$$N_R = \frac{dn}{dt} \cdot T_i, \quad \frac{dn}{dt} \approx \text{constant}. \tag{A1}$$

Here, dn/dt denotes a rate of number of positron emitter nuclei per time of beam irradiation. The residual number of positron emitter nuclei immediately after irradiation, N_{act}, can be expressed using Eq. (A1) by the following equations:

$$\begin{aligned}
N_{act} &= \frac{dn}{dt} \cdot \Delta t \cdot \exp\left(-\frac{\ln 2}{T_{1/2}} \cdot \Delta t \cdot m\right) \\
&\quad + \frac{dn}{dt} \cdot \Delta t \cdot \exp\left(-\frac{\ln 2}{T_{1/2}} \cdot \Delta t \cdot (m-1)\right) + \cdots \\
&\quad + \frac{dn}{dt} \cdot \Delta t \cdot \exp\left(-\frac{\ln 2}{T_{1/2}} \cdot \Delta t \cdot 0\right) \\
&= \sum_{m=0}^{l} \frac{dn}{dt} \cdot \Delta t \cdot \exp\left(-\frac{\ln 2}{T_{1/2}} \cdot \Delta t \cdot m\right) \\
&\quad \text{(where } l, m = \text{sample number)} \\
&= \sum_{t'=0}^{T_i} \frac{dn}{dt} \cdot \frac{t'}{m} \cdot \exp\left(-\frac{\ln 2}{T_{1/2}} \cdot t'\right) \\
&\quad \text{(where } \Delta t \cdot l = T_i, \Delta t \cdot m = t') \\
&\to \int_0^{T_i} \frac{dn}{dt} \cdot \exp\left(-\frac{\ln 2}{T_{1/2}} \cdot t'\right) dt' \quad (\text{as } m \to \infty, \Delta t \to 0) \\
&= \frac{dn}{dt} \cdot \frac{T_{1/2}}{\ln 2} \cdot \left[\exp\left(-\frac{\ln 2}{T_{1/2}} \cdot t'\right)\right]_{T_i}^{0} \\
&= \frac{dn}{dt} \cdot \frac{T_{1/2}}{\ln 2} \cdot (1 - 2^{-T_i/T_{1/2}}) \\
&= N_R \cdot \frac{T_{1/2}}{T_i \cdot \ln 2} \cdot (1 - 2^{-T_i/T_{1/2}}).
\end{aligned} \tag{A2}$$

Here, if

$T_{1/2} \gg T_i$:

$$\begin{aligned}
N_{act} &\approx N_R \cdot \frac{T_{1/2}}{T_i \cdot \ln 2} \cdot \left(1 - \left(1 - \frac{\ln 2}{T_{1/2}} \cdot T_i\right)\right) \\
&= N_R \cdot \frac{T_{1/2}}{T_i \cdot \ln 2} \cdot \frac{\ln 2}{T_{1/2}} \cdot T_i = N_R.
\end{aligned} \tag{A3}$$

And, if

$$T_{1/2} \ll T_i; \quad N_{act} \approx N_R \cdot \frac{T_{1/2}}{T_i \cdot \ln 2} = \frac{dn}{dt} \cdot \frac{T_{1/2}}{\ln 2} = \text{constant}. \tag{A4}$$

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ORIGINAL PAPER

Changes in pelvic and systemic platinum concentrations during negative-balance isolated pelvic perfusion: correlation between platinum concentration and method of administration in a pig model

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Abstract
Purpose To assess the effect of altering the method of administration during negative-balance isolated pelvic perfusion (NIPP) on the platinum concentration in the pelvic or systemic circulation.
Methods Twenty female pigs were used in this study. The abdominal aorta and the infra-renal vena cava were occluded with two balloon catheters and blood in the extracorporeal circuit was circulated with twin rotary pumps. NIPP was then performed with cisplatin (5 mg/kg) in 15 pigs. Three types of NIPP administration method (group A: 1 bolus, B: 2 same doses boluses, C: 3 same doses boluses) were used, five pigs being subjected to each treatment. The remaining five pigs were administered cisplatin systemically as a control study (group D). The platinum concentrations in the pelvic and systemic circulation were measured and compared.
Results (1) Pelvic circulation: There was a tendency for the platinum concentration to increase as the bolus time decreased. The platinum concentration in groups A and B was significantly ($P < 0.05$) higher than that in group C. Significant differences ($P < 0.05$) between groups A and B until 10 min after the start of NIPP. (2) Systemic circulation: Significant differences ($P < 0.05$) were observed between NIPP groups and D during NIPP. The platinum concentration in group D was five times higher than that in group C. (3) Plasma pelvic to systemic exposure ratio: there were no significant differences among the three NIPP groups.
Conclusions The platinum concentrations in the pelvic and systemic circulation increased as the bolus time decreased. The plasma pelvic to systemic exposure ratio was not influenced by bolus time.

Keywords Isolated pelvic perfusion · Negative-balance isolated pelvic perfusion · Pig model

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Introduction

During the last four or five decades, there have been many attempts to enhance tumor response by isolated pelvic perfusion (IPP) therapy in which anticancer drugs at high concentrations are delivered to the tumor tissue as selectively as possible. The first regional perfusion technique, initiated by Creech et al. (1958), was the use of an extracorporeal circuit to deliver a high concentration of drug to a regional arterial/venous circuit in an extremity. IPP was first developed by Austen et al. (1959) and has been used by several medical groups in an effort to control advanced malignancies of the bladder, uterus and rectum (Austen et al. 1959; Watkins et al. 1960; Stehlin et al. 1960; Shingleton et al. 1961; Lawrence et al. 1961, 1963; Collins 1989; Wile and Smolin 1987; Wile et al. 1985; Turk et al. 1993;

Wanebo and Belliveau 1999; Wanebo et al. 1996, 2003; Guadagni et al. 1998). However, IPP therapy has not been used as a therapeutic strategy for advanced pelvic cancers. Even in an isolated setting, anticancer agents can easily leak into the systemic circulation (Lawrence et al. 1961, 1963; Wile and Smolin 1987; Wile et al. 1985; Collins 1989; Turk et al. 1993; Wanebo and Belliveau 1999; Wanebo et al. 1996, 2003). Therefore, it is impossible to perform such therapy in patients with renal dysfunction and the amount of anti-cancer agents is strictly limited.

We hypothesized that drug leakage via highly developed collateral vessels in the pelvis into the systemic circulation would be decreased by reducing the blood pressure in the pelvic venous circulation during IPP and for this purpose we developed a twin-pump system for the extracorporeal circuit to modulate the in–out flow rate in an IPP pig model (Murata et al. 2005). We devised a novel IPP technique that allowed control of a negative-balance in–out flow rate, which we refer to as negative-balance isolated pelvic perfusion (NIPP) and found that this clearly reduced drug leakage into the systemic circulation. In the present study, in order to determine the most appropriate method of administration, we evaluated the contribution of drug administration time to platinum concentration in the pelvic and systemic circulation in a pig model.

