.0%)	93 (13.3%)		348 (49.9%)
remaining (N=17)	7 (1.0%)	2 (.3%)	4 (.6%)	4 (.6%)	χ2=17.18 DF=6 n.s.	17 (2.4%)
cystadenocarcinoma	2 (.3%)	0 (0%)	0 (0%)	0 (0%)		2 (.3%)
hepatoblastoma	4 (.6%)	0 (0%)	4 (.6%)	4 (.6%)		12 (1.7%)
sarcoma	1 (.1%)	2 (.3%)	0 (0%)	0 (0%)		3 (.4%)
minor resections	2 (.3%)	0 (0%)	0 (0%)	0 (0%)	χ2=9.01 DF=6 n.s.	2 (.3%)
major resections	5 (.7%)	2 (.3%)	1 (.1%)	3 (.4%)		11 (1.6%)
OLT	0 (0%)	0 (0%)	3 (.4%)	1 (.1%)		4 (.6%)
Total	***159 (22.8%)***	***156 (22.3%)***	***173 (24.8%)***	***210 (30.1%)***		***698 (100%)***

Abbreviations: CCA: Cholangiocellular Carcinoma; iCCA: Intrahepatic CCA; phCCA: perihilar CCA (Klatskin tumor); dCCA: Distal CCA; HCC: Hepatocellular carcinoma; OLT: orthotopic Liver Transplantation; n.s: Not Significant

Table 2b: SRFA procedures of primary tumors of the liver (N=1,006) with regard to the periods

SRFA (N=1006)	GROUP A	GROUP B	GROUP C	GROUP D	Total
	2002 - 2006	2007-2011	2012-2016	2017-2021	
iCCA (N=127)	5 (.5%)	26 (2.6%)	57 (5.7%)	39 (3.9%)	127 (12.6%)
HCC (N=879)	66 (6.6%)	134 (13.3%)	294 (29.2%)	385 (38.3%)	879 (87.4%)
Total	71 (7.1%)	160 (15.5%)	351 (%)	424 (42.1%)	1006 (100%)

Abbreviations: SRFA, stereotactic radiofrequency ablation; iCCA, intrahepatic cholangiocellular carcinoma; HCC, hepatocellular carcinoma

Table 3a: Surgery only of secondary tumors to the liver (N=494) concerning the periods

	GROUP A 2002 - 2006	GROUP B 2007-20011	GROUP C 2012-2016	GROUP D 2017-2021	P	total
CRLM (N=315), primary site	81 (16,4%)	97 (19.6%)	72 (14.6%)	65 (13.2%)		315 (63.8%)
right hemicolon	15 (3.0%)	22 (4.5%)	18 (3.6%)	24 (4.9%)	right vs. left	79 (16.0%)
left hemicolon	39 7.9%)	47 (9.5%)	32 6.5%)	30 (6.1%)	χ2=9.63; DF=6	148 (30.0%)
Rectum	27 (5.5%)	28 (5.7%)	22 (4.5%)	11 (2.2%)	P<.01	88 (17.8%)
minor resections	51 (10.3%)	56 (11.3%)	41 (8.3%)	42 (8.5%)	χ2=1.35; DF=3 n.s.	190 (38.5%)
major resections	30 (6.1%)	41 (8.3%)	31 (6.3%)	23 (4.7%)		125 (25.3%)
NELM* (N=42), primary site	7 (1.4%)	6 (1.2%)	11 (2.2%)	18 (3.6%)		42 (8.5%)
foregut	1 (.2%)	1 (.2%)	1 (.2%)	0 (0%)	χ2=19.68; DF=15	3 (.6%)
midgut	4 (.8%)	4 (.8%)	2 (.4%)	3 (.6%)	n.s.	13 (2.6%)
hindgut	1 (.2%)	0 (0%)	0 (0%)	1 (.2%)		2 (.4%)
pancreas (pNET)	1 (.2%)	1 (.2%)	6 (1.2%)	11 (2.2%)		19 (3.8%)
lung	0 (0%)	0 (0%)	1 (.2%)	2 (.4%)		3 (.6%)
cancer of unknown origin (CUP)	0 (0%)	0 (0%)	1 (.2%)	1 (.2%)		2 (.4%)
minor resections	5 (1.0%)	2 (.4%)	8 (1.6%)	12 (2.4%)	χ2=9.04; DF=6	27 (5.5%)
36	2 (.4%)	4 (.8%)	3 (.6%)	3 (.6%)	n.s.	12 (2.4%)
OLT	0 (0%)	0 (0%)	0 (0%)	3 (.6%)		3 (.6%)
non-CRLM non-NELM (N=139), primary site	29 (5.9%)	42 (8.5%)	38 (7.7%)	28 (5.7%)		137 (27.7%)
upper GI	6 (1.2%)	7 (1.4%)	1 (.2%)	1 (.2%)	χ2=40.62; DF=30	15 (3.0%)
small bowel	2 (.4%)	0 (0%)	5 (1.0%)	4 (.8%)	P<.05	11 (2.2%)
colorectal	1 (.2%)	3 (.6%)	0 (0%)	1 (.2%)		5 (1.0%)
pancreas	3 (.6%)	6 (1.2%)	6 (1.2%)	5 (1.0%)		20 (4.0%)
reproductive organs	7 (1.4%)	5 (1.0%)	14 (2.8%)	5 (1.0%)		31 (6.3%)
endocrine organs	3 (.6%)	2 (.4%)	2 (.4%)	1 (.2%)		8 (1.6%)
breast	2 (.4%)	5 (1.0%)	0 (0%)	2 (.4%)		9 (1.8%)
kidney	2 (.4%)	1 (.2%)	1 (.2%)	1 (.2%)		5 (1.0%)
lung	0 (0%)	1 (.2%)	2 (.4%)	1 (.2%)		4 (.8%)
unknown (CUP)	0 (0%)	4 (.8%)	0 (0%)	1 (.2%)		5 (1.0%)
others	3 (.6%)	8 (1.6%)	7 (1.4%)	6 (1.2%)		25 (4.9%)

