Table 2. Deaths from Toxic Events in Phase 1 Oncology Trials.

Trial	No. of Trials	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events*
			no. (%)
Total	460	11,935	58 (0.49)
Cytotoxic chemotherapy			
One investigational agent	92	2,621	15 (0.57)
Multiple investigational agents	12	305	2 (0.66)
Combination of investigational and FDA-approved agents	88	2,594	20 (0.77)
FDA-approved agents only	29	925	6 (0.65)
Immunomodulator			
One investigational agent	13	235	0
Multiple investigational agents	28	730	1 (0.14)
Combination of investigational and FDA-approved agents	19	443	0
Receptor or signal transduction			
One investigational agent	51	1,565	3 (0.19)
Multiple investigational agents	7	99	2 (2.02)
Combination of investigational and FDA-approved agents	61	1,081	8 (0.74)
Antiangiogenesis			
One investigational agent	15	402	0
Combination of investigational and FDA-approved agents	9	171	1 (0.58)
Gene transfer			
One investigational agent	7	107	0
Combination of investigational and FDA-approved agents	1	5	0
Vaccine			
One investigational agent	15	297	0
Multiple investigational agents	7	218	0
Combination of investigational and FDA-approved agents	6	137	0

* Deaths include all those reported as possibly, probably, or definitely related to the treatment.

icity, with 17.4 percent of participants experiencing at least one grade 4 toxic event; vaccine trials had the lowest rate, with no grade 4 toxic events reported (Table 3). Among all 11,935 participants assessed in the 460 studies, 5251 grade 4 toxic events were reported.

FIRST-IN-HUMAN TRIALS

Of 460 trials, 117 (25.4 percent) involving a total of 3164 participants assessed for a response to therapy were considered first-in-human trials — that is, studies designed to establish initial information on toxicity and dose for agents not previously tested in humans (Table 4). The overall response rate in these studies was 4.8 percent, as compared with 13.1 percent in the other studies. The toxicity-related death rate in first-in-human studies was 0.26 percent, as compared with 0.58 percent in studies not considered first-in-human trials. Studies of cytotoxic chemotherapeutic agents made up the largest group of first-in-human trials (36.8 percent). Of the vaccine studies sponsored by the Cancer Therapy Evaluation Program, 82.1 percent were first-in-human trials.

Table 3. Grade 4 Toxic Events in Phase 1 Oncology Trials.

Trial	No. of Trials	No. of Patients Assessed for Toxic Events	Patients with a Grade 4 Toxic Event	Average No. of Grade 4 Toxic Events per Patient
			%	
Total	168	3465	14.3	1.9
Cytotoxic chemotherapy				
One investigational agent	20	408	15.0	1.6
Multiple investigational agents	3	23	4.3	2.0
Combination of investigational and FDA-approved agents	17	475	14.5	1.8
FDA-approved agents only	3	159	34.0	2.4
Immunomodulator				
One investigational agent	2	43	2.3	1.0
Multiple investigational agents	10	207	9.7	2.2
Combination of investigational and FDA-approved agents	5	101	4.0	1.8
Receptor or signal transduction				
One investigational agent	29	839	13.0	1.7
Multiple investigational agents	6	67	19.4	2.0
Combination of investigational and FDA-approved agents	51	752	18.1	2.0
Antiangiogenesis				
One investigational agent	9	143	5.6	1.6
Combination of investigational and FDA-approved agents	6	101	17.8	1.8
Gene transfer				
One investigational agent	1	26	11.5	1.7
Combination of investigational and FDA-approved agents	1	5	0	0
Vaccine				
One investigational agent	3	20	0	0
Multiple investigational agents	2	96	0	0

TRIALS WITH FDA-APPROVED AGENTS

Overall, 213 studies (46.3 percent) included at least one FDA-approved anticancer agent. Response rates were higher in trials with FDA-approved agents than in trials without FDA-approved agents (Table 5). These studies had an overall response rate of 17.8 percent, as compared with 4.8 percent for studies not including FDA-approved anticancer agents. The toxicity-related death rate was higher (0.65 percent) than for trials that did not include FDA-approved anticancer agents (0.35 percent).