Materials and methods

Animal model and general anesthesia

All animal experiments were conducted in accordance with the Guidelines of Nippon Medical School University for Animal Care and Experimentation. Twenty adult female pigs weighing 34–40 kg (average: 36 kg) were used in this study and all procedures were performed with the animals under general anesthesia. The animals were placed supine and general anesthesia was induced with an intramuscular injection of ketamine hydrochloride (300 mg/pig) and maintained with sevoflurane (Maruishi Pharmaceutical Co. Ltd., Osaka, Japan).

Monitoring of the systemic circulation

Peripheral arterial oxygen saturation was maintained above 90% and monitored with a probe applied to the ear. Each animal was continuously monitored during the procedure using electrocardiography. In all 20 pigs, both internal jugular veins were exposed through a cut-down incision and two cannula sheaths (5 Fr; Medikit Co. Ltd. Japan) were inserted into each of them. The cannula sheath in the right jugular vein was used to collect blood samples and to monitor central venous pressure (CVP) and the other sheath was used to administrate other agents by intravenous drip infusion. The thyrocervical artery was exposed and a 5 Fr cannula sheath was inserted to monitor blood pressure during the procedures. CVP and arterial blood pressure were recorded before and at 0, 5, 10, 15, 20, 25 and 30 min after the start of perfusion.

Catheter technique and experimental groups

Additional procedures were performed in 15 pigs subjected to NIPP. Both common femoral arteries and veins were exposed through a cut-down incision and sheaths (6 and 9 Fr each; Medikit Co. Ltd., Tokyo, Japan) were inserted into each of them, as shown in Fig. 1 (Murata et al. 2005). The cannulas had specially designed side-arms to allow high flow and to keep the pressure in the pump-system low during withdrawal and return of the blood through the cannulas. After systemic heparinization (120 U/kg), two balloon catheters (30 mm balloon with 5 Fr shaft, Forte Co. Ltd., Tokyo, Japan) were placed in the abdominal aorta and the infrarenal vena cava (IVC) at the level of the L3/4 intervertebral space.

Among the 20 pigs, 15 were evaluated for the contribution of drug administration time to platinum concentration in the pelvic and systemic circulation by using three sets of bolus infusions. After occlusion of the abdominal aorta and IVC with the two balloon catheters, blood was withdrawn from the veins with one of the rotary pumps and returned to the arteries through the cannulas with the other rotary pump. Five animals were allocated to each group; a total cisplatin (Nippon Kayaku Co. Ltd., Tokyo, Japan) dose of 5 mg/kg was

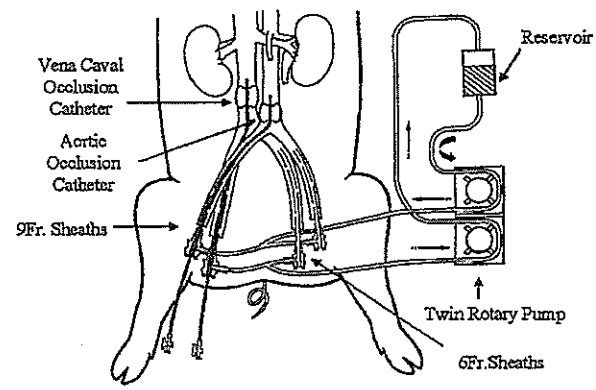

Fig. 1 Schema of the negative-balance isolated pelvic perfusion system used in a pig model (Murata et al. 2005)

administered into the reservoir (Fig. 1) in one bolus (group A), in two equal boluses at 0 and 10 min after the beginning of perfusion (group B), or in three equal boluses at 0, 10 and 20 min after the beginning of perfusion (group C). The volume withdrawn was fixed of 20 ml/min higher than the volume returned (300 ml/min). The remaining five pigs (group D) were subjected to systemic intravenous administration of cisplatin in three equal boluses as a control study. In this group, cisplatin was administered for 1 min per bolus. The reason why we used much higher dose of cisplatin than that used with humans was to obtain a data of blood kinetics of high cisplatin dose for clinical application because there were very few papers with double or triple doses of cisplatin.

Management of systemic circulation

The animals were administered the other agents by intravenous drip infusion via the cannula sheath in the left jugular vein during IPP, because the reduction of blood volume caused by increasing the volume withdrawn and the volume of the blood samples would have caused anemia in the pigs. In view of the volume of blood loss during NIPP, the intravenous drip infusion rate was set at 25 ml/min in each group. The cisplatin was infused for 30 min. In group D, the intravenous drip infusion rate was set at 5 ml/min. All results were performed independently five times.

Angiography

Before NIPP, isolated pelvic angiography was performed with the twin rotary pumps in each animal ($n = 15$) to confirm establishment of the IPP system. Isolated pelvic angiography was performed by infusion of non-ionic contrast material (300 mg/ml; iodine, iohexol, Daiichi Pharmaceutical Co. Ltd., Japan) at a rate of 5 ml/s through the arteries with a rotary pump and was withdrawn at a rate of 5 ml/s through the veins with the other rotary pump. The duration of angiography was 30 s and the total volume of contrast material infused was 100 ml. Recording of the fluoroscopic images on video tape was begun at the start of contrast material infusion. NIPP was performed after confirming that no contrast material had entered the inferior vena cava above the occluding balloon.

Analysis of pharmacokinetics

In NIPP groups, plasma platinum concentration was measured in blood samples collected from the arterial and venous sides of the pump and from the systemic venous circulation (superior vena cava) at 0, 5, 10, 15, 20, 25 and 30 min after the start of NIPP. Blood samples in groups B and C were collected 10 and 20 min prior to the second or third injection of cisplatin. In group D, the plasma platinum concentration was also measured in blood samples collected from the systemic venous circulation (superior vena cava) at 0, 5, 10, 15, 20, 25 and 30 min after the start of cisplatin infusion. Blood samples in group D were collected 10 and 20 min prior to the second or third injection of cisplatin.

Statistical analysis

The plasma samples were digested with nitric acid for analysis of metal species. Platinum concentrations in the serum were measured by atomic absorption spectrophotometry (Varian SpectrAA 300/400). Drug exposure was measured as the area under the serum concentration–time curve until 30 min after the start of perfusion. All data are shown as means ± SD. Results were compared by ANOVA with repeated measures and Games–Howel method as post hoc comparisons. Differences at $P < 0.05$ were considered statistically significant.

Results

Effect of NIPP on the systemic circulation

Hemodynamic parameters, arterial blood pressure (BP), heart rate (HR), blood oxygen saturation (SAT) and CVP were measured during NIPP to evaluate its effect on the systemic circulation. Each animal was hemodynamically stable throughout all the procedures.

Pharmacokinetics of the serum platinum concentration in the pelvic circulation

Serum plasma platinum .concentrations in the pelvic circulation

The maximum plasma platinum concentrations in the pelvic circulation on the arterial side (Table 1; Fig. 2) were 75.0 (15.5) mg/l in group A, 55.8 (7.3) mg/l in group B and 38.2 (5.6) mg/l in group C. The average platinum concentration was 43.6 (9.0) mg/l in group A, 37.9 (2.0) mg/l in group B and 28.3 (1.6) mg/l in group C. The maximum plasma platinum concentrations in the pelvic circulation on the venous side (Table 1; Fig. 3) were 59.7 (15.8) mg/l in group A, 38.9 (7.4) mg/l in group B and 29.2 (4.3) mg/l in group C. The average

Table 1 Platinum concentration in the NIPP groups and the systemic intravenous administration group

	Platinum			
	1 Bolus (A)	2 Boluses (B)	3 Boluses (C)	4 Boluses (D)
Plasma pelvic to systemic exposure ratio (SD) during NIPP	15.5 (9.1):1.0	16.0 (3.2):1.0	19.3 (8.4):1.0	–
Plasma drug concentrations (SD)				
Maximum pelvic concentration (mg/l)				
In the arterial site	75.0 (15.5)	55.8 (7.3)	38.2 (5.6)	–
In the venous site	59.7 (15.8)	38.9 (7.4)	29.2 (4.3)	10.4 (0.9)[a]
Average of pelvic concentration				
In the arterial site	43.6 (9.0)	37.9 (2.0)	28.3 (1.6)	–
In the venous site	37.5 (10.8)	29.4 (4.2)	23.4 (1.8)	8.0 (1.4)[a]
Pelvic concentration at end of NIPP				
In the arterial site	27.0 (9.0)	26.0 (2.2)	30.7 (4.7)	–
In the venous site	21.7 (9.0)	23.0 (4.7)	27.2 (3.5)	8.8 (1.3)[a]
Systemic venous concentration				
Maximum	3.8 (1.6)	3.1 (0.4)	2.3 (0.8)	10.4 (0.9)
Average	3.2 (1.3)	2.2 (0.4)	1.5 (0.6)	8.4 (1.4)

[a] The systemic platinum concentrations in group D are used as synonymous with the pelvic venous concentrations

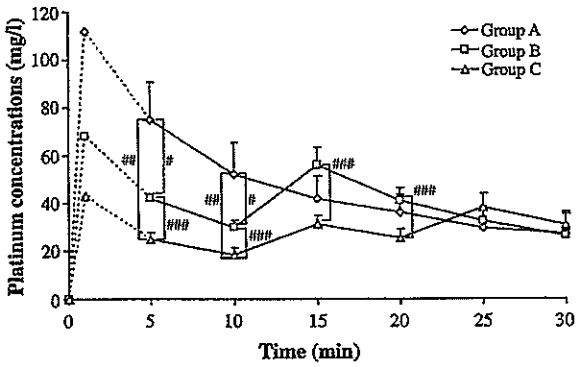

Fig. 2 Comparison of the pelvic arterial platinum concentrations when the bolus time was one (group A), two (group B) and three (group C). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$

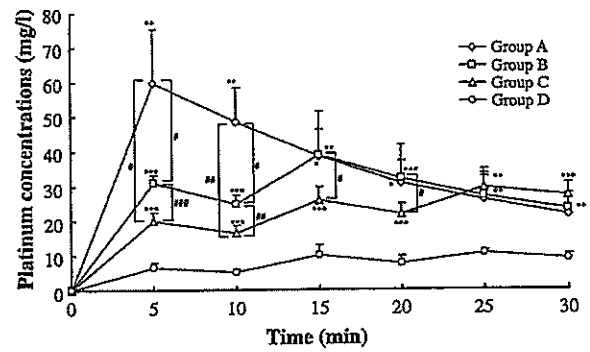

Fig. 3 Comparison of the pelvic venous platinum concentrations among four groups. The systemic platinum concentrations in group D are used as synonymous with the pelvic venous concentrations. Comparison among NIPP groups ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$). Comparison of NIPP groups versus group D ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)

platinum concentration was 37.5 (10.8) mg/l in group A, 29.4 (4.2) mg/l in group B and 23.4 (1.8) mg/l in group C. The maximum platinum concentrations in group A in the pelvic circulation on the arterial or venous sides were significantly ($P < 0.05$) higher than those in groups B and C. Those in group B were significantly ($P < 0.05$) higher than those in group C. The average platinum concentrations (based on the serum concentration–time relationship from 0 to 30 min after the start of drug perfusion) in group A were significantly ($P < 0.05$) higher than those in group C, but there were no significant differences between groups A and B, or between groups B and C. With regard to platinum concentration on the arterial side, although that in group A was significantly higher than that in group B ($P < 0.05$) or C ($P < 0.01$) until 10 min after the start of NIPP, that in group B tended to be higher than that in group A after 15 min and was significantly ($P < 0.001$) higher than that group C until 20 min after the start of NIPP. With regard to platinum concentrations on the venous side, that in group A was significantly ($P < 0.05$) higher than that in group B or C until 10 min after the start of NIPP, that in group B was significantly ($P < 0.05$) higher than that in group C until 20 min after the start of NIPP. If the systemic platinum concentrations in group D were the same as the pelvic venous concentrations, these platinum concentrations were significantly lower than those in group A ($P < 0.05$) until 20 min after the start of NIPP, B ($P < 0.01$), or C ($P < 0.01$) during NIPP. The serum platinum concentration in group D was three times lower than that in the pelvic venous circulation in group C.

Serum plasma platinum concentrations in the systemic circulation

On the other hand, the maximum plasma platinum concentrations in the systemic venous circulation (Table 1; Fig. 4) were 3.8 (1.6) mg/l in group A, 3.1 (0.4) mg/l in group B, 2.3 (0.8) mg/l in group C and 10.4 (0.9) mg/l in group D. The average platinum concentrations were 3.2 (1.3) mg/l in group A, 2.2 (0.4) mg/l in group B, 1.5 (0.6) mg/l in group C and 8.0 (1.4) mg/l in group D. The systemic platinum concentration in group D was significantly higher than that in group A at 5 ($P < 0.01$), 15 ($P < 0.05$), 25 ($P < 0.001$) and 30 min ($P < 0.01$), B ($P < 0.05$), or C ($P < 0.05$) during NIPP and was five times higher than that in the systemic circulation in group C. However, there were no significant differences among NIPP groups, at least within the limited number of pigs employed.

Plasma pelvic to systemic exposure ratio during NIPP

The plasma pelvic to systemic exposure ratio (Table 1) was 15.5 (9.1):1.0 in group A, 16.0 (3.2):1.0 in group B and 19.3 (8.4):1.0 in group C. There were no significant differences among the three NIPP groups. However, there was a tendency for systemic leakage to increase as the platinum concentration in the pelvic circulation increased.

Discussion

The aims of regional chemotherapy are to increase drug efficacy in the treated area by creating a locally highly drug concentration and to avoid systemic toxicity by decreasing the degree of systemic drug exposure.

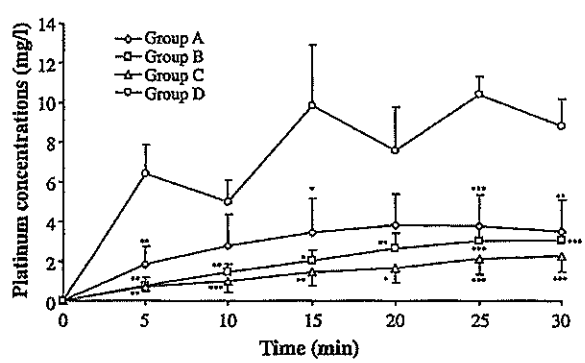

Fig. 4 Comparison of systemic venous platinum concentrations among four groups. Comparison among NIPP groups ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$). Comparison of NIPP groups versus group D ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)

IPP is the only regional perfusion technique that permits delivery of a drug into the pelvic circulation at a higher concentration than in the systemic circulation. However, leakage of anticancer drugs can easily occur from the pelvic into the systemic circulation during IPP (Lawrence et al. 1961, 1963; Wile et al. 1985, 1987; Collins 1989; Turk et al. 1993; Wanebo and Belliveau 1999;Wanebo et al. 1996; Belliveau et al. 2005). To realize the full potential of IPP therapy, we devised a novel IPP technique that allowed control of the negative-balance in–out flow rate, thus reducing drug leakage into the systemic circulation. This NIPP technique makes it possible to dramatically decrease drug leakage from the pelvic into the systemic circulation (Murata et al. 2005). To optimize the performance of NIPP therapy, it is necessary to acquire data about the correlation between the method of administration and the concentrations of platinum in the pelvic and systemic circulation.

As expected, the serum plasma platinum concentration in the pelvic circulation on both the arterial and venous sides tended to increase as the anticancer agent bolus time decreased. On the other hand, the serum plasma platinum concentration in the systemic circulation tended to increase as the bolus time decreased. A significant difference was observed between groups A and B, or between A and C until 10 min after the start of NIPP and between groups B and C until 20 min after the start of NIPP. As for the systemic platinum concentration in group D, it was significantly higher than that in NIPP groups during NIPP and was five times higher than that in group C with the same three boluses. However, there were no significant differences among NIPP groups, at least within the limited number of pigs employed. If the systemic platinum concentration in group D was the same as the pelvic venous concentration, then this platinum concentration was significantly lower than that in NIPP groups during NIPP. The serum platinum concentration in group D was three times lower than that in the pelvic venous circulation in group C. Our present results suggest that a high dose of anticancer agent can be used for NIPP therapy without increasing the severity of complications. Consequently, the serum platinum concentration in the pelvic circulation was much higher than achievable by systemic chemotherapy. Thus, the full potential of IPP therapy will be realized if the NIPP method is used.

The most interesting result of this study was that the plasma pelvic to systemic exposure ratio was 15.5 (9.1):1.0 in group A, 16.0 (3.2):1.0 in group B and 19.3 (8.4):1.0 in group C, there being no significant differences among the three NIPP groups. This suggests that the bolus times for NIPP therapy can be chosen

according to the various situations of the patients, such as the type of tumor, tumor size, grading of malignancy, or general condition, especially renal function under conditions of hydronephrosis. For example, three or more boluses can be chosen for patients with renal dysfunction, or one or two boluses can be chosen depending on tumor size or grading of malignancy in patients whose general condition is good.

In summary, NIPP allows a high concentration of anticancer drug to be delivered into the pelvic circulation, while maintaining a low concentration in the systemic circulation. The plasma platinum concentration in the pelvic circulation tended to increase as the bolus time of the anticancer agent decreased. On the other hand, the platinum concentration in the systemic circulation tended to increase as the bolus time decreased. There were no significant differences in the plasma pelvic to systemic exposure ratio among bolus times. These results suggest that bolus times in NIPP therapy can be chosen according to various situations in individual patients. Based on the above findings and additional isolated dialysis of anticancer agents in the pelvic cavity after NIPP therapy (Murata et al. 2005), we have performed NIPP therapy in patients with inoperable or recurrent cancer and obtained good control of tumor progression.

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Innovative Therapeutic Development of Isolated Liver Perfusion: Applicability to the Treatment of Hepatic Malignancy

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Purpose

To evaluate the effect of total isolated liver perfusion on hepatic circulation and the feasibility of a percutaneous approach in a pig model.

Materials and Methods

In twenty-five pigs undergoing total isolated liver perfusion (**Fig. 1**), the unilateral common femoral artery and the bilateral common femoral veins and the right jugular vein were exposed through a cut-down incision, and sheaths (8 Fr., 12 Fr., 9 Fr. and 9 Fr. each) were inserted into each of them. The thyrocervical artery was exposed, and a 5 Fr. cannula sheath was inserted to monitor blood pressure during the procedure. Arterial blood pressure were recorded before, and 0, 5, 10, 15, 20, 25, and 30 minutes after the start of perfusion. Catheters were placed in the proper hepatic artery and the inferior vena cava (IVC). The portal vein branch was punctured by a PTCD needle under ultrasonographic guidance, and a 12 Fr. sheath was inserted. Then, a balloon catheter was inserted into the portal vein trunk. We developed two kinds of balloon catheters, a first version (n=19) and a second version (n=6). They had specially designed side arms to allow high flow and to keep the pressure in the pump-system low during withdrawal and return of the blood through the catheter. After systemic heparinization (120U/kg), balloons were used to occlude the proper hepatic and the portal vein trunk and the infrahepatic and suprahepatic IVC. Blood was withdrawn from the portal vein with one rotary pump (120ml/min) and returned to the proper hepatic artery (120ml/min) with contrast medium or cisplatin (2.5mg/kg) through the balloon catheter with another rotary pump. To maintain blood pressure blood was withdrawn from the infrahepatic IVC with one rotary pump and returned to the jugular vein through the sheath with another rotary pump. Blood was withdrawn from the superior mesenteric vein and returned to the jugular vein through the sheath with a rotary pump. Perfusion was carried out for 30 min.

Results

The 19 pigs with the first version of the balloon catheter were hemodynamically unstable. It was impossible to assess the effect of the new isolated liver perfusion system. The remaining 6 pigs with the second version of

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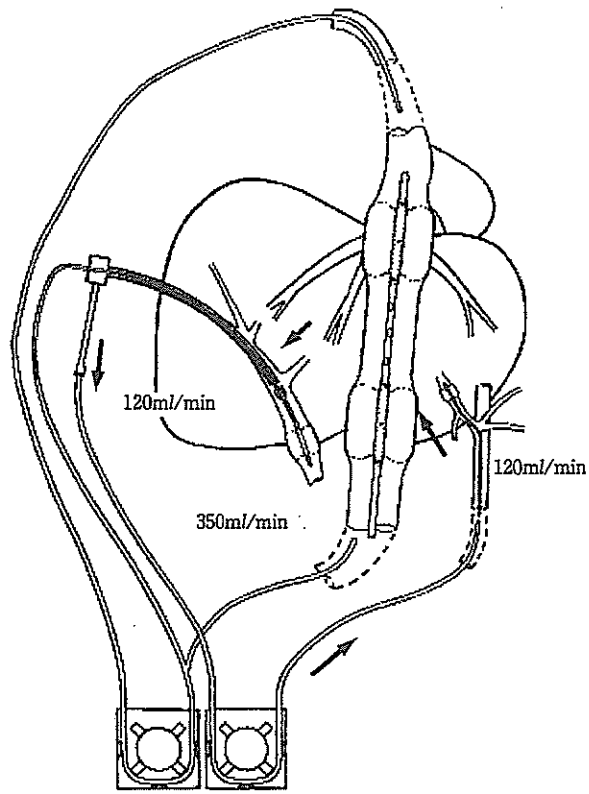

Fig. 1. Illustration of new isolated liver perfusion

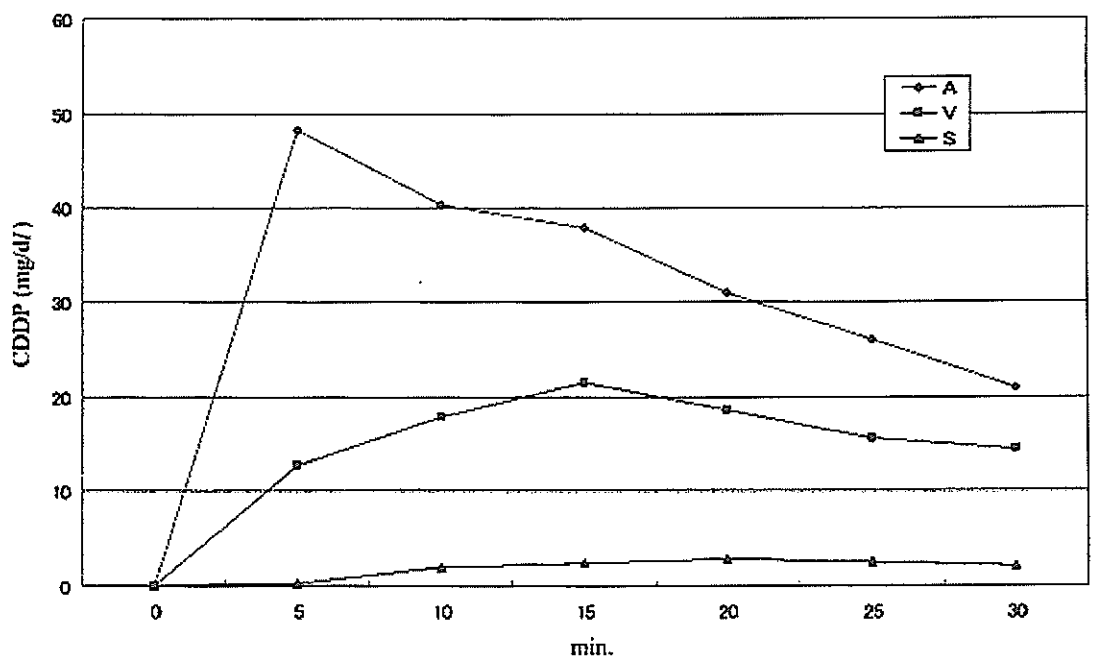

Fig. 2 Concentration of CDDP

the balloon catheter were hemodynamically stable. During complete occlusion of hepatic veins contrast medium was seen to drain in a reverse direction into the portal vein in 6 pigs. Collateral vessels could not be demonstrated. Concentrations of cisplatin in the hepatic artery, the portal vein, and the systemic circulation are shown in **Fig. 2.**

Conclusion

Total isolated perfusion accomplished by occlusion of the IVC and the portal vein in combination with aspiration applied in the portal circulation results in rapid and extensive arterioportal shunting without visualization of collateral vessels. This percutaneous approach is technically feasible, but its hemodynamic safety must be evaluated before clinical application.

第20回 ● がんについての市民公開講演会（2006年6月3日）

がん医療の進歩
～過去・現在・未来～

野村和弘
国立がんセンター中央病院 前院長，現 東京労災病院 院長

野村和弘（のむら・かずひろ） 1967年東京大学医学部卒。1972年東京大学医学部脳神経外科教室助手。1973年国立がんセンター病院脳神経外科医員。1975年から米国州立カリフォルニア大学脳神経外科脳腫瘍研究センター留学を経て1999年国立がんセンター中央病院副院長，2002年同院病院長。2006年春より東京労災病院院長。専門の脳神経外科領域のみならず，日本のがん医療の進歩のために多方面で活躍。

がん医療は，日々ものすごい勢いで進歩しています。われわれ「がん専門」と称している医療者でも，ちょっと勉強を怠ると乗り遅れてしまうような事態が生じているくらいです。しかし，「温故知新」というのはがん医療においても大事なことで，過去があってこそ現在がある，そして未来が発展する，という観点から，今日のテーマを立てさせていただきました。広範なテーマではありますので，少しずついろいろな分野を垣間見ていこうと考えていますが，それによって皆さんの，がん医療に対する知識が少しでも増え，がん医療に対して興味を持っていただけたら幸いと思います。

§1 がんとは？

◉がんの死亡率

この講演会シリーズでも「がんとは何か？」については，さまざまなアプローチからの説明があったと思いますが，簡単におさらいしてみたいと思います。

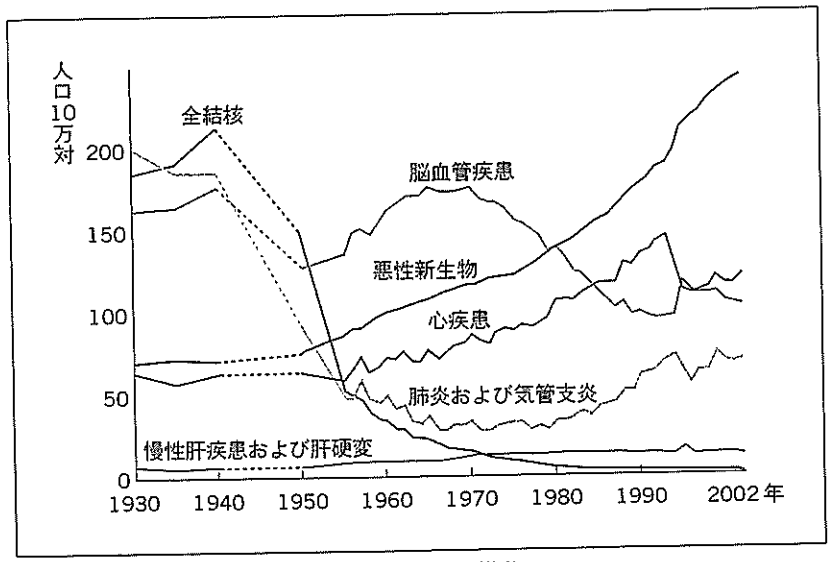

図1　死亡率の推移

図1は日本で亡くなられる方の死亡原因を示すグラフです。「がんは恐ろしい，恐ろしい」と言っているうちに，1981年に死亡原因としてがんが一番多くなってしまいました。このグラフは「人口10万人に対する比」で書かれています。高齢化社会と言われる現在，がんにかかりやすい状況の方は年々増加していますが，2003年の統計では32万人の方ががんで亡くなっており，新幹線のぞみの乗客数である1300人とほぼ同数の方々が，毎日がんで亡くなっていることになります。

◍がん発生のメカニズム

図2に「がん化のメカニズム」を示します。私たちのからだをかたちづくる細胞の1個1個には「核」と呼ばれるものがあり，この中に「DNA」，いわゆる遺伝子が入っています。この遺伝子の情報が細胞が分裂しても受け継がれることで，ヒトはヒト，サルはサルというかたちで生物は形成されます。この情報の中にはもっと細かいものも含まれており，たとえば「皮膚になれ」という指令を受けると，きちんと皮膚となるべき場所で，皮膚の細胞として形成されます。正常な場合は秩序正しく細胞は分裂・増殖していくのですが，さまざまな発がん物質――紫外線であったり，たばこであったり――は細胞の遺伝子に傷をつけてしまいます。生物のからだは大変よくできており，ちょっとやそっとの遺伝子の傷は治してしまい，仮に治せない場合でもその細胞は死んでし

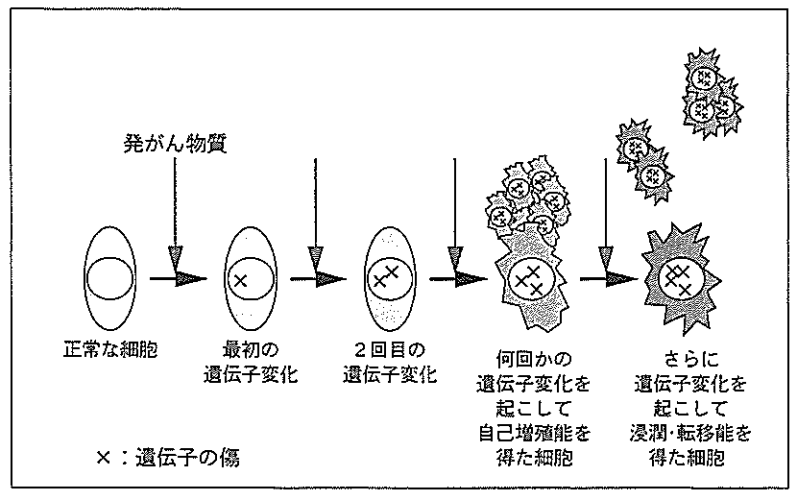

図2　がん化のメカニズム（〔資料4〕より引用）

まって（細胞死），遺伝子を受け継ぐことができません。死んだ細胞の部分に新しい細胞ができ，それを補ってくれればいいわけです。

ところが，なかには遺伝子に損傷が生じても頑張ってしまう細胞がある。遺伝子そのものに変化が起き，不死身の細胞になってしまい，外から何のコントロールも受けずにどんどん増えていってしまう（自己増殖）。そうした細胞ががん細胞で，それがその場所だけにとどまらず，他の臓器にじわじわ拡がったり（浸潤），リンパ液や血液などに乗って転移したりする。こうした力を備えた細胞が増えてしまうと，正常な組織に対して悪影響を及ぼすと同時に，これを叩く術（すべ）が非常に制限されてしまいます。

図3は，組織レベルでそのプロセスをみたものです。たとえば正常な皮膚であれば，そこで細胞はきれいに並んでいますが，そこに発がん物質により遺伝子に傷害を受けたおかしな細胞が増えてくると，自己増殖して周りの組織を破壊したり，外へ出て行くような異常な組織になってしまいます。

がんが進行し，浸潤や転移を起こしてしまうと治療は困難になりますが，早期にがんを見つければ，それだけからだにやさしい治療でがんを治すことできます。がんセンターでは2004年「がん予防・検診研究センター」を設立しましたが，これはそこのところをもう一度考え直そうとする施設です。このことについてはまた後ほどお話させてもらいます。

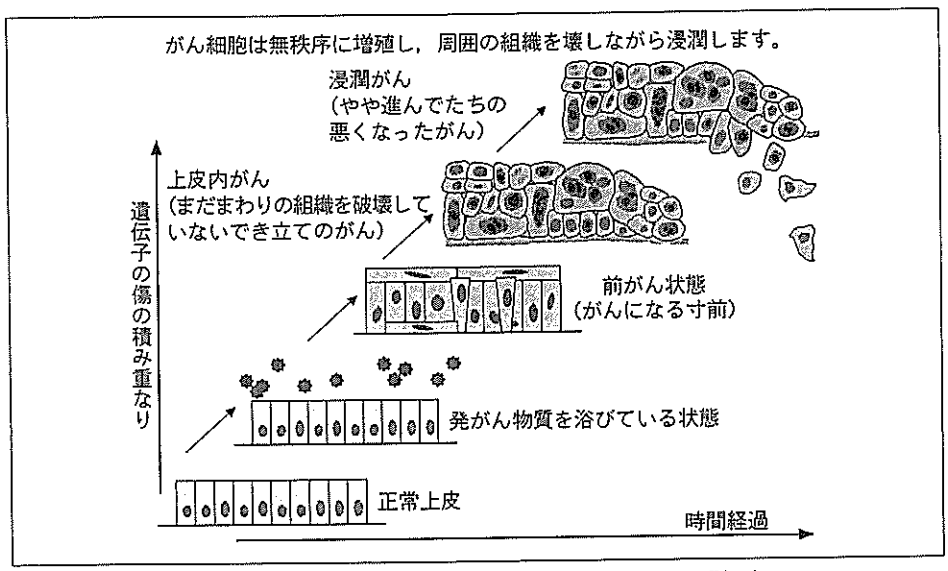

図3 組織レベルでのがん化の進展（〔資料3〕より引用）

◍臓器レベルでのがんの発生

大腸がんの発生を例として，もう一度いまの話を振り返ってみましょう（図4)。胃や食道などの消化管はみな似たような構造なのですが，大腸は壁が5層に分かれています。一番内側（食べたものが消化される側）は「粘膜」，その周りに少し硬い「粘膜筋板」があり，その外側に「粘膜下層」，「筋膜」，「漿膜部」があります。大腸がんは，この「粘膜」にとどまっている段階で治療してしまえば，再発率は1％程度と，ほとんど治ってしまいます。

大腸がんの検診などで「ポリープ」という言葉を耳にされた方もいらっしゃると思いますが，粘膜の上に「いぼ」のように飛び出た「腺腫」のことをポリープと呼びます。ポリープも遺伝子の異常から生じるものですが，さらに1つ，2つと遺伝子異常が加わると，悪性化してがんになる可能性も高くなってきます。一方，飛び出ないタイプの大腸がんもあり，潰瘍のような状況で，どんどん下に入っていきます。余談ですが，日本ではこうしたタイプのがんもずいぶん前から見つけており，早期の治療であれば治すことができると主張していたのですが，当初海外では「そういうことはあり得ない」と否定的だったのです。最近ようやく，米国等でも，日本で言っていることが正しいと納得されてきました。

実は，私もポリープの大腸がんでした。「便潜血検査」を受けると血が混ざっており，精密検査を行いました。ファイバーで検査するとポリープのがんがあ

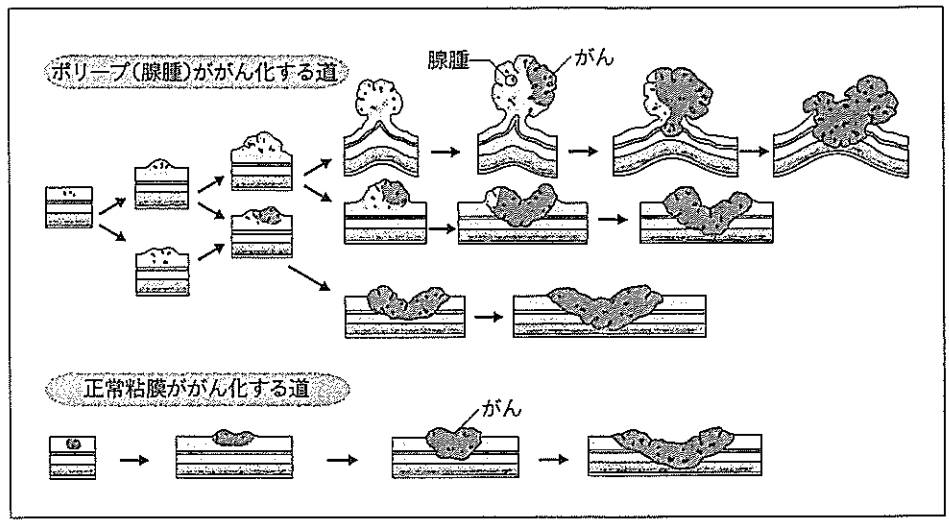

図4　大腸がんの発生（〔資料1〕より引用）

り，この場合はお腹を切らなくても，内視鏡で見ながらループ状の電気を通すワイヤーでくるくるっと回し，焼き切ってしまいます。あとに潰瘍は残りますが，粘膜の潰瘍はすぐに治りますから，次の日にはもう知らん顔して診療に当たることができる状況でした。

§2　切って治すがん治療の進歩～10年前の手術，現在の手術，将来の外科

ここまで「がんとは何か？」について，発生のメカニズムからお話しましたが，ここからは，そのがんをどう治してきたのかの歴史についてお話します。まず手術療法など，「切って治す」治療法についてご説明します。

かつての，江戸時代までの手術は，4，5人で患者さんを押さえつけて行うようなものでした。そこに，皆さんご存じの華岡清洲が，1805年「曼陀羅華（まんだらげ）」という生薬を作って，世界に先駆けて全身麻酔下で乳がんの摘出術を行いました。その後，15～20年くらいたって，海外で気管麻酔による全身麻酔が行われています。

◎10年前の手術と現在の手術

がんの手術については，ほんの10年前までは，「がんがありそうなところ，細胞が飛んでいそうなところは全部切って取る」という発想で手術法が開発されてきました。胃がんであれば胃を2/3くらい取ってしまう。がんが目で見え

る範囲のさらに5センチくらい先まで取ることで，再発を防ごうという考え方です。それだけ胃を取ってしまえば，手術後に患者さんにいろいろな後遺症が残ります。「ダンピング症候群」という言葉を耳にされた方もおられると存じますが，胃切除後，食後に冷や汗やめまい，あるいは腹痛などの症状が起こることがあります。そういう問題が生じても，とにかく命を助けることを最優先にして，再発が生じない術式を一生懸命考えて行ってきました。

そうした治療を繰り返すうちに，手術で切り取った，患者さんの貴重な胃がんの標本が残ります。何千もの標本を検討するうちに，先ほどご説明したように「粘膜層にとどまっているがんでは，1%も再発がない」というようなことが明らかになってきました。逆に言えば，手術をしても，1%弱だけれども再発はある。そうであれば，それほど大きく切除しなくても，がんがあるところだけ取ってしまえばいいのではないか。リスクとして同じくらいであれば，患者さんのからだにやさしい治療のほうがいいという考え方が，だんだん知られるようになってきました。そうした検討から，胃がんであれば胃がんが，どの範囲まで進行していれば，どの程度の切除や治療が妥当なのかということが徐々に明らかになっていったのです。

◎内視鏡的治療の発展

私の大腸がんの治療もそうでしたが，お腹をメスで開かなくても可能な「内視鏡的治療」が，そうした検討の中から登場してきました。内視鏡でのぞきながら，さまざまな治療用具を内視鏡と同様に挿入して，がんの部分を切り取ってしまいます。私の大腸がんのように「ポリープ」様のものであれば「切除しやすそう」というのは何となくご理解いただけると思いますが，中には難しいかたちのがんもあります。そこから，さまざまな工夫がなされてきました。

まず，内視鏡によるがんの早期発見の工夫としては，がんが見えやすいように染色するという方法が考えられました。がん組織も極めて早期には，正常の粘膜にまぎれてしまい，はっきり見えないことがあります。そこに色素を用いてがんを着色することで，内視鏡の画像でもはっきりとがん組織が分かるようになります。

また，ポリープ様ではない，平べったいがんも存在します。そうした場合は，がん組織の下に食塩水を注入し，がんを浮き上がらせて，内視鏡で切除しやすいようにします。また，大きながん組織を剥ぎ取るときに，胃に穴が開いてしまっては大変です。そこで通常の電気メスの先にシリコンのボールを付けて，

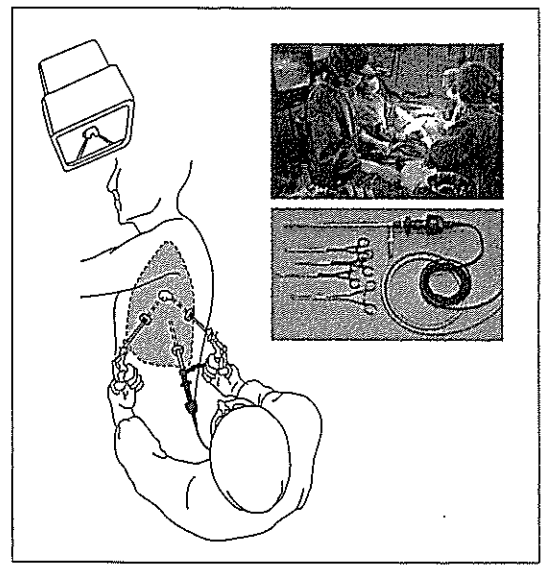

図5　体腔鏡手術による肺がんの縮小手術
（〔資料2〕より引用）

胃に穴が開かないような工夫をしたメスをがんセンターの医師が考えました。このような工夫を積み重ねることにより，より安全に内視鏡的治療が行えるようになってきました。

◉体腔鏡による治療

胃の場合は，「口」という「穴」から治療器具を入れて，治療することができます。では，それができないような臓器のがんはどうするのか。

たとえば肺がんの手術は，40～50センチもからだを開いて，術者の手が入るように肋骨も切り取って行うものです。ですから，術後も患者さんは，少なくとも切った肋骨が治るまでベッドにいる必要がありました。そこに登場したのが「体腔鏡」（肺は胸にありますから「胸腔鏡」と呼ばれます）です（図5）。3カ所に小さな穴を開け，その1つに内視鏡を入れて，別の穴からは柄の長い手術器具を挿入し，モニタの画面を見ながら治療を行います。手を入れなくてもすみますから，穴は小さいものでいいのですが，外から操作するわけですから，高度な技術が要求されます。その技術を習得する必要はありますが，患者さんの負担は極めて少なく，手術後3～4日もすれば退院できます。がんセンターでこの治療を行った患者さんは，治療の次の日にはもう歩いています。リハビリを早く行ったほうが日常生活の復帰も早期に可能となります。

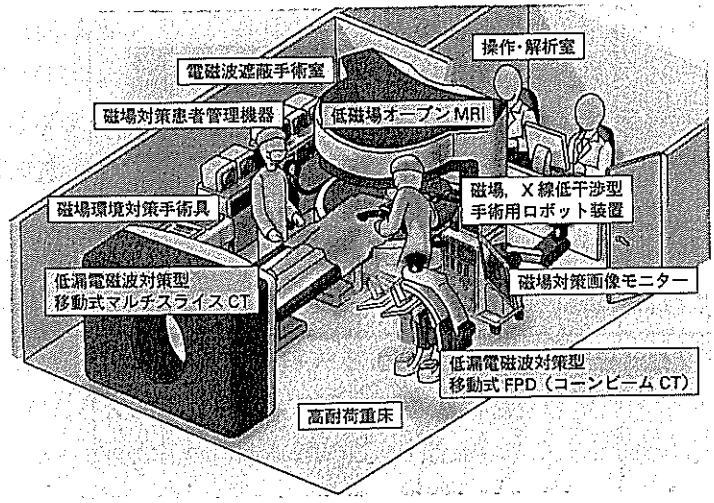

図6　近未来の手術室（初期構築手術場環境）

◉外科手術のこれから

胃がんが見つかると，胃全摘術や胃の2/3を切り取るような手術が当たり前であったのは，ほんの10年ほど前のことです。その後，多くの研究が進むことで，内視鏡や体腔鏡による治療が可能となりました。では，ここまで進んだ外科の治療がこれからどう展開していくのか。

まず「手術名人の技術均てん化」があります。手術というのは皆さんご想像のように，術者の熟練の度合いに左右される側面があり，手術が極めて上手な外科医が「ゴッド・ハンド（神の手）」と呼ばれるようなこともあります。しかし，手術を受ける人のみんながその外科医のところに行ったら，その人はもう手いっぱいで治療ができません。ですから，名人ではなくても，あるいはたくさんの手術経験を踏まなくても，普通の技術を身につけさえすれば，「名人」と呼ばれる人と同じ水準の手術ができる。こうした技術を開発する必要があります。その方法として，1つはロボット技術の導入があり，もう1つはナビゲーター，コンピュータを使っての画像解析の技術をフルに用いて，より安全に手術を行おうということで，現在研究が進められています。

たとえば骨盤の中の臓器を手術するとします。骨盤内には膀胱も直腸も，いろいろな消化管が複雑に存在します。その奥を手術しようとすると，その前にある臓器を押し分けて入っていく必要があります。ですから，まず大きく開ける必要があるのですが，「名人」と呼ばれる人は，それを極力小さくすることができます。血管を傷つけると大出血を起こしますから，指を入れただけで，

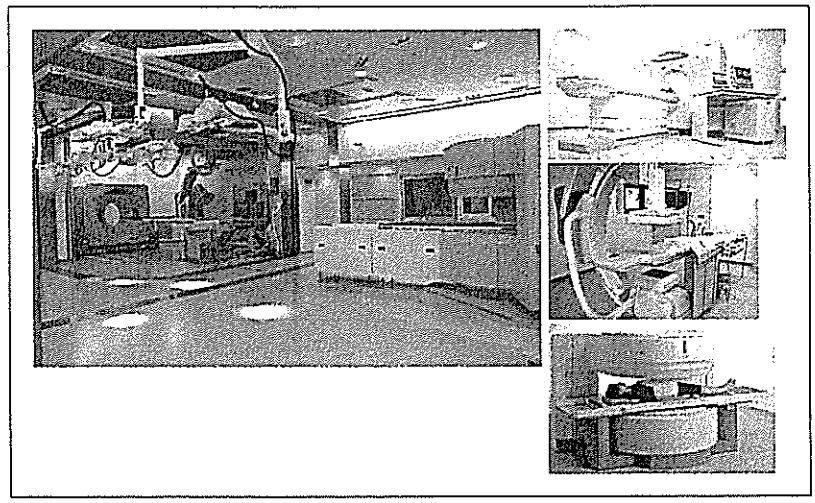

図7　国立がんセンターに設置されたMRX手術室

目で見ずにその血管をとらえて，出血しないようにクリップを入れて縛る。これも名人でなければできないことで，たくさんの経験を積み習得できる技術です。しかし，コンピュータの画像によって，手術で傷をつけてはいけない血管や神経を把握できれば，ある程度の技術さえあれば，名人でなくても安全な手術ができる。そういう方向に外科手術は進んでいくと思います。

がんセンターの小林寿光博士が2年ほど前に考案した「軟性内視鏡」という概念の治療機器（手術用ロボット装置）があります。もうすぐ実践に使えるところまで研究が進んできていますが，いままで曲げることができなかった機器を，柔らかい素材で作ることで曲げられるようになっています。こうした発想で作ったさまざまな機器を内視鏡で操作できるようになれば，より安全で，しかも治癒率の高い手術ができると考えられます。

図6は未来の手術室を予想したものですが，ロボットのアームを入れ，コンピュータで画像を作りながら操作していく。どんな臓器があって，どんな危険なものがあるかを把握しながら，安心してがんを摘出できるという環境です。しかし，そこまでにはさまざまな技術開発が必要です。たとえば画像を作る，皆さんもご存じの「MRI」という装置は，ものすごい磁気を出します。手術に用いる機器は，そうした磁気への対策がなされていなければ，適切な画像を得ることができません。がんセンターで2005年8月に「MRX手術室」という新しい手術室をつくりました（図7）。そこには「コーンビームCT」と呼ばれる，レントゲン透視ができ，しかも立体にものが見えるという新しいCTや，

全身の臓器を撮影して立体像として見せることのできるヘリカルCT，「オープンMRI」と呼ばれる，手術台が入るようなスタイルのMRIが導入されています。こうした新しいイメージング・システムをそろえた手術場をつくることで，どのようにしたら安全で，からだにやさしい手術ができるかを工夫しているわけです。

§3 切らずに行うがん治療の進歩

次に「切らずに行う治療」についてお話したいと思います。ただし，放射線治療については，先ほど池田先生からご説明がありましたので割愛させていただき，化学療法（お薬による治療）を中心にご説明したいと思います。

◎これまでの化学療法

池田先生のお話から，放射線治療というのはがんを「焼き切る」という治療法ではなく，DNAに作用し，正常細胞とがん細胞の性質のわずかな差を標的とした治療法であることがご理解いただけたと存じます。実は化学療法も同様で，正常細胞とがん細胞の，わずかな薬剤の感受性の差を利用して治療するものです。がん細胞の薬剤に対する感受性が正常細胞よりもちょっと高いという差を利用してがんをやっつけようということです。これも放射線治療と同様に，化学療法の場合でも，がんの種類によって感受性は異なります。抗がん剤の感受性が高いがんの代表にセミノーマがありますが，正常組織に影響を与えず，がん細胞にだけ感受性が高い（がん特異性が高い）という抗がん剤はそれほど多くありません。

また，手術や放射線治療は「局所治療」と呼ばれており，がん組織が存在する部位にのみ治療を施すものです。一方，化学療法は，経口や点滴で投与することになりますから，患者さんの全身に作用します。正常細胞とのわずかな差を狙うのが化学療法ですから，副作用も全身的に現れてしまう可能性が高くあります。つまり，化学療法はじゅうたん爆撃のようなもので，これをからだ全体にやったのではたまりません。

ですから，正常細胞に影響を与えず，がんにだけ作用するような薬物を開発することが，化学療法の大きな課題なのです。