表 3A　レシピエントの年齢・性別：死体肝移植

Age	0～9	10～19	20～29	30～39	40～49	50～59	60～69	70～79	Total
Male	7	5	10	22	29	29	17	0	119
Female	12	10	6	20	13	23	16	0	100
Total	19	15	16	42	42	52	33	0	219

表 3B　レシピエントの年齢・性別：生体肝移植

Age	0～9	10～19	20～29	30～39	40～49	50～59	60～69	70～79	Total
Male	898	259	167	229	428	1,034	445	2	3,462
Female	1,264	282	205	244	427	853	503	15	3,793
Total	2,162	541	372	473	855	1,887	948	17	7,255

表 4A　レシピエントの原疾患：死体肝移植，初回移植

	Age of Recipient		Total
	＜18 y.o.	≧18 y.o.	
Cholestatic Diseases	12	36	48
Biliary Atresia	9	11	20
Primary Biliary Cirrhosis	0	13	13
Primary Sclerosing Cholangitis	3	10	13
Alagille Syndrome	0	1	1
Caroli Disease	0	1	1
Hepatocellular Diseases	0	46	46
HCV	0	20	20
HBV	0	11	11
Alcoholic	0	5	5
NASH	0	3	3
AIH	0	2	2
Cryptogenic Cirrhosis	0	5	5
Vascular Diseases	0	2	2
Budd-Chiari	0	2	2
Neoplastic Diseases	1	18	19
Hepatocellular Carcinoma	0	18	18
Hemangioma	1	0	1
Acute Liver Failure	5	37	42
HBV	1	12	13
Drug-induced	0	6	6
Autoimmune Hepatitis	0	3	3
Viral（≠HBV）	1	0	1
Hemochromatosis	1	0	1
Unknown	2	16	18
Metabolic Diseases	2	12	14
Wilson Disease	1	4	5
Citrullinemia	0	4	4
Familial Amyloid Polyneuropathy	0	2	2
Glycogen Storage Disease	0	1	1
OTC Deficiency	1	1	2
Others	0	2	2
Polycystic Liver	0	2	2
Total	20	153	173

表 4B　レシピエントの原疾患：生体肝移植，初回移植

	Age of Recipient		Total
	＜18 y.o.	≧18 y.o.	
Cholestatic Diseases	1,869	1,008	2,877
Biliary Atresia	1,715	182	1,897
Primary Biliary Cirrhosis	0	616	616
Primary Sclerosing Cholangitis	24	166	190
Alagille Syndrome	78	3	81
Byler's Disease	35	2	37
Caroli Disease	6	9	15
Congenital Bile Duct Dilatation	5	7	12
Others	6	23	29
Hepatocellular Diseases	43	1,323	1,366
HCV	1	598	599
HBV	0	269	269
Alcoholic	0	194	194
Autoimmune Hepatitis	3	80	83
NASH	2	57	59
Cryptogenic Cirrhosis	29	119	148
Others	8	6	14
Vascular Diseases	37	38	75
Budd-Chiari Syndrome	7	34	41
Congenital Absence of Portal Vein	25	2	27
Others	5	2	7
Neoplastic Diseases	88	1,462	1,550
Hepatocellular Carcinoma	8	1,423	1,431
HCV	0	859	859
HBV	0	412	412
Alcoholic	0	62	62
Primary Biliary Cirrhosis	0	18	18
NASH	0	12	12
Others	8	60	68
Hepatoblastoma	70	1	71
Liver Metastatis	1	18	19
Hemangioma	4	6	10
Others	5	14	19
Acute Liver Failure	222	479	701
HBV	7	143	150
Drug-induced	2	34	36
Autoimmune Hepatitis	2	30	32
Viral（≠HBV）	13	15	28
Unknown	190	253	443
Others	8	4	12
Metabolic Diseases	233	204	437
Wilson Disease	60	60	120
Familial Amyloid Polyneuropathy	0	79	79
OTC Deficiency	50	2	52
Citrullinemia	11	41	52
Glycogen Storage Disease	20	9	29
Methylmalonic Acidemia	26	0	26
Primary Hyperoxaluria	14	6	20
CPS deficiency	14	0	14
Tyrosinemia	13	0	13
Others	25	7	32
Others	23	37	60
Total	2,515	4,551	7,066

表 4C　レシピエントの原疾患：肝細胞性疾患の内訳（生体肝移植，1989～2013 年）

Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
HCV	0	0	0	0	0	0	0	0	1	0	9	13	21	38	33	53	71	53	38	37	46	49	47	46	44	599
HBV	0	0	0	0	0	0	0	2	2	2	13	12	18	21	17	30	31	27	18	17	13	13	8	15	10	269
Alcohol	0	0	0	0	0	0	0	0	1	1	3	3	4	1	8	8	16	15	15	18	18	23	13	22	25	194
AIH	0	0	0	0	0	0	0	0	0	0	3	2	6	7	3	7	7	4	11	4	7	6	6	3	7	83
NASH	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	2	2	2	7	4	10	10	8	11	59
Cryptogenic	0	0	1	1	1	0	3	1	5	6	9	7	7	3	4	13	10	16	14	11	6	6	12	5	7	148
Others	0	0	0	0	0	1	0	0	1	2	0	2	1	0	0	3	0	0	1	0	1	0	0	1	1	14
Total	0	0	1	1	1	1	3	3	10	11	37	40	58	70	65	115	137	117	99	94	95	107	96	100	105	1,366

表 5A　移植肝：死体肝移植

	Age of Recipient		Total
	＜18 y.o.	≧18 y.o.	
Monosegment	2	0	2
Lateral Segment	10	0	10
Left Lobe	3	0	3
Left Lobe + Caudate Lobe	1	3	4
Right Lobe	1	10	11
Right Trisegment	1	9	10
Whole Liver	12	167	179
	30	189	219

表 5B　移植肝：生体肝移植

	Age of Recipient		Total
	＜18 y.o.	≧18 y.o.	
Monosegment	121	0	121
Lateral Segment	1,809	5	1,814
Posterior Segment	4	102	106
Left Lobe	491	925	1,416
Left Lobe + Caudate Lobe	100	1,080	1,180
Right Lobe	84	2,509	2,593
Whole Liver (Domino)	0	23	23
Dual Graft (Left + Right Lobes)	0	2	2
	2,609	4,646	7,255

表 6A　ドナーの年齢・性別：死体肝移植

Age	0～9	10～19	20～29	30～39	40～49	50～59	60～69	70～79	Unknown	Total
Male	1	6	15	22	34	23	10	2	9	122
Female	1	4	11	16	20	23	17	2	1	95
Unknown	1	0	0	0	0	0	0	0	1	2
Total	3	10	26	38	54	46	27	4	11	219

表 6B　ドナーの年齢・性別：生体肝移植

Age	0～9	10～19	20～29	30～39	40～49	50～59	60～69	70～79	Total
Male	0	46	1,139	1,323	732	496	191	1	3,928
Female	0	20	699	1,196	749	534	130	1	3,329
Total	0	66	1,838	2,519	1,481	1,030	321	2	7,257

のレシピエント 6 人の内訳は，1 人が小児（左葉を移植された），5 人が大人（右葉 3，左葉 2）であった。ドミノ移植の年次数の変遷を**表 8** に示す。なお，ドミノ移植の二次ドナーは，すべて家族性アミロイドポリニューロパチー（FAP）であった。

生体肝移植におけるレシピエントとドナーの ABO 血液型適合度を**表 9** に示す。「dual graft」のうち 1 例は，ABO 一致のドナーと ABO 適合のドナーの 2 人から移植されていたので，集計から除いた。このため，**表 9** の合計は生体肝移植の総数 7,255 より 1 少ない 7,254 になっている。なお，「dual graft」の他の 1 例は，ABO 適合の 2 人のドナーから移植されていたので，

表7　生体ドナーの続柄

	Age of Recipient		Total
	＜18 y.o.	≧18 y.o.	
Mother	1,371	251	1,622
Father	1,106	229	1,335
Son	0	1,405	1,405
Daughter	0	609	609
Brother	12	475	487
Sister	4	355	359
Nephew	0	62	62
Grandmother	51	2	53
Aunt	24	11	35
Cousin	2 (Male 2)	28 (Male 23, Female 5)	30
Uncle	12	11	23
Grandfather	21	0	21
Niece	0	11	11
Father's cousin	2 (Male 1, Female 1)	0	2
Grandson	0	1	1
Cousin's son	0	1	1
Wife	0	597	597
Husband	0	493	493
Brother-in-law	0	23	23
Son-in-law	0	18	18
Sister-in-law	0	8	8
Father-in-law	2	3	5
Nephew-in-law	0	4	4
Mother-in-law	0	3	3
Daughter-in-law	0	4	4
Grandfather-in-law	1	0	1
Uncle-in-law	0	1	1
Common-law husband	0	1	1
Common-law wife	0	1	1
Friend	0	1 (Female)	1
Domino	1 (Male)	40 (Male 20, Female 20)	41
	2,609	4,648	7,257

表8　ドミノ肝移植数の推移（1989～2013年）

Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
≧18 years	0	0	0	0	0	0	0	0	0	0	3	5	4	1	7	4	2	1	1	4	4	2	0	0	2	40
＜18 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
Total	0	0	0	0	0	0	0	0	0	0	3	5	4	1	8	4	2	1	1	4	4	2	0	0	2	41

表9　生体肝移植におけるレシピエントとドナーの ABO 血液型適合度

	Age of Recipient		Total
	＜18 y.o.	≧18 y.o.	
Identical	1,717	3,148	4,865
Compatible	535	1,040	1,575
Incompatible	357	457	814
	2,609	4,645	7,254

表10　生体肝移植における ABO 不適合移植数の推移（1989～2013 年）

Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
≧18 years	0	0	1	0	0	1	1	0	5	3	5	5	17	13	22	33	47	31	47	42	39	35	44	33	33	457
＜18 years	0	0	4	4	11	12	9	11	14	9	13	8	13	21	13	20	24	18	21	18	27	23	24	16	24	357
Total	0	0	5	4	11	13	10	11	19	12	18	13	30	34	35	53	71	49	68	60	66	58	68	49	57	814

表11　移植後の累積生存率と累積生着率

	Patient Survival (%)							Graft Survival (%)						
	n	1 year	3 year	5 year	10 year	15 year	20 year	n	1 year	3 year	5 year	10 year	15 year	20 year
Cadaveric Donor	219	84.7	81.4	80.2	72.8			219	83.8	80.5	79.3	71.9		
Heart-beating	216	85.9	82.6	81.3	73.8			216	85.0	81.6	80.4	73.0		
Non-heart-beating	3	0.0						3	0.0					
Living Donor	7,255	83.8	79.6	77.1	71.9	67.8	66.1	7,255	83.1	78.6	76.0	69.9	65.0	62.1

表12　脳死肝移植におけるレシピエントの累積生存率

		n	Cumulative Survival (%)			
			1 year	3 year	5 year	10 year
Primary or Retransplant	Primary	170	90.6	88.1	86.5	82.0
	Re- and Re-re-transplantation	46	68.9	62.8	62.8	41.8
Recipient Age	＜18	28	85.7	85.7	85.7	85.7
	18≦	188	86.0	82.1	80.6	69.3
Indication (Primary)	Cholestatic Disease	46	92.9	92.9	92.9	83.6
	Biliary Atresia	18	94.1	94.1	94.1	94.1
	Primary Biliary Cirrhosis	13	91.7	91.7	91.7	45.8
	Primary Sclerosing Cholangitis	13	90.0	90.0	90.0	90.0
	Hepatocellular Disease	46	86.6	80.9	80.9	80.9
	HCV	20	84.7	78.2	78.2	
	HBV	11	81.8	81.8	81.8	
	Neoplastic Disease	18	81.2	81.2	81.2	
	HCC	17	86.7	86.7	86.7	
	Acute Liver Failure	42	92.0	88.4	88.4	88.4
	HBV	13	84.6	84.6	84.6	84.6
	Unknown	18	100.0	90.0	90.0	
	Metabolic Disease	14	100.0	100.0	83.3	83.3

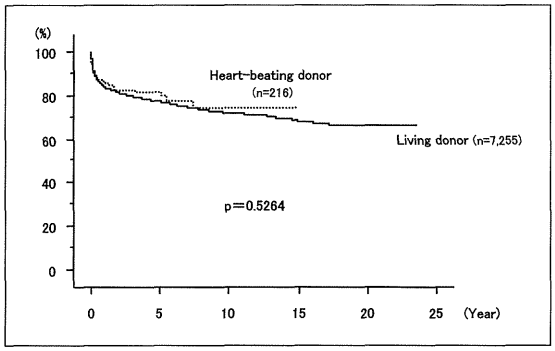

図1　生体肝移植と脳死肝移植における累積生存率

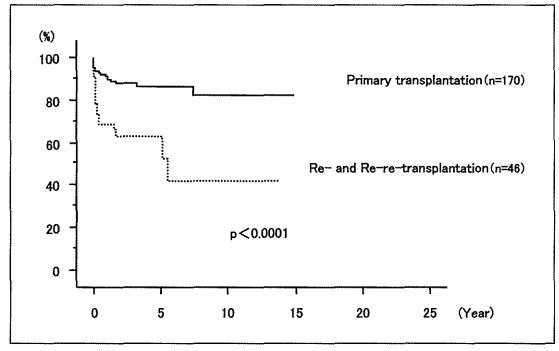

図2　脳死肝移植における初回移植と再移植の累積生存率

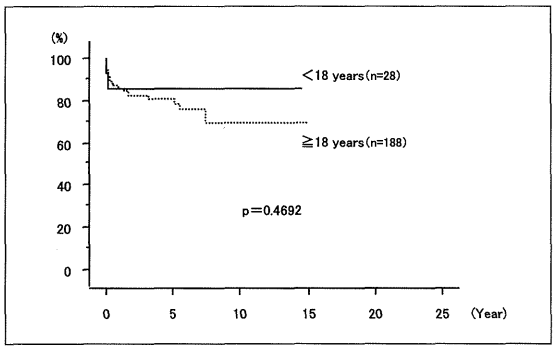

図3　脳死肝移植における年齢別の累積生存率

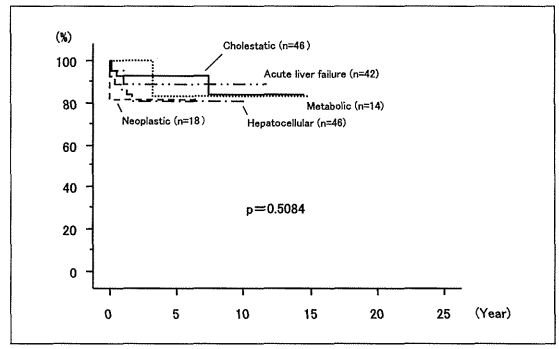

図4　脳死肝移植における疾患別の累積生存率

「適合」に含めた。ABO不適合の頻度は，大人9.8%，小児13.7%であった。**表10**に，大人・小児別のABO不適合移植数の年次推移を示す。

移植後の累積生存率，生着率（**表11**）とも，生体肝移植と死体肝移植の間に差がなかった。生体肝移植と脳死肝移植との比較においても差はなかった（**図1**）。以下，疾患（群）別の生存率データについては，10移植以上の疾患（群）については必ず記載し，それ以下の場合は必要に応じて記載することとする。

死体肝移植のうち，脳死肝移植の予後は，以下の通りであった（**表12**）。

1）再移植/再々移植は，初回移植に比し予後が有意に悪かった（$p<0.0001$，**図2**）。

2）小児と大人では，小児の方がよい傾向であったが，有意差はなかった（**図3**）。

3）脳死肝移植の疾患群別の予後には有意差を認めなかった（**図4**）

生体肝移植の予後は，以下の通りであった（**表13-1**，**表13-2**）。

1）再移植/再々移植は，初回移植に比し予後が有意に悪かった（$p<0.0001$，**図5**）。

2）レシピエントの性別では女性の予後が有意によかった（$p=0.0047$，**図6**）。

3）小児と大人では，後者で有意に予後が悪かった（$p<0.0001$，**図7A**）。10歳ごとに区切った年齢群で比較した場合も同様に有意差を認めた（$p<0.0001$，**図7B**）。なお，0～9歳を0歳と1～9歳の2群に分けて比較したが，両群間に差を認めなかった。

4）原疾患別の予後を検討した。まず，6つの疾患群について比較すると，有意な差が認められた（$p<0.0001$，**図8A**）。個々の疾患群の検討では，胆汁うっ滞性疾患の中で疾患の間で予後に有意差を認めた（$p<0.0001$，**図8B**）。肝細胞性疾患では，疾患間に生存率の有意な差を認めた（$p=0.0226$，**図8C**）。HCVとHBVを比較しすると，後者の予後が有意によかった（$p=0.0010$）。腫瘍性疾患では，疾患群内で予後に有意差を認めた（$p=0.0010$，**図8D**）。腫瘍性疾患のうち，胆管細胞癌（n=9）の予後は1年66.7%，3年・5

表 13-1　生体肝移植におけるレシピエントの累積生存率-1

		n	Cumulative Survival (%)					
			1 year	3 year	5 year	10 year	15 year	20 year
Primary or Retransplant	Primary	7,066	84.5	80.3	77.7	72.5	68.3	66.6
	Re- and Re-re-transplantation	189	58.6	55.5	54.0	51.0	51.0	
Recipient Gender	Male	3,462	83.9	78.4	75.4	69.7	66.3	63.9
	Female	3,793	83.8	80.7	78.7	74.0	69.4	68.1
Recipient Age	＜18	2,609	89.0	87.4	86.2	83.5	81.2	80.5
	18≦	4,646	80.8	75.2	72.0	64.9	56.4	31.9
	～9	2,162	90.0	88.4	87.6	85.1	83.8	83.5
	10～19	541	84.7	83.5	80.6	76.5	68.7	66.1
	20～29	372	80.8	76.5	74.4	68.2	59.7	
	30～39	473	78.3	72.3	69.2	65.3	57.1	57.1
	40～49	855	80.2	75.7	73.9	65.8	56.7	
	50～59	1,887	81.4	75.1	71.0	64.5	59.4	
	60～69	948	80.7	74.5	71.1	60.7	41.8	
	70～79	17	81.2	74.5	59.6	59.6		
Indication (Primary)	Cholestatic Disease	2,877	88.0	86.3	85.0	81.0	77.3	76.2
	Biliary Atresia	1,897	91.2	90.1	89.2	86.4	84.6	84.3
	Primary Biliary Cirrhosis	616	81.4	78.9	77.5	72.0	61.2	
	Primary Sclerosing Cholangitis	190	78.5	73.7	69.4	54.9	39.8	
	Alagille Syndrome	81	92.6	91.3	91.3	86.5	86.5	86.5
	Byler's Disease	37	91.8	89.0	86.0	82.4	56.6	56.6
	Caroli Disease	15	80.0	80.0	70.0	70.0	70.0	
	Congenital Bile Duct Dilatation	12	58.3	58.3	58.3	58.3		
	Hepatocellular Disease	1,366	80.4	75.8	73.2	64.3	59.8	59.8
	HCV	599	78.2	72.0	68.3	58.4		
	HBV	269	84.5	80.3	78.9	72.8	72.8	
	Alcoholic	194	83.5	80.8	78.8	58.4		
	Autoimmune Hepatitis	83	77.5	76.1	76.1	72.1		
	NASH	59	81.1	81.1	75.7	56.8		
	Cryptogenic Cirrhosis	148	79.3	75.3	72.6	65.3	59.8	59.8
	Vascular Disease	75	93.0	88.3	86.5	86.5	86.5	86.5
	Budd-Chiari	41	89.4	83.9	80.8	80.8	80.8	80.8
	Congenital Absence of Portal Vein	27	96.3	91.7	91.7	91.7	91.7	
	Neoplastic Disease	1,550	84.2	74.7	69.4	61.0	50.7	50.7
	HCC	1,431	84.4	74.6	69.4	61.2	46.7	46.7
	Hepatoblastoma	71	86.7	83.1	75.6	75.6	75.6	
	Liver Metastasis	19	73.7	68.0	56.7	12.8		
	Hemangioma	10	90.0	90.0	77.1	77.1		
	Acute Liver Failure	701	75.0	71.8	70.1	67.7	66.1	64.5
	HBV	150	77.5	74.7	74.0	73.0	73.0	
	Drug-induced	36	77.7	77.7	74.4	74.4	74.4	74.4
	Autoimmune Hepatitis	32	71.0	71.0	71.0	71.0		
	Viral (≠HBV)	28	63.0	63.0	63.0	63.0		
	Unknown	443	74.5	70.4	68.4	68.4	62.4	62.4
	Metabolic Disease	437	89.9	86.8	84.9	82.9	74.9	62.2
	Wilson Disease	120	90.6	89.6	87.8	85.6	75.1	75.1
	Familial Amyloid Polyneuropathy	79	96.2	89.3	84.1	78.5	67.0	53.6
	OTC Deficiency	52	96.1	96.1	96.1	96.1	96.1	
	Citrullinemia	52	96.1	96.1	96.1	96.1	88.1	
	Glycogen Storage Diseases	29	85.7	68.8	68.8	68.8	51.6	
	Methylmalonic Acidemia	26	84.6	84.6	84.6	84.6		
	Primary Hyperoxaluria	20	62.6	62.6	62.6	62.6	62.6	
	CPS Deficiency	14	92.9	92.9	92.9			
	Tyrosinemia	13	92.3	76.9	76.9	76.9	76.9	

表 13-2　生体肝移植におけるレシピエントの累積生存率-2

		n	Cumulative Survival (%)					
			1 year	3 year	5 year	10 year	15 year	20 year
Donor Age	10～19	66	84.6	81.4	77.8	74.1	74.1	74.1
	20～29	1,838	86.1	83.0	80.7	76.7	72.9	72.1
	30～39	2,519	87.0	83.2	81.0	76.0	73.1	72.4
	40～49	1,481	82.5	78.2	76.0	70.2	64.9	62.9
	50～59	1,030	78.3	71.9	68.7	62.1	52.3	38.8
	60～	323	68.6	62.9	57.8	50.0	47.8	
ABO Compatibility	Identical	4,865	84.8	80.6	78.1	73.0	68.7	66.3
	Compatible	1,575	84.5	80.3	77.5	72.1	69.0	69.0
	Incompatible	814	76.4	72.3	70.3	65.2	60.3	60.3

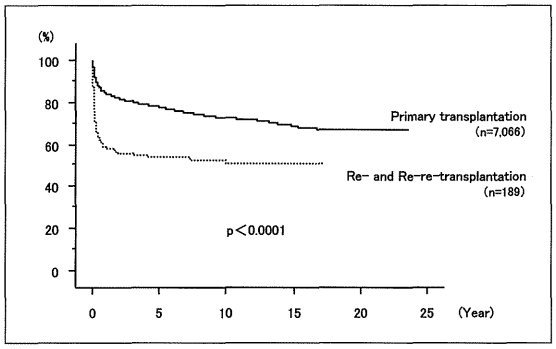

図 5　生体肝移植における初回移植と再移植の累積生存率

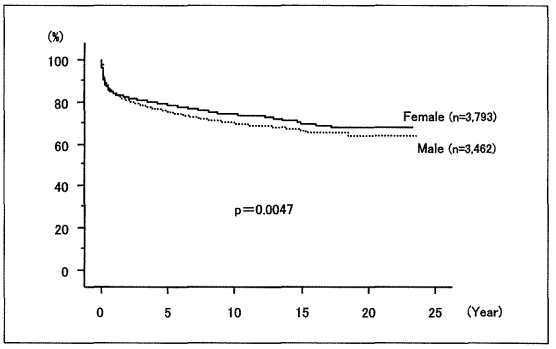

図 6　生体肝移植における性別の累積生存率

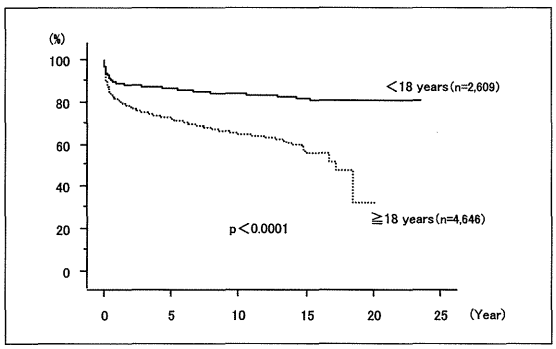

図 7A　生体肝移植における年齢別の累積生存率

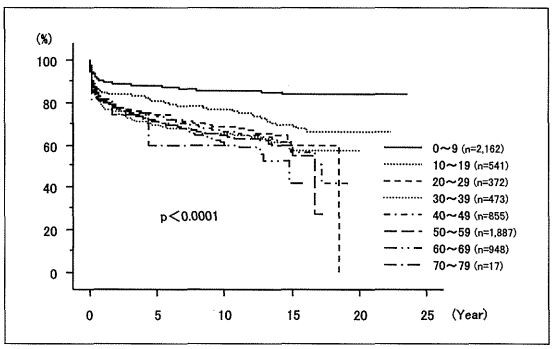

図 7B　生体肝移植における年齢別の累積生存率（10 歳ごとの年齢群比較）

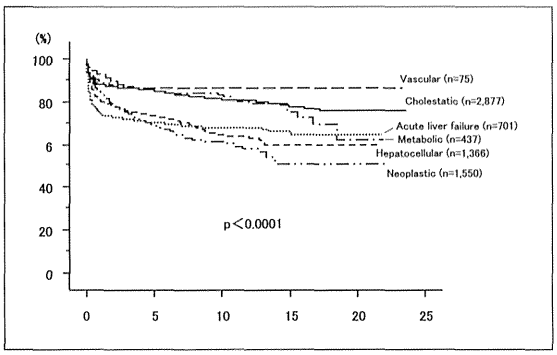

図 8A　生体肝移植における疾患群別の累積生存率

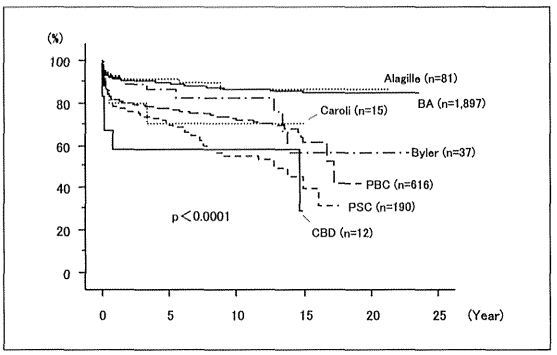

図 8B　生体肝移植における胆汁うっ滞性疾患の累積生存率

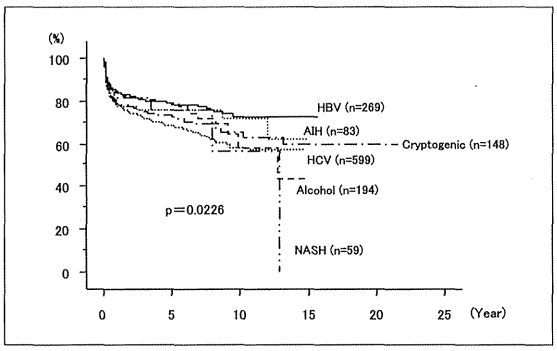

図 8C　生体肝移植における肝細胞性疾患の累積生存率

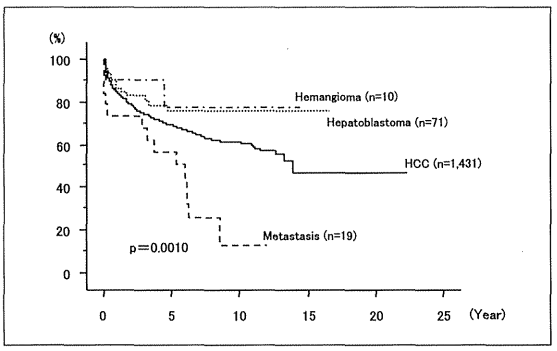

図 8D　生体肝移植における腫瘍性疾患の累積生存率

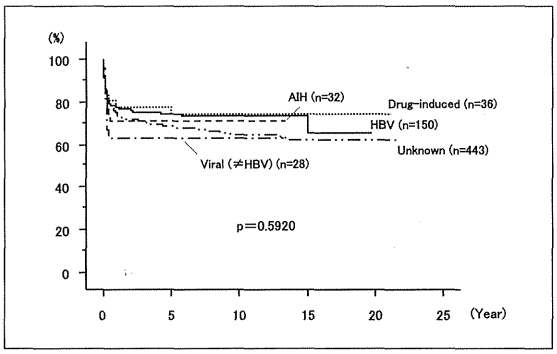

図 8E　生体肝移植における急性肝不全の累積生存率

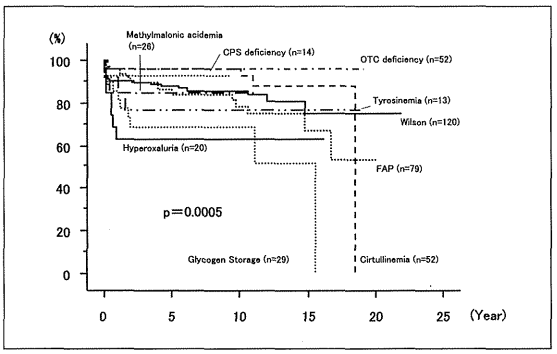

図 8F　生体肝移植における代謝性疾患の累積生存率

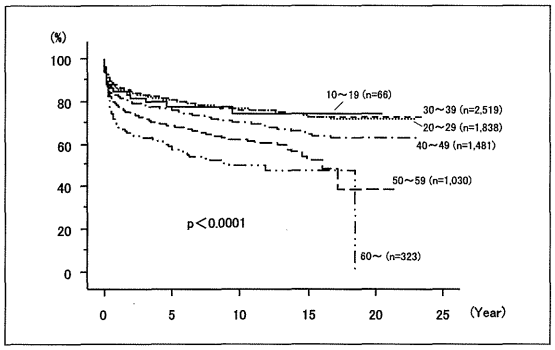

図 9　生体肝移植におけるドナー年齢別の累積生存率

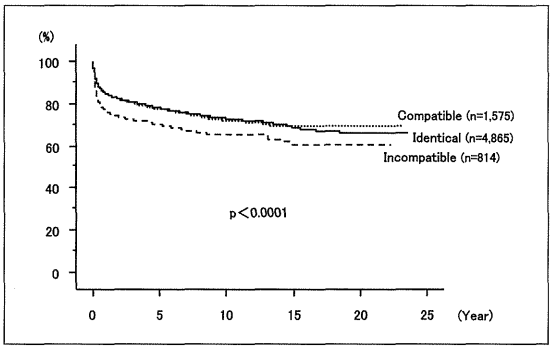

図 10A　生体肝移植における ABO 血液型適合度別の累積生存率

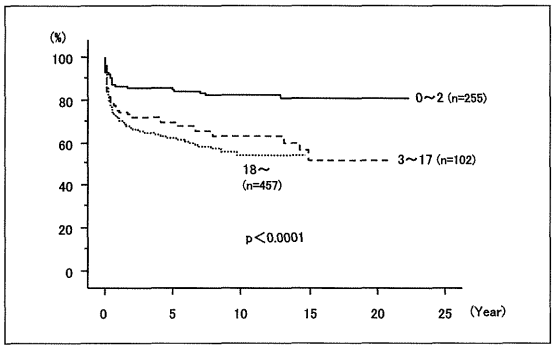

図 10B　生体肝移植の ABO 血液型不適合群におけるレシピエント年齢別の累積生存率

年・10 年・15 年 55.6%，epithelioid hemangioendothelioma（n=7）は 1 年 71.4%，3 年・5 年 57.1% であった。急性肝不全の中では，疾患間に生存率の有意な差を認めなかった（**図 8E**）。代謝性疾患では，疾患の間に有意差を認めた（p=0.0005，**図 8F**）。なお，プロピオン酸血症（n=9）は 1 年・3 年 100%，5 年・10 年 83.3% であった。「その他」の疾患群中では，先天性肝線維症は 1 年・3 年・5 年・10 年・15 年・20 年とも 87.5%，多発性肝嚢胞症は 1 年 82.4%，3 年 75.5%，5 年 67.1%，10 年 47.9% であった。症例数は少ないが，特発性門脈圧亢進症（n=8）は 1 年・3 年・5 年・10 年 37.5%，GVHD（n=4）は 1 年 75.0%，3 年 50.0%，5 年 25.0% であった。

なお，再移植の適応疾患は，以前は「移植肝不全」とされることが多かったが，近年病態の理解が進むとともに，より特異的な病名が付けられるようになってきている。本研究会の登録においても再移植の適応疾患の整理を進めており，次回の報告では，再移植後の予後について，より詳細な報告を行うことができると考えている。

5）レシピエントの ABO 血液型は，予後に影響を与えなかった（data not shown）。

6）ドナーの性別は，レシピエントの予後に影響を与えなかった（data not shown）。

7）ドナーの年齢を，10 歳ごとに区切った年齢群で比較すると，有意差を認めた（p<0.0001，**図 9**）。HCV の症例に限って比較した場合も同様の結果であり，60 歳以上のドナーから移植された HCV 症例（n=38）の生存率は特に悪く 1 年 53.1%，3 年 47.2%，5 年 38.6% であった（最高齢は 66 歳）。

8）ドナーの ABO 血液型は，予後に影響を与えなかった（data not shown）。

9）レシピエントとドナーの ABO 血液型適合度別の予後をみると，血液型不適合群は，一致群，適合群に比し有意に予後が悪かった（p<0.0001，**図 10A**）。

不適合群においてレシピエントの年齢別に予後をみると，今回も 0～2 歳と 3 歳の間に差を認めた。そこで，0～2 歳，3～17 歳，18 歳以上，の 3 群に分けて比較すると，0～2 歳（つまり 36 カ月未満）は 1 年 86.4%，3 年 85.5%，5 年 84.8%，10 年 82.5%，15 年・20 年 80.6% と良好であったのに対し，3～17 歳は 1 年 75.2%，3 年 72.0%，5 年 69.1%，10 年 63.3%，15 年・20 年 51.5%，18 歳以上は 1 年 70.9%，3 年 64.8%，5 年 62.3%，10 年 54.2% と有意に悪かった（p<0.0001，**図 10B**）。

ABO 不適合移植に対しては，2000 年半ばよりいわゆる門注療法が，また，2004 年半ばより rituximab の投与が行われ，予後が改善してきている。そこで，前期（2000 年以前），中期（2001 年～2004 年），後期

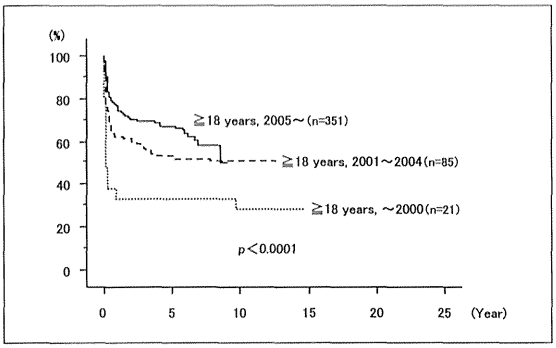

図 10C　生体肝移植の ABO 血液型不適合群におけるレシピエント年齢別・時期別の累積生存率（18 歳以上）

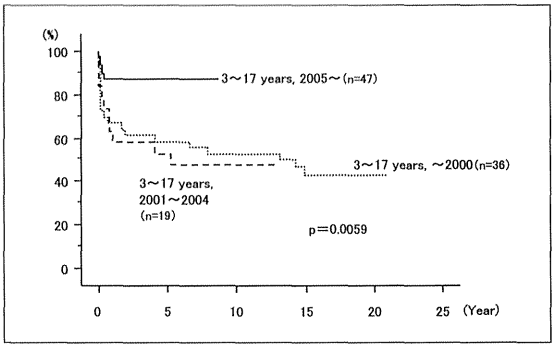

図 10D　生体肝移植の ABO 血液型不適合群におけるレシピエント年齢別・時期別の累積生存率（3～17 歳）

（2005 年以降）の 3 期に分けて比較した。18 歳以上では，前　期（1 年・3 年・5 年 33.3%，10 年 28.6%）→中期（1 年 62.4%，3 年 56.5%，5 年 52.9%，10 年 50.6%）→後 期（1 年 75.4%，3 年 69.0%，5 年 66.7%）と，次第に予後が改善していた（p＜0.0001，**図 10C**）。3～17 歳では，後期（1 年・3 年・5 年 87.0%）に著明な予後の改善がみられた（p=0.0059，**図 10D**）。0～2 歳では有意差はなかった。

Ⅳ. おわりに

肝移植研究会が 1992 年以来行ってきた症例登録の第 14 回の集計結果を誌上で公にすることができた。先に挙げたすべての移植施設の皆様のご協力の賜であり，稿を終えるにあたり改めて感謝の意を表したい。

文責：日本肝移植研究会
猪股裕紀洋，梅下浩司，上本伸二

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RETROSPECTIVE STUDY

Clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors

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Abstract

AIM: To present our experiences in studying the clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs).

METHODS: The subjects included 9 patients with NF-pNETs who underwent pancreatectomy between April 1996 and September 2012. The surgical procedure, histopathological findings, and prognosis were assessed.

RESULTS: All tumors were incidentally detected by computed tomography. The median diameter was 10 mm (5-32 mm). One patient was diagnosed with von Hippel-Lindau disease, and the others were sporadic cases. For the histopathological findings, 7 patients were G1; 1 patient was G2; and 1 patient, whose tumor was 22 mm, had neuroendocrine carcinoma (NEC). One patient who had a tumor that was 32 mm had direct invasion to a regional lymph node and 1 patient with NEC, had regional lymph node metastases. Six of the 7 patients with sporadic NF-pNETs, excluding the patient with NEC, had tumors that were smaller than 10 mm. Tumors smaller than 10 mm showed no malignancy and lacked lymph node metastasis.

CONCLUSION: Sporadic NF-pNETs smaller than 10 mm tend to have less malignant potential. These findings suggest that lymphadenectomy may be omitted for small NF-pNETs after further investigation.

Key words: Pancreatic neuroendocrine tumor; Pancreatic neuroendocrine carcinoma; Nonfunctioning; Lymphadenectomy; Treatment

Core tip: We present our experience in studying the clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors (NE-pNETs). In the present study, six of the 7 patients with sporadic NF-pNETs, excluding the patient with NEC, had small tumors that were less than 10 mm. These small tumors showed no sign of malignancy or lymph node metastasis. Additionally, these cases did not have recurrence, including lymph node and distant metastasis, for more than 10 years after surgery. These findings suggest that small NF-pNETs tend to have less malignant potential and no lymph nodes metastasis. Lymphadenectomy may be omitted in the future for small NF-pNETs after further investigation.

Furukori M, Imai K, Karasaki H, Watanabe K, Oikawa K, Miyokawa N, Taniguchi M, Furukawa H. Clinicopathological

features of small nonfunctioning pancreatic neuroendocrine tumors. *World J Gastroenterol* 2014; 20(47): 17949-17954 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i47/17949.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i47.17949

INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are relatively rare, accounting for 1%-2% of all pancreatic neoplasms[1]. Although pNETs progress slowly and have better a prognosis than pancreatic cancer, pNETs have malignant potential, including features of local invasion, lymph node metastasis, and distant metastasis. The appropriate diagnosis and treatment of pNETs are crucial. These tumors are classified into functioning pNETs (F-pNETs), which present with specific symptoms due to excess hormones, and nonfunctioning pNETs (NF-pNETs), which do not present with these symptoms. Because NF-pNETs do not present with specific symptoms, they are often detected as large tumors in the advanced stage, with distant metastasis or invasion to adjacent organs. However, improvements in diagnostic imaging over the last few decades have led to the incidental detection of small NF-pNETs *via* diagnostic imaging for the work-up of other conditions. The incidence of malignancy reportedly increases with larger NF-pNETs[2,3]. However, even small NF-pNETs have malignant potential and may spread to lymph nodes or metastasize to distant sites. Therefore, once NF-pNETs are diagnosed, all cases are considered for surgical resection[4]. The significance of lymph node metastasis in the NF-pNETs has been reported[5-9]; the prognosis is poor with a 5-year survival of 49.4%, even after resection, in cases with lymph node metastasis[7]. Therefore, lymphadenectomy, in addition to tumor resection, is recommended when the tumor is malignant or when lymph node metastasis is suspected. However, there are no standard criteria for lymphadenectomy when small, asymptomatic, and incidentally detected NF-pNETs are identified. The inclusion of lymphadenectomy during surgery for NF-pNETs remains controversial.

In the present study, we report 9 cases of NE-pNETs treated at our hospital over the last 16 years.

MATERIALS AND METHODS

Between 1996 and 2012, 26 patients with pNETs underwent pancreatectomy at Asahikawa Medical University Hospital, of whom 9 patients were diagnosed with NF-pNETs and were further investigated. The diagnosis of pNET was established by histopathological examination and immunohistochemical staining of surgical specimens with chromogranin A, synaptophysin, and neuron-specific enolase stain. Tumors were classified as nonfunctioning regardless of the plasma hormone levels or immune activity of the tissue if the patient lacked the clinical symptoms that are typically caused by excess hormones. The patients' medical records were retrospectively reviewed. All patients were pathologically classified according to the criteria established by the WHO 2010 classification of endocrine tumors[4]. An immunohistochemical staining assay for Ki67 was performed for all patients. The Ki67 proliferative index is expressed as a percentage based on the count of Ki67-positive cells in a set of 2000 tumor cells in areas with the highest immunostaining, which was evaluated with the MIBI antibody, and the cases were classified into the following 3 categories: G1 (mitoses/10 HPFs < 2 and/or Ki67 index < 3), G2 ($2 \leqslant$ mitoses/10 HPFs $\leqslant 20$ and/or $3 \leqslant$ Ki67 index $\leqslant 20$), and neuroendocrine carcinoma (NEC) (mitoses/10 HPFs > 20 and/or Ki67 index > 20). The tumor size was defined by the largest diameter of the tumor. A TNM stage group was assigned to each case based on the European Neuroendocrine Tumor Society (ENETS) staging classification for pNETs[10]. The postoperative follow-up included clinical examination, the blood neuron specific γ-enolase (NSE) level, and contrast-enhanced computed tomography (CT) scanning. CT scans were performed every 6 to 12 mo in the first year, then annually thereafter.

RESULTS

In this study, the tumors identified as NF-pNETs accounted for 2.8% of all pancreatic neoplasms (9/220) and for 35% of pNETs (9/26). Table 1 summarizes the clinical features, surgical procedure, histopathological findings, prognosis, WHO classification, and ENETS TNM classification of the 9 patients diagnosed with NF-pNETs. These patients included 3 men and 6 women with a mean age of 67 years (range, 47-75 years) at the time of surgery. One patient with von Hippel-Lindau disease had previously undergone enucleation of the pNETs; the others were sporadic cases. All patients with NF-pNETs were asymptomatic, and none had evidence of distant metastasis. In all cases, the pancreatic tumors were incidentally detected by radiological investigation during evaluations for unrelated conditions. None of the patients had a preoperatively elevated blood level of NSE. Three patients underwent endoscopic ultrasonography-fine needle aspiration (EUS-FNA) and were preoperatively diagnosed with pNETs (No. 2, 6, and 8). All patients underwent surgical resection of the pancreas: 3 patients underwent distal pancreatectomy (DP), 2 patients underwent pylorus-preserving pancreatoduodenectomy (PPPD), 2 patients underwent subtotal stomach-preserving pancreatoduodenectomy (SSPPD), and 2 patients underwent partial resection of the pancreas. R0 resection was performed in all patients, except in 1 patient who underwent partial resection with positive surgical margins (No. 5). Regional lymphadenectomy was performed in 5 of the 9 patients (No. 2, 3, 6, 7, and 8). The median tumor diameter was 10 mm (range, 5-32 mm). All patients, except for the patient with von Hippel-Lindau disease (4 tumors), had a single tumor. Six patients had tumors located in the head

Table 1 Clinical and pathological status of 9 patients with nonfunctioning pancreatic neuroendcrine tumors

No	Age (yr)	Sex	Size (mm)	Location	Number of tumor	EUS-FNA	Preoperative diagnosis	Surgical procedure	Lymphadenectomy	Metastases		Motoses	Ki67/ MiB-1 (%)	WHO classification 2010	TNM classification (ENET)	Prognosis (mo)
										Lymph node	Distant					
1	58	F	32	Ph	1	No	Pancreatic tumor	DP	No	Direct Invasion	No	0	0.2	NET G1	T2N1M0	59 alive
2	73	M	22	Ph	1	No	NET	PPPD	Regional	No	No	1	5.8	NET G2	T2NOMO	39 alive
3	67	F	22	Pb	1	Done	NET G1	DP	Regional	Positive	No	20	20	NEC	T2N1M0	14 alive
4	74	F	10	Pb	1	No	Islet cell tumor	DP	No	No	No	0	1.6	NET G1	T1N0M0	196 alive
5	61	M	10	Pb	1	No	Islet cell tumor	Partial resection	No	No	No	0	0.1	NET G1	T1N0M0	135 alive
6	51	F	9	Ph	1	Done	NET G1	PPPD	Regional	No	No	0	1	NET G1	T1N0M0	64 alive
7	47	F	6 2.1 1.2 1.2	Ph	4	No	NET	SSPPD	Regional	No	No	0	0.9	NET G1	T1N0M0 Stage I	22 alive
8	75	M	6	Ph	1	Done	NET G1	SSPPD	Regional	No	No	0	< 1	NET G1	T1N0M0	20 alive
9	56	F	5	Ph	1	No	Cartinoid	Partial resection	No	No	No	0	0.4	NET G1	T1N0M0	34 alive

EUS-FNA: Endoscopic ultrasonography-fine needle aspiration; Ph: Head of pancreas; Pb: Body of pancreas; DP: Distal pancreatectomy; PPPD: Pylorus-preserving pancreatoduodenectomy; SSPPD: Subtotal stomach preserving pancreatoduodenectomy.

of the pancreas, while 3 patients had tumors located in the body of the pancreas. Seven patients were classified as G1, and 1 patient with a tumor that was 22 mm in diameter was classified as G2. Although 1 patient, with a tumor that was 22 mm in diameter, was diagnosed as G1 by preoperative EUS-FNA, the final diagnosis was neuroendocrine carcinoma (NEC). None of the patients, except two cases, had no lymph nodes metastasis; one with lymph node metastasis had a tumor that was 32 mm in diameter with direct invasion to the regional lymph nodes, and the other had NEC with regional lymph nodes metastasis. Six of the 7 patients with sporadic NF-pNETs had small tumors that were less than 10 mm in size; one patient with NEC had a larger tumor. Tumors that were less than 10 mm in size showed no malignancy, were well differentiated, and lacked lymph node metastasis. Six patients were classified as Stage I , 1 patient was classified as Stage IIa, and 2 patients were classified as Stage IIIb. With respect to the postoperative complications, three patients had a pancreatic fistula, one patient was classified as Grade B (No. 3), and 2 patients were classified as Grade A (No. 1 and 2) according to the ISGPS criteria. None of the patients in this study had exocrine or endocrine insufficiency. The mean follow-up period was 63 mo (range, 14-196 mo). All of the patients are currently alive without disease recurrence according to radiological imaging.

DISCUSSION

In the present study, we examined the NF-pNETs in 9 patients who underwent pancreatectomy at our institution over the last 16 years. For all of the patients, the tumors were incidentally detected by diagnostic imaging during a work-up for other conditions. Most tumors were small, with a diameter of 5-32 mm (median: 10 mm), and none of the tumors showed evidence of distant metastasis. While the larger tumors tended to be associated with direct invasion of the lymph nodes and lymph node metastases, a high Ki-67 index, and an advanced TNM stage, tumors that were smaller than 10 mm in diameter lacked malignancy and lymph node metastasis.

NF-pNETs are relatively rare, and only 9 patients presented with NF-pNETs at our institution over the last 16 years. In Western nations, pNETs occur at an incidence of 1 per 100000 individuals and represent 1%-2% of all pancreatic neoplasms[1]. Over the last few years, however, this incidence has increased[11,12]. An epidemiological study by NETWork Japan in 2005 estimated that the incidence of pNETs per 100000 individuals is 2.23 patients in Japan. Compared with Western nations, Japan has a 2- to 3-fold higher incidence of pNETs[3]. In total, 30%-50% of all pNETs are nonfunctioning[3,13]; however, because NF-pNETs do not present with characteristic clinical symptoms due

to excess hormones, they often go unnoticed until they are in the advanced stages. Previously, NF-pNETs were often detected as larger tumors that were accompanied by nonspecific pressure symptoms, such as abdominal pain or discomfort; abdominal distension; or a palpable mass in advanced stages with distant metastasis or local invasion. The number of NF-pNETs that have been incidentally detected has increased due to the advances in diagnostic imaging over the last few decades. Compared with other pancreatic tumors, pNETs progress slowly and are associated with a better prognosis. However, they have malignant potential, including local invasion, lymph node metastasis, or distant metastasis. More than half of NF-pNETs are malignant[3,13]. Therefore, most recommendations favor surgical resection for all patients, even for small NF-pNETs[4].

Numerous retrospective studies have previously examined the poor prognosis for NF-pNETs[6,7,14-21]. According to these studies, the predictors of the prognosis for NF-pNETs include the presence of liver metastases and incomplete resection of the tumor.

Several studies have indicated that lymph node metastasis is a poor prognostic factor[5-9]. In addition, Boninsegna *et al*[8] reported that lymph node metastasis is a prognostic factor for the recurrence of malignant pNETs after curative surgery. If malignancy of the tumor or lymph node metastasis is suspected, pancreatic resection with the addition of lymphadenectomy is recommended. It is often difficult to judge preoperatively whether a tumor is benign or malignant, except in patients with distant metastases or local invasion.

The tumor size appears to correlate with the malignant potential of NF-pNETs. Bettini *et al*[2] reported that the chance of malignancy significantly increases when the size of NF-pNETs exceeds 20 mm. A Japanese epidemiological study also found a significant correlation between NF-pNETs that exceed 20 mm in diameter and the presence of distant metastases[3]. Pancreatic resection and prophylactic regional lymphadenectomy are recommended for treating possible malignancy when the tumors exceed 20 mm in diameter[4]. However, several studies have failed to identify a correlation between the tumor size and prognosis[5,13,22,23], and other studies have demonstrated that even tumors smaller than 10 mm can be malignant[24,25]. Therefore, surgical resection is recommended even in small tumors.

Currently, the association between the tumor size and the incidence of lymph node metastasis is controversial. Hashim *et al*[9] reported that there is an increased probability of nodal metastasis when the tumor size is larger than 15 mm. Tsutsumi *et al*[26] reported an increased prevalence of lymph node metastasis in patients with gastrinomas and non-gastrinoma who have tumor sizes of 15 mm or larger. In contrast, Parekh *et al*[27] reported that the tumor size is not associated with lymph node metastasis. A number of studies have reported that the incidences of lymph node metastases for patients with NF-pNETs smaller than 20 mm and 15 mm are 14.4% and 8%, respectively[2,9,26-29]. Over the last few decades, the number of NF-pNETs that are incidentally detected with diagnostic imaging has increased, and compared with symptomatic NF-pNETs, tumors that are incidentally detected have a good prognosis and low risk of malignancy[2,21].

In the present study, one of the 9 patients was diagnosed with von Hippel-Lindau disease, and this patient should be considered separately because the biological properties of sporadic pNETs and hereditary pNETs, such as MEN-1 and von Hippel-Lindau disease, are different with respect to the incidence, number of tumors, and prognosis. One of the 8 patients with sporadic NF-pNETs had NEC with a tumor size of 22 mm. Except for the case with NEC, the direct invasion and metastasis to the lymph nodes was only observed in a relatively large tumor with a diameter size of 32 mm. Tumors smaller than 10 mm in diameter showed no signs of malignancy, were well differentiated, and lacked lymph node metastasis. Additionally, none of the cases had recurrence, including in the lymph nodes or direct metastasis, for more than 10 years after surgery. Lymphadenectomy may be omitted in the future after further investigation of a large number of small NF-pNETs. However, Hashim *et al*[9] reported that even tumors smaller than 10 mm metastasize at a rate of 12%. Additionally, lymphadenectomy is often omitted for small pNETs that are larger than 10 mm in size; the possibility of lymph node metastasis may be underestimated in those cases. Omission of lymphadenectomy needs to be carefully considered with further study. Even when lymphadenectomy is omitted, long-term follow-up is essential because there is a risk of late recurrence. If malignancy is confirmed postoperatively, oncologically appropriate lymphadenectomy must be considered based on the factors that determine the malignant potential, such as the Ki67 index, tumor differentiation status, surgical margin, and vascular invasion such as lymphoductal, neural, and venous[19,20].

In the present study, CgA, PP, and other hormones were not measured; it is important to measure these hormones to identify recurrences during follow-up.

The present study is limited by its small sample size, single institution bias, and retrospective nature. In the future, a larger number of patients at multiple centers should be studied.

In summary, we found that small NF-pNETs tend to have less malignant potential. In the present study, six of 7 cases of sporadic NF-pNETs, except for a case with NEC, were small tumors (smaller than 10 mm diameter). These small tumors showed no evidence of malignancy, were well differentiated, and lacked lymph node metastasis. This finding indicates that lymphadenectomy may be omitted in the future for small NF-pNETs, particularly for those tumors that are incidentally detected after further investigation. When lymphadenectomy is omitted, long-term follow-up is essential, and additional resection should be considered if malignancy is confirmed postoperatively. The tumor size can easily be measured pre-

operatively, and further study is expected to find other factors for predicting the malignant potential of small NF-pNETs.

COMMENTS

Background

Even small NF-Pancreatic neuroendocrine tumors (pNETs) have malignant potential and may spread to lymph nodes or metastasize to distant sites. Therefore, oncologic resection with regional lymphadenectomy is currently recommended. Increasingly smaller NF-pNETs are being identified with improved and more frequent radiological imaging. However, because the clinicopathological features of extremely small NF-pNETs are not yet known, there are no standard criteria for performing a lymphadenectomy when small, asymptomatic NF-pNETs are identified.

Research frontiers

NF-pNETs have malignant potential and may spread to lymph nodes or metastasize to distant sites. However, the clinicopathological features of extremely small NF-pNETs are not yet known. In this study, the authors present their experience with the clinicopathological features of small NF-pNETs (diameters less than 10 mm).

Innovation and breakthroughs

Small NF-pNETs are being identified with improved and more frequent radiological imaging. However, few studies have examined small NF-pNETs with diameters less than 10 mm. In this study, tumors with diameters less than 10 mm showed no evidence of malignancy, were well differentiated, and lacked lymph node metastasis. Additionally, there were no recurrences after the operations, including in the lymph nodes or direct metastasis, for more than 10 years after surgery.

Applications

A previous study reported that the incidence of lymph metastasis is higher for larger tumors. Our findings indicate that lymphadenectomy of small NF-pNETs may be omitted in the future after further investigation of a large number of patients with small NF-pNETs.

Terminology

pNETs are relatively rare disease and progress slowly and are associated with a better prognosis. However, they have malignant potential, including local invasion, lymph node metastasis, or distant metastasis. pNETs are classified into functioning pNETs, which present with specific symptoms due to excess hormones, and nonfunctioning pNETs (NF-pNETs), which do not present with these symptoms.

Peer review

The present manuscript by Furukori *et al* focuses on the need of lymphadenectomy in NF-pNETs < 10 mm and suggests that in these tumors the lymphadenectomy can be omitted. The concept is very challenging.

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Primary colon cancer with a high serum PIVKA-II level

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ABSTRACT

INTRODUCTION: Protein induced by vitamin K absence/antagonist-II (PIVKA-II) is an abnormal protein, and several reports have demonstrated the efficacy of PIVKA-II in the diagnosis of hepatocellular carcinoma (HCC). We report an extremely rare case of adenocarcinoma of the colon with a high serum PIVKA-II level.

PRESENTATION OF CASE: A 95-year-old woman presented with right lower quadrant pain and appetite loss. An abdominal computed tomography scan and ultrasonography showed an ascending colon tumor and multiple metastatic tumors in the liver. The serum level of PIVKA-II was extremely high, 11,900 ng/mL. Colonoscopic examination revealed a tumor accompanied by an ulcer in the ascending colon, which was highly suspicious for malignancy. Multiple biopsies showed well-differentiated adenocarcinoma of the colon, which was evaluated as colon cancer, stage IV. PIVKA-II-productive colon cancer was confirmed. Chemotherapy with TS-1 was administered. The patient died 3 months after initial admission.

DISCUSSION: The expression of PIVKA-II was detected in non-cancer areas, with non-specific expression observed in plasma cells in our case. There might be some possibility that hepatoid differentiation exists in other regions of the colon tumor or in the liver tumor, parenchymal cells or lung metastases, which were composed of PIVKA-II-positive and AFP-negative cells.

CONCLUSION: To the best of our knowledge, high serum levels of PIVKA-II resulting from colon adenocarcinoma have not been reported previously. We report this rare case together with a review of the literature.

1. Introduction

Protein induced by vitamin K absence or antagonist II (PIVKA-II) is a newly recognized tumor marker for hepatocellular carcinoma (HCC) [1]. PIVKA-II has been shown to be a useful and specific marker for the diagnosis of HCC. However, PIVKA-II levels may increase in patients with tumors other than HCC [2]. PIVKA-II-producing gastric cancer and embryonal carcinoma have been reported recently [3]. Here, we report a rare case of advanced colon cancer in a patient with a high serum PIVKA-II level. To the best of our knowledge, a high serum level of PIVKA-II resulting from colon adenocarcinoma has not been reported previously.

2. Presentation of case

A 95-year-old Japanese woman presented with a 3-week history of upper abdominal discomfort, dysphagia, and loss of appetite. Upon physical examination, a smooth mass measuring 20 cm in its largest dimension was palpated in the right upper abdomen. She did not drink and took no medications including warfarin or antibiotics. At admission, laboratory findings revealed leukocytosis of 13,200 /mm^3; 233 U/L aspartate aminotransferase (AST); 32 U/L alanine aminotransferase (ALT); 791 U/L alkaline phosphates (ALP); 440 U/L g-glutamyl transferase (GGT); 6.4 g/dl total protein; and 1.2 mg/dL total bilirubin. The level of C-reactive protein (CRP) was 9.3 mg/mL (normal range, 0.5–0.8 mg/mL). The serum level of carcinoembryonic antigen (CEA) was extremely high, 1270 ng/mL (cutoff, 2.5 ng/mL); the α-fetoprotein (AFP) level was 2 ng/mL (cut-off of 10 ng/mL); and the level of CA 19–9 was extremely high,

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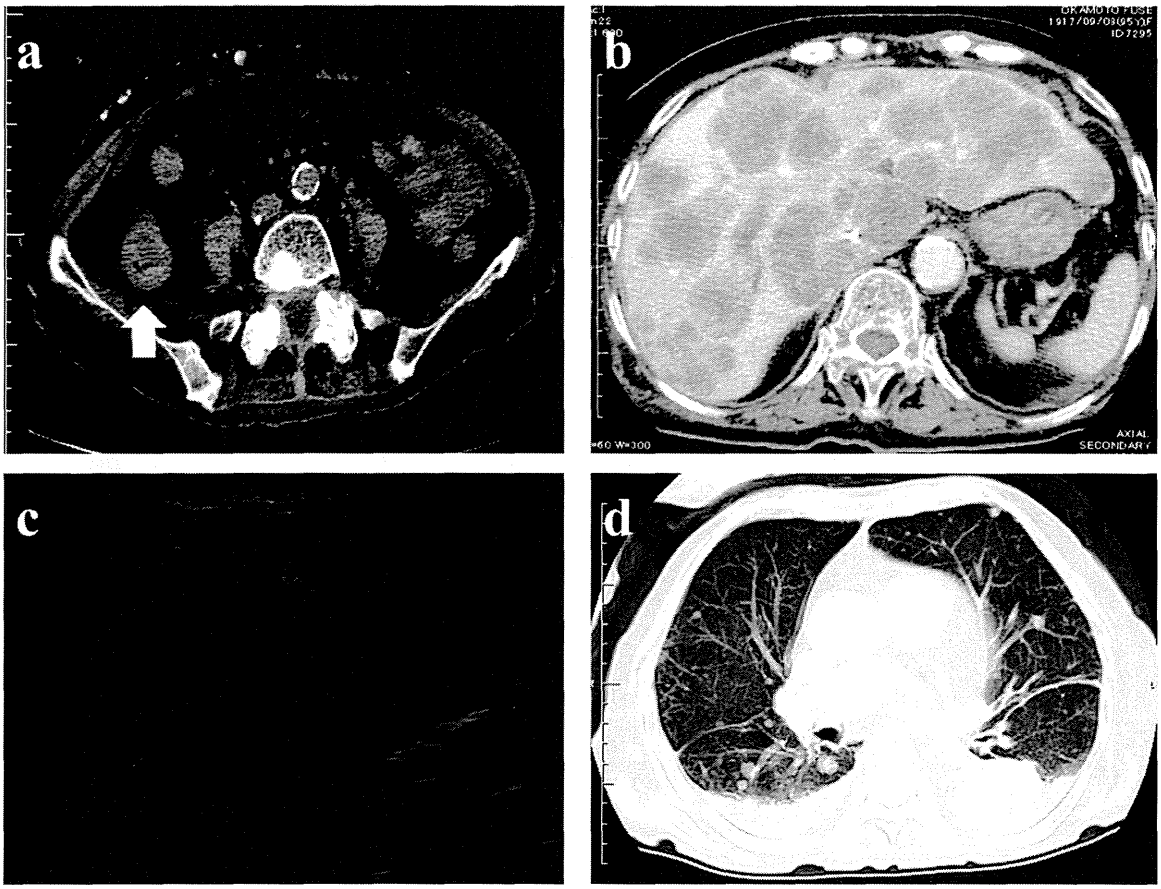

Fig. 1. **a** and **b**: An abdominal computed tomography (CT) study showed a tumor with a diameter of 6 cm occupying the right upper abdominal quadrant together with multiple liver lesions (arrow). **c:** Ultrasonography showed well-defined hypoechoic liver tumors. **d:** Chest CT scan showed multiple lung lesions.

3070 U/mL (cutoff of 37 U/mL). The level of PIVKA-II was also extremely high, 11,900 AU/mL(cutoff, 40 AU/mL). An abdominal computed tomography (CT) scan and ultrasonography showed multiple liver lesions, ascites, and a tumor with a diameter of 6 cm occupying the right upper abdominal quadrant, but no lymph node enlargement was identified (Fig. 1a–c). A chest CT scan showed multiple lung lesions (Fig. 1d). The colonoscopic examination revealed a tumor accompanied by a giant ulcer on the ascending colon (Fig. 2a). Multiple biopsies showed well-differentiated tubular adenocarcinoma of the colon at stage IV (Fig. 2b). Hepatoid-differentiated cells were not detected in the biopsy specimens. Monoclonal antibody raised against PIVKA-II (Eisai, Chiba, Japan) was used for immunohistochemical analysis, but cancer cells were not positive for PIVKA-II (Fig. 2c). Non-cancer cells (mainly plasma cells) were non-specifically positive (Fig. 2d). An immunohistochemical study showed that CEA- and CA19–9-positive and AFP- and glypican-3 (GP-3)-negative cells were present in the tumor (Fig. 3a–d). The patient was administered palliative chemotherapy with TS-1. The patient died of liver failure 3 months after the initial admission. An autopsy was not performed.

3. Discussion

PIVKA-II is a circulating precursor of prothrombin, which is found in the blood of patients who are deficient in vitamin K [4]. In 1984, Leibman et al [1]. reported PIVKA-II levels to be significantly elevated in HCC patients. The clinical usefulness of PIVKA-II in the detection of HCC has been demonstrated in many studies [5,6]. PIVKA-II has been reported to predict the progression of HCC patients because those with higher PIVKA-II levels had a significantly higher frequency of intrahepatic metastasis, portal or hepatic vein tumor thrombosis and capsular infiltration [7,8]. It is proposed that PIVKA-II may be useful primarily as a prognostic biomarker, predicting rapid tumor progression and poorer prognosis [7]. These findings may be explained by an in vitro study showing that PIVKA-II stimulates cell proliferation and cell migration of vascular endothelial cells by binding to the kinase insert domain receptor, alternatively referred to as vascular endothelial growth factor receptor-2 [9]. The increased production of the prothrombin precursor in tumor cells, abnormalities in vitamin K-dependent carboxylation, and vitamin K deficiency in tumor tissues have been speculated to be the underlying mechanisms of PIVKA-II production in HCC [10]. PIVKA-II-producing gastric cancers occur initially as common gastric adenocarcinoma and the hepatoid component arises during tumor progression. The stomach is one of the most common sites in which hepatoid adenocarcinomas have been described, the reason for which is unknown. Almost all cases were with advanced cancers and the hepatoid pattern is observed in the invasive portion. It has been indicated that the hepatoid-differentiated foci of the gastric adenocarcinoma may produce the prothrombin precursor in addition to both AFP and PIVKA-II [2]. It seems to that the clinicopathological features of PIVKA II-producing gastric cancer resemble those of AFP-producing gastric cancer, especially AFP-producing hepatoid adenocarcinoma [11]. The hepatoid pattern is often detected histologically, and the production of PIVKA-II by tumor cells usually is confirmed immunohistochemi-