DISCUSSION

We comprehensively reviewed phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program between 1991 and 2002. The overall response rate in these trials was 10.6 percent, which is higher than previously reported, whereas the toxicity-related death rate, 0.49 percent, is similar to that of previous reports. Rates of response and of toxicity-related death among classic phase 1 trials of single chemotherapeutic agents are similar to those reported in other reviews, but classic trials account for only 22 percent of participants in this review.

Response rates in phase 1 oncology trials have been reported to be 4 to 6 percent, with toxicity-related death rates reported to be 0.5 percent or lower.[8-16] In our review, however, we found that response rates in recent phase 1 oncology trials exceeded 10 percent, with stable disease or less-than-partial re-

Table 4. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials Involving the First Use of an Agent in Humans.

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate*	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events†
			%		*no. (%)*
Total					
First use of an agent in humans	117	3164	4.8	3498	9 (0.26)
All other trials	343	7238	13.1	8437	49 (0.58)
Cytotoxic chemotherapy					
First use of an agent in humans	43	1298	5.0	1422	7 (0.49)
All other trials	178	4359	15.0	5023	36 (0.72)
Immunomodulator					
First use of an agent in humans	16	404	7.4	431	1 (0.23)
All other trials	44	842	16.6	977	0
Receptor or signal transduction					
First use of an agent in humans	27	742	3.8	853	1 (0.12)
All other trials	92	1621	8.0	1892	12 (0.63)
Antiangiogenesis					
First use of an agent in humans	8	200	7.0	228	0
All other trials	16	270	7.0	345	1 (0.29)
Gene transfer					
First use of an agent in humans	0	0	0	0	0
All other trials	8	92	3.3	112	0
Vaccine					
First use of an agent in humans	23	520	3.1	564	0
All other trials	5	54	1.9	88	0

* The overall response rate includes both complete and partial responses.
† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

sponse having been achieved in an additional 34.1 percent of participants. Rates of toxicity-related death have not increased over time, and more than 85 percent of participants had no grade 4 toxic events. As compared with other reviews, these data suggest that participants may benefit more from current phase 1 oncology trials than previously believed.

A recent review of single-agent trials showed that there was a decrease in tumor-response rates over time,[13] which was attributed to the use of newer, more specific agents and changes in trial design. In our review, response rates per year varied without a clear pattern. When these rates were grouped in three-year intervals, there was a decrease in complete or partial responses from 1991 to 2002 but an increase in rates of stable disease. Little change in the benefit to participants over time was seen when response rates were grouped with stable disease.

In our view, it is inaccurate to refer to phase 1 oncology studies as if they are all similar to one another. Nearly half of the trials we studied included at least one FDA-approved agent, and less than half included chemotherapeutic agents. Different types of phase 1 oncology studies are associated with very different response rates. For instance, the response rate among patients who were treated with immunomodulators was 13.6 percent, yet the rate was just 3.0 percent for patients treated with vaccines. Trials that included one or more FDA-approved anticancer agents showed higher response rates than did those involving only investigational agents. For these reasons, it may be misleading to summarize phase 1 oncology trials with the use of a single response rate.

Risk, as measured by toxicity-related death rates and grade 4 toxic events, also varies according to the type of trial. The average toxicity-related death rate for trials of cytotoxic chemotherapeutic agents was 0.67 percent but just 0.07 percent for those in-

Table 5. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials, According to Whether FDA-Approved Agents Were Used.

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate*	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events†
			%		*no. (%)*
Single investigational agent	193	4580	4.2	5227	18 (0.34)
Multiple investigational agents	54	1203	7.1	1352	5 (0.37)
Combination of investigational and FDA-approved agents	184	3827	15.8	4431	29 (0.65)
FDA-approved agents only	29	792	27.4	925	6 (0.65)

* The overall response rate includes both complete and partial responses.
† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

volving immunomodulators, and no toxicity-related deaths were reported in gene-transfer or vaccine trials. Grade 4 toxic events were more common in chemotherapy trials, especially those involving multiple agents, than in all other trials. Trials of FDA-approved drugs, which evaluated the safety of higher doses or combinations of drugs, appeared to be associated with the highest rates of toxicity (a death rate from toxic events of 0.65 percent, vs. 0.35 percent for other trials) but also had the highest overall response rate (17.8 percent, vs. 4.8 percent for other trials). Overall, newer, nonchemotherapeutic agents are associated with lower rates of toxic events.

Classic phase 1 studies of single investigational chemotherapeutic agents, which were the only trials included in previous reviews, showed an overall response rate of 4.4 percent and a toxicity-related death rate of 0.57 percent. These rates are almost identical to those previously reported.[8-16] In this study of trials sponsored by the Cancer Therapy Evaluation Program and initiated between 1991 and 2002, classic phase 1 trials accounted for only 22 percent of all participants. Similarly, the testing of investigational agents never before studied in humans is commonly thought of as a defining characteristic of phase 1 oncology trials. In our review, these first-in-human studies represented less than a quarter of phase 1 studies and enrolled less than a third of participants. Response rates, but also toxicity-related death rates, are lower in studies that test agents for the first time in humans than in those that do not test agents for the first time.

When the risks and benefits associated with phase 1 oncology trials are weighed, factors other than response rates and toxicity should be taken into account. Investigational treatments may have clinically meaningful benefits — reduced pain, increased appetite, energy, and activity, weight gain, reduced fatigue, or increased ability to perform daily activities.[20,25,26] Some of these benefits might accrue from research participation itself; for some persons, contributing to research and potentially helping future cancer patients may also be an important benefit.[27] At the same time, participation in research may involve additional burdens: multiple visits or long hours at the clinic, unpleasant procedures, and the possible financial costs associated with participation in research studies.[28]

This study has several limitations. First, our data are derived only from trials sponsored by the Cancer Therapy Evaluation Program. Although the program is a major sponsor of phase 1 oncology trials in the United States[29] and the use of data from the program avoids publication bias, any differences that might be found in the phase 1 trials with other sponsors have not been captured. It is possible that the response rates associated with trials of promising agents sponsored by pharmaceutical companies could be higher than those reported here. Second, for trials involving gene transfer, the findings should be interpreted with caution because of the small number of trials and the possibility that outliers influenced the data. Finally, our reporting of grade 4 toxic events is limited. Patient-specific data on grade 4 toxic events came from one monitoring source, which, although it includes some first-in-human trials, is generally used to monitor later phase 1 studies and may not be entirely representative of phase 1 oncology studies. Moreover, the data on grade 4 toxic events are reported without distinguishing among the types of toxic events.

Since not all toxic events have similar medical consequences, evaluation of the risks in phase 1 trials should include both the types and the frequency of events experienced by participants.

In conclusion, reliance on a single estimate of the response rate or the toxicity-related death rate for phase 1 oncology trials is misleading, since rates of response and toxicity vary according to the type of trial. Potential participants and their families, oncologists, investigators, members of institutional review boards, ethicists, and others interested in weighing the risks and benefits of phase 1 studies and making decisions about their acceptability should be aware of the complexity and variety of such trials, know the details about the trial they are considering, and carefully evaluate all relevant risks and benefits.

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Interaction model between elastic objects for haptic feedback considering collisions of soft tissue

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Summary The simulation of organ–organ interaction is indispensable for practical and advanced medical VR simulator such as open surgery and indirect palpation. This paper describes a method to represent real-time interaction between elastic objects for accurate force feedback in medical VR simulation. The proposed model defines boundary deformation of colliding elements based on temporary surface forces calculated by temporary deformation. The model produces accurate deformation and force feedback considering collisions of objects as well as prevents unrealistic overlap of objects. A prototype simulator of rectal palpation is constructed on general desktop PC with a haptic device, PHANToM. The system allows users to feel different stiffness of a rear elastic object located behind another elastic object. The results of experiments confirmed the method expresses organ–organ interaction in real-time and produces realistic and perceivable force feedback.

1. Introduction

Virtual reality (VR) technologies enable physicians to interact with flexibly customized simulated environments based on visual, auditory and haptic feedback without potentially harmful contact with real patients. For this reason, VR-based simulation has

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attracted considerable attention as a key technology for the advancement of medical treatments and improvement of quality of human life. In the field of medicine, VR simulators are applied for uses such as education, therapy and rehabilitation, procedural training, surgical planning, rehearsal, and interoperative support [1,2]. Though many simulators have been developed, and a few even commercialized [3–6], most have dealt with single organ objects without handling collisions between multiple organ objects [4–9]. This makes them unsuitable for VR simulation of the human body, a system with many organs which often collide. Haptic feedback is especially important in delicate surgical pressures requiring fine sensations, especially when slightly excessive pressure can injure a patient. Haptic sensation is also significant in palpation: as the physician examines the characteristics of an organ beneath the body surface with the tips of his or her fingers, collisions of the soft tissues are inevitable. This paper proposes a model of interaction between soft tissues, in order to provide a virtual environment simulating haptic feedback from the collisions of soft tissues.

Palpation and surgery simulations require the use of physics-based deformable models to accurately calculate the deformation and force caused by physical action on soft tissue. This adds considerably to the challenge of simulation, however, as physics-based deformation models generally require more computations than the geometry-based deformation models used in computer graphics. A comprehensive simulation of multiple characteristics of soft tissue all at once is tremendously difficult. Elasticity, a property related to force and displacement, is one of the most important characteristics of soft tissue. Accordingly, this paper treats soft tissues as elastic objects and seeks to model the interactions between them. The interaction model presented here must perform three important functions.

1. To allow interactive manipulation in real-time.
2. To take into account the physical properties of colliding objects.
3. To produce an adequate visual reality.

Interactive manipulation, an operation performed in both palpation and surgery, requires real-time computation of soft tissue deformation and reaction forces. When a soft elastic object and a hard object collide, the former deforms more, as shown in Fig. 1. In addition, the reaction forces during the collision depend on the extent of the deformations in the collision area. Thus, the interaction model must represent the deformation on the basis of the physical properties of both elastic objects. Visual reality is one of the most important functions for effective simulation. Excessive invasion of colliding objects must be avoided.

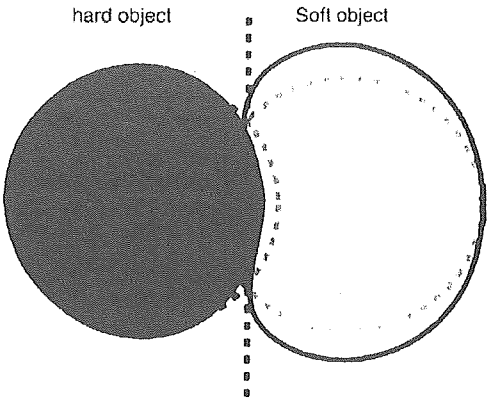

Fig. 1 Deformation caused by collision of elastic objects with different stiffnesses. The soft object deforms more than the hard object.

In this paper, we propose an interaction model between elastic objects that performs the above functions. After describing the proposed model, we evaluate its performance and validity by applying it to the development of a rectal palpation simulator.

2. Background

The simulation of physical phenomena has been a key technology to enhance visual and haptic reality in medical simulations. Studies in biomechanics and computer graphics in the field have devoted particularly close attention to soft tissue modelling [10–13]. Many kinds of physics-based deformable models have been proposed for deformation and force feedback [13–19]. One such model, the mass-spring model, represents an object as points of mass joined by springs [15,16]. Though effectively applied for a variety of uses, the model does not perform adequately when simulations require accurate calculation of deformation and reaction force [7]. The mass-spring model also requires fine-tuning of physical parameters to represent certain physical characteristic, and improper parameter values lead to system instability. The boundary element model (BEM) and long element model (LEM) have also been proposed for deformation and force feedback. Though both are capable of fast computation [12,17,18], they have limitations in surgical and palpation simulations. An organ with internal lesions possesses several distinct physical properties, yet BEM assumes that an organ is homoge-

neous. Organs also tend to be complex in shape, yet LEM is poor at representing anything but simple shapes. A fourth alternative, the finite element (FE) model, has been regarded as the most accurate model for many years, but it is also the most computationally expensive [19]. Thankfully, recent progress of computers and computational methods has improved the outlook. With innovations such as condensation and Hirota's method [19,20], computation and simulation with haptic interaction can now be performed in real-time by the FE method.

Thousands of studies in mechanical engineering and VR have focused on the interaction between elastic objects. None, however, have been able to theoretically solve the contact problem. While the Hertz theory [21] is sometimes applied to the contact problem for convenience, it cannot be applied for arbitrary shapes. In VR simulation, several methods for describing collision responses have been proposed for the modelling of interactions between elastic objects [22,23]. Sibille et al. solve the contact problem by projecting colliding nodes to a plane which passes the barycenter of the colliding nodes and is oriented perpendicularly to the average normal vector of the colliding nodes (see Fig. 2) [22]. Though effective in curtailing the invasion of colliding objects, this method models deformation and haptic force based on geometrical information rather than information on the actual physical properties of the objects. Joukhadar et al. apply forces proportional to the invading volume of colliding objects onto the surfaces of the objects [23]. Their method fails to consider the physical properties of the volume, however, and it does not permit real-time computation of the invading volume (as they describe in their paper). Overall, the existing methods do not seem to provide adequate solutions for the above functions.

None of the rectal palpation simulators so far developed [24,25] have attempted to simulate the deformation and interaction between the rectum and prostate. This functional limitation compromises the flexibility of the simulation conditions and obfuscates the visual and haptic realities.

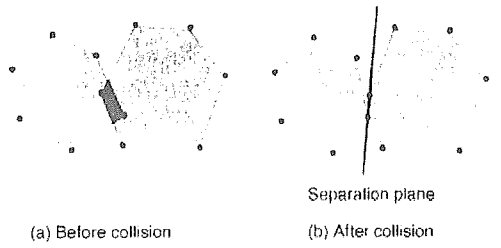

Fig. 2 Geometrical interaction model by Sibille et al.

3. Design considerations

There are two ways to represent multiple organs: with a single elastic object representing multiple organs or with multiple elastic objects representing multiple organs.

Several simulators [26,27] use the former method, treating multiple organs as a single elastic object. Methods which rely on the filling of finite elements into gaps between elastic objects are unsuitable in situations where contact regions often change. When the contact regions of organs are changed, the topology of each object changes and the global stiffness matrix needs to be reassembled. It also becomes necessary to re-compute the pre-processing stage, including the inversion of the global stiffness matrix [20]. This presents a significant problem, as the re-computation is generally slower than the haptic refresh rate (about 300 Hz) [2]. As an added problem, limitations in storage volumes would make it extremely difficult to pre-compute and store all of the possible models. Given the representation capabilities and resources of today's computers, we conclude that multiple organs must be modelled as multiple independent objects.

4. Computational methods

4.1. Interaction model between elastic objects

Our interaction model between elastic objects focuses on physics-based force feedback taking into account the physical properties of colliding objects. We define "interaction" as the process which determines the deformation in the collision area based on the physical properties of the colliding objects. Though the extent of deformation by collisions is theoretically unsolved, as mentioned earlier, it presumably depends on the physical properties of the colliding objects. Thus, the deformation is determined based on surface forces temporarily calculated by specifying temporary displacements, where surface forces are derived from physical properties and can be calculated rapidly by the finite element method using Hirota's model [20]. Collisions are detected by testing whether a node has moved into the internal side of the surface of another object.

The illustration in Fig. 3 outlines the proposed model. The actual displacements of the colliding elements of object A, B are calculated as $|\vec{b}| : |\vec{a}|$. The displacements are thus given to the elements

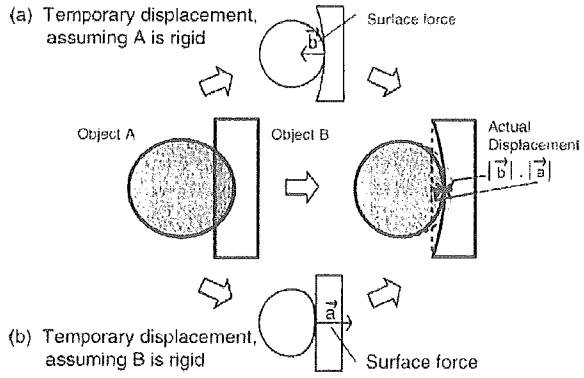

Fig. 3 Interaction model between elastic objects. Object A is regarded as a rigid body and surface force $\vec{b}$ is calculated on object B (see (a)). Object B is regarded as a rigid body and surface force $\vec{a}$ is calculated on object A as well (see (b)). The actual displacements of the colliding elements of object A, B are calculated as $|\vec{b}| : |\vec{a}|$ and given to the elements and transferred.

and the elements are transferred, as the surface forces indicate the degree of resistance to invasion of the colliding objects.

4.2. Calculation of interaction

The calculation of interaction consists of the following procedures:

1. Detection of colliding elements.
2. Calculation of temporary displacements.
3. Temporary deformation.
4. Calculation of temporary surface forces.
5. Calculation of actual displacements.

The temporary deformation and the temporary surface forces are based on the finite element method, a method which produces accurate deformation and reaction forces. The simulation in this study represents soft tissue as tetrahedral meshes. The detection of the colliding elements depends on the collision detection algorithm. The calculation of interaction depends on external methods, as shown in Fig. 4.

The steps in each procedure are outlined below.

- Detection of colliding elements.
  Collisions are checked by testing whether a node has moved inside a polygon of another object. If collisions are detected on both sides of the objects, the following procedures are carried out.
- Calculation of temporary displacements.
  If a collision between a node 'X' of object A and a polygon 'S' of object B is detected, the polygon S is displaced perpendicularly, as shown in Fig. 5.

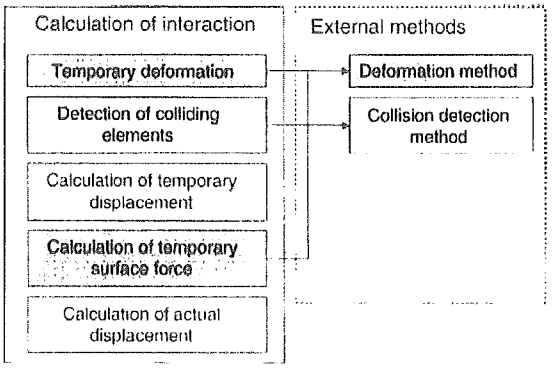

Fig. 4 The components of the interaction method and their dependence on the deformation and collision detection methods.

The vector of temporary displacement $\overrightarrow{u_{temp\_B}}$ is:

$$\overrightarrow{u_{temp\_B}} = \overrightarrow{FX} \tag{1}$$

where F is the perpendicular foot of nodes X to S.

Temporary displacements of nodes P, Q, and R are $\overrightarrow{u_{temp\_B}}$. The new positions, P′, Q′, and R′ are as follows.

$$\begin{aligned} \overrightarrow{P'} &= \overrightarrow{P} + \overrightarrow{u_{temp\_B}} \\ \overrightarrow{Q'} &= \overrightarrow{Q} + \overrightarrow{u_{temp\_B}} \\ \overrightarrow{R'} &= \overrightarrow{R} + \overrightarrow{u_{temp\_B}} \end{aligned} \tag{2}$$

In the same way, a temporary displacement $\overrightarrow{u_{temp\_A}}$ is calculated and given to the polygon of object A.

- Temporary deformation.
  The temporary deformation is calculated based on the finite element method using Hirota's model [20] with temporary displacements.
- Calculation of temporary surface forces.

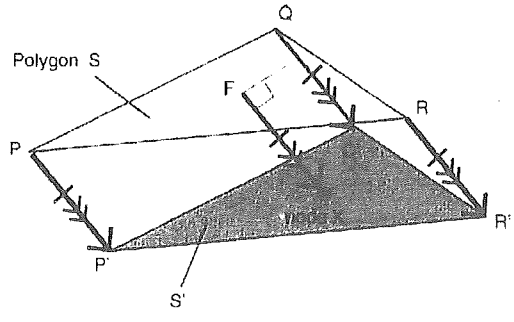

Fig. 5 Temporary displacement of the polygon. The polygon S is transferred perpendicularly with distance between the points F and X.

A temporary surface force $\vec{f}$ of polygon S is defined as an average vector of nodal forces on P′, Q′, R′:

$$\vec{f} = \frac{\vec{f_P} + \vec{f_Q} + \vec{f_R}}{3} \tag{3}$$

where $\vec{f_P}, \vec{f_Q}, \vec{f_R}$ are the nodal forces on P′, Q′, R′. This calculation gives the temporary surface forces based on the stiffnesses.

- Calculation of actual displacements.

  Actual displacements of colliding elements of the object A, B are calculated as $|\vec{f_B}| : |\vec{f_A}|$ and given to the elements, as surface forces indicate the degree of resistance to invasion of colliding objects.

To visualize the contact boundary of the colliding area realistically, the simulation displaces the polygon of only one object and the node of another object, instead of displacing the polygons of both objects. The sum of the displacements of the polygon and the node are $\overrightarrow{u_{temp\_B}}$. The node is positioned on the polygon. Accordingly, this method avoids invasion and separation between the polygon and node. It also reduces the computation of the finite element method, as the displacement of only one polygon instead of two results in the displacement of fewer nodes (three nodes are displaced for each polygon). Displacements $\vec{u_A}$ and $\vec{u_B}$ of colliding elements of object A, B are as follows:

$$\vec{u_A} = -\frac{|\vec{f_B}|}{|\vec{f_A}| + |\vec{f_B}|}\overrightarrow{u_{temp\_B}} \tag{4}$$

$$\vec{u_B} = \frac{|\vec{f_A}|}{|\vec{f_A}| + |\vec{f_B}|}\overrightarrow{u_{temp\_B}} \tag{5}$$

where $\overrightarrow{u_{temp\_B}}$ is a vector of temporary displacements, $\vec{f_A}$ and $\vec{f_B}$ are surface forces on the colliding polygons of object A, B, respectively, $\vec{u_A}$ is given to the node of object A, and $\vec{u_B}$ is given to the component nodes of the polygon of object B.

This method enables us to determine the deformations in the collision area with due consideration of the physical properties of the colliding objects.

5. System description

5.1. Structure of the system

As previously mentioned, collisions between multiple organs are especially important to consider in the haptic displays of palpation simulations. Our group addresses this challenge by developing a rectal palpation simulator and using it to evaluate the proposed model. Rectal palpation is a very common and important manipulation in urology. A physician inserts his or her index finger through the anus of the patient and palpates the prostate gland indirectly through the rectal wall to assess the condition of the gland.

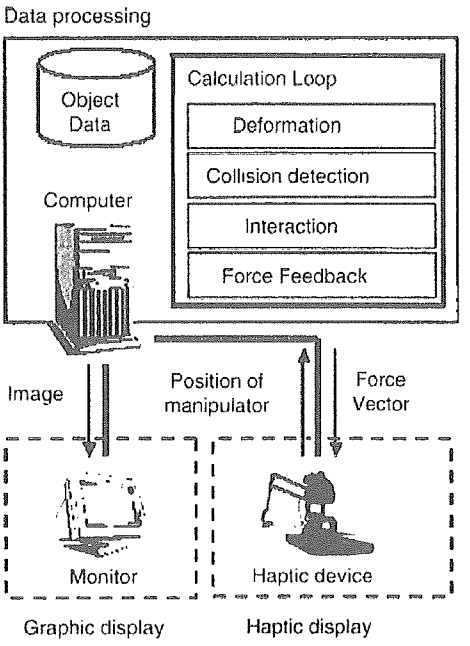

Fig. 6 Structure of the rectal palpation simulator. The figure shows the three system components used to simulate organ–organ interaction with a haptic display: a data processing unit, graphic display unit, and haptic display unit. The data processing unit interacts with the other units.

Fig. 6 illustrates the structure of our rectal simulator system. The system consists of a graphic part, a haptic part, and a data processing part. The data processing program is coded in Visual C++ and run on a general computer with dual Pentium III 933 MHz CPUs and 1 GB of main memory. The system is equipped with a PHANToM Premium 1.0A haptic device (SensAble Inc., Woburn, MA).

Organ object data are generally obtained from medical imaging modalities such as CT, MRI, and cross-sectional images. *Amira*™ (Mercury Computer Systems Inc. [28]) semi-automatically segments the data and divides them into tetrahedral elements for finite element computations, and stores geometry data such as vertices (nodes), tetrahedrons, and surface triangles (polygons). Real-time simulation with haptic display is achieved by applying a static and linear model and fast computation techniques such as condensation [19] and Hirota's method [20].

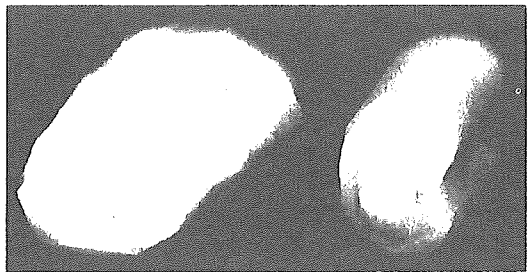

Fig. 7 Rectal object (left) and prostate object (right) used for the rectal palpation simulation.

Table 1 Finite element representation of objects

Model	Total nodes (free surface nodes)	Tetrahedron
Rectum	282 (207)	889
Prostate	360 (110)	1312

Inverse stiffness matrices representing the stiffness of objects are pre-computed and stored for the physics simulation. The manipulator position is updated from a haptic device. The reaction force, a parameter calculated in the physics simulation, is conveyed to the user kinaesthetically via the haptic device.

5.2. Modelling of objects

Fig. 7 shows the rectal and prostate objects, the principal objects in the simulation of rectal palpation. The rectal object is re-constructed from RGB data from the Visible Human Dataset [29]. The prostate object is generated by piling up cross-sectional images of the prostate. Table 1 shows the number of nodes in the finite element representation of the objects. The "free surface nodes" are non-fixed nodes located on the surface.

A Poisson ratio of 0.40 is given to both objects in view of the high water content and low compressive features of human organs [30]. A Young modulus of 1.0 MPa is given to the rectal object and 1.0 and 5.0 MPa are given to two types of prostate objects, respectively, one representing a normal prostate and the other representing a hardened gland.

6. Status report

6.1. Calculation time

We examined the calculation time when a sphere-shaped object A and cubic object B collide. Both objects are in contact and a moving point pushes a point of object A from the opposite side of the contact region. The calculation times for deformation, interaction, and total computation of one cycle are shown in Fig. 8.

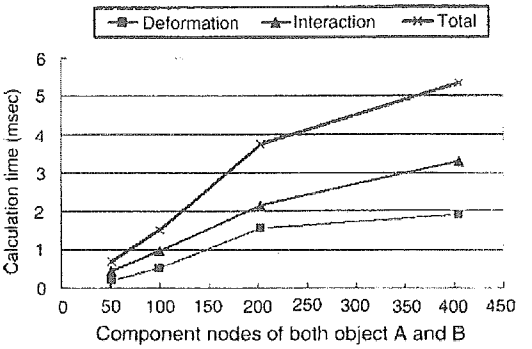

Fig. 8 Calculation times for deformation, interaction, and total computation. The total calculation time for the two 200-noded objects, less than 4 ms, indicates that the method is applicable to objects up to this scale and level of complexity.

The horizontal axis indicates the number of component nodes of both objects A and B. The vertical axis indicates the calculation time (ms). Only about 10% of the nodes of both objects are fixed, hence 90% of the total are free nodes on the surface.

As the graph shows, the time duration of the deformation and interaction increases linearly with