minor resections	20 (4.0%)	34 (6.9%)	33 (6.7%)	23 (4.7%)	χ2=3.45; DF=3	110 (22.3%)
major resections	9 (1.8%)	8 (1.6%)	5 (1.0%)	5 (1.0%)	n.s.	27 (5.5%)
total	**117 (23.7%)**	**145 (29.4%)**	**121 (24.5%)**	**111 (22.5%)**		**494(100%)**

* Fisher´s exact test

Abbreviations: CRLM: Colorectal Liver Metastases; NELM: Neuroendocrine Liver Metastases; nonCRLM non NELM: Metastases other than CRLM or NELM; OLT: Orthotopic Liver Transplantation; NET: Neuroendocrine tumor; GI: Gastrointestinal tract; n.s: Not Significant

Table 3b: SRFA procedures of secondary tumors to the liver (N=1,015) concerning the periods

SRFA (N=1,015)	GROUP A	GROUP B	GROUP C	GROUP D	P	Total
	2002 - 2006	2007-2011	2012-2016	2017-2021		
CRLM (N=609)	36 (3.5%)	103 (10.1%)	132 (13.0%)	338 (33.3%)	χ2= 36.86; DF=6	609 (60.0%)
NELM (N=67)	1 (.1%)	13 (1.3%)	27 (2.7%)	26 (2.6%)		67 (6.6%)
nonCRLM non NELM (N=339)	21 (2.1%)	87 (8.6%)	101 (10.0%)	130 (12.8%)		339 (33.4%)
Total	58	202	260	494		1,015
	-5.70%	-19.90%	-25.60%	-49.80%		-100%

Abbreviations: SRFA: Stereotactic Radiofrequency Ablation; CRLM: Colorectal Liver Metastases; NELM: Neuroendocrine Liver Metastases; non-CRLM non NELM: Metastases other than CRLM or NELM

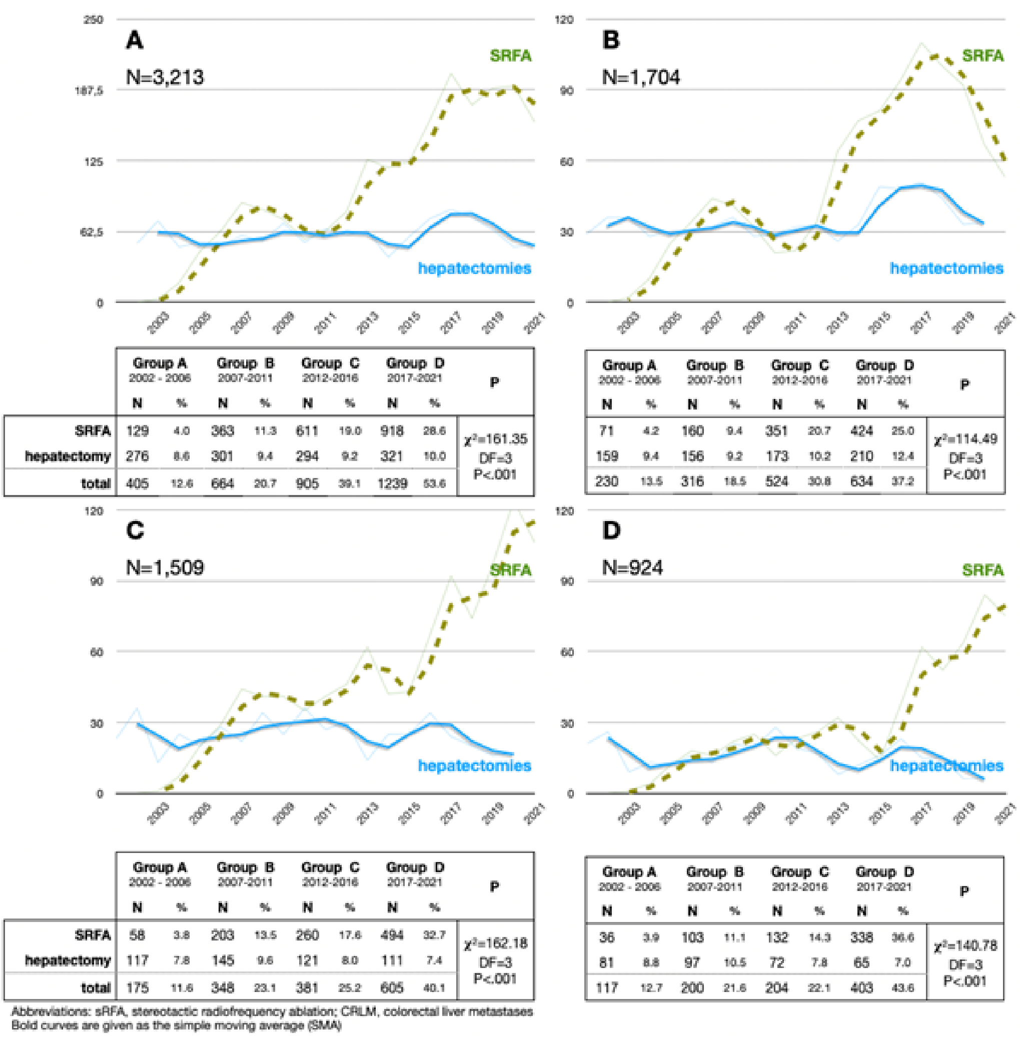

Figure 1: Surgically (solid line) and interventional (SRFA, dotted line) treated primary and secondary liver tumors. A, complete cohort; B, primary tumors; C, secondary tumors; D: CRLM; bold curves represent the simple moving average (SMA).

5. Conclusions

The essential data of patients who received local liver-directed therapy were prospectively documented over an adequately long time in a proprietary database system. The advantage of this database lies in the high quality of the data, which a third party can check based on unalterable original data directly retrievable in the system. This work describes the time course of 3,217 procedures on 2,099 patients with primary and secondary liver malignancies treated at the Medical University of Innsbruck. Parallel developments with other hepatobiliary and transplant surgery centers were apparent. Only one-third (31.5%) of all liver resections were performed in women. The ratio is balanced for resections (40.9% female patients), as already noted in a preliminary study [49]. On the other hand, there is only a tiny percentage (11.8%) of female recipients in liver transplantation. The difference is due to the higher incidence of HCC in men, and women are likely to be disadvantaged in the usual allocation parameters applied [50]. In addition, second to the establishment of complex liver surgery, the increasing attention to parenchyma-sparing resections and the introduction of minimally invasive procedures are apparent over the years. Thus, the data reflect a continuing trend of colorectal carcinoma from the left site to the right hemicolon, with the implication of a fundamentally worse outcome ("sidedness matters") [51]. In the first decade, 45% of left-sided colorectal carcinomas (i.e., from the left flexure to the rectum) were observed, decreasing to 30% in the subsequent decade. In contrast, the proportion of right-sided colorectal carcinomas increased from 11% to 13%. Notably, rectal ancer with treated liver metastases decreased considerably in frequency in the second decade. Preoperative radio chemotherapy of locally advanced deep rectal cancer, which has been routinely performed at our institution since 1994 and has been increasingly aggressively pretreated [52–56], may provide an explanation. Intensified pre-treatment is associated with cumulatively higher doses of systemic therapy that could have led to fewer distant metastases. It is also consistent with the literature that most locally treated secondary malignancies of the liver still originate in the colorectal region. In our cohort of patients, twice as many CRLM (N=315) were resected as NELM (N=42) and non-CRLM non-NELM (N=137) together. CRLM patients (N=1509), in turn, accounted for nearly two-thirds of the patients with secondary malignancies (N=924; 61%). Furthermore, it is worth mentioning that there were changes in the indication for liver resection of non-CRLM non-NELM patients. Metastasectomies were performed less frequently with increasing statistical significance (P<.05) for tumors at the upper gastrointestinal tract (UGI), endocrine organs, and breast carcinomas. Increasingly more frequently, however, metastasectomies for liver metastases from reproductive organs, pancreas, and small bowel were carried out. Ovarian carcinoma was the leading representative in reproductive organs, ductal carcinoma (PDAC) in the pancreas, and GIST in the small intestine. Today, OLT can cure many patients with primary and malignant liver tumors, which is possibly the only option. The term "Transplant Oncology" reflects the increasing importance of this new field (25), and the indication for transplantation with expanded criteria for malignant disease [57] is increasingly advocated. This trend is also reflected in our data in that via normothermic machine perfusion (59), the donor pool can be expanded, and thus increasingly more patients with malignancies of the liver can be transplanted. It has been the case for up to 25% in the last five years. Thus, in addition to the primary indication of HCC, patients with iCCA, a Klatskin tumor, and NELM were increasingly transplanted. Another topic is the development of local treatment of liver malignancies towards the sparing of the parenchyma and consequently the increased use of minimally invasive procedures. A statistically significant (P<.001) development from 1.1% in the first years to almost 11% MIS in the last five years can also be demonstrated in this work.

Minimally invasive local curative methods also include ablation procedures. While this is used internationally very frequently intraoperatively as an adjunct to resection, especially of bilobar metastases, the Departments of the Medical University of Innsbruck have taken a different path. iRFA was used only sporadically at our department. An SRFA method was developed at the beginning of the Millennium that is not comparable to the conventional one. Not only that needles can be placed precisely in 3D navigation and CT control for ablation. With the so-called multi-probe SRFA, employing 36 needles and more, even huge areas can be treated with a sufficient ablation margin of approximal 1 cm [44]. An intraoperatively verified safety margin of 0.5 cm in HCC and 1cm in CRLM is regarded as A0 (compared to R0 for surgical resections) [44]. Accordingly, this method was developed as an alternative to resection and used primarily when there is a gross disproportion between resection extent and tumor burden. The method also has limitations [60] but has steadily increased in use. In the first decade, surgical measures still predominated. In the second decade, the ratio turned in favor of SRFA. Reversal of local therapy directed to the liver is seen in primary and secondary tumors. Especially in the last two years, this increase in SRFA procedures and decrease in liver resections was dramatically evident. After years of almost constant resection frequencies particularly impressive in CRLM, liver resection decreased. An explanation can also be found in the operating room and bed capacity restrictions of the SARS-CoV-2 (COVID-19) pandemic [61]. Due to the SRFA, especially the postoperative stay is significantly shorter, which significantly eases the beds' utilization, and necessary liver-directed local therapy could be performed with a slight delay. However, a decline in SRFA interventions in patients with HCC (Figure 1) was observed during the COVID pandemic. We could show that liver-directed local therapy has evolved over the years. Increasing numbers of patients receive minimally invasive local therapies with curative intent for at least chronicity of the malignant disease. This assumption needs to be subsequently evaluated for new methods such as SRFA.

6. Acknowledgments

The authors declare that the research was conducted without any commercial or financial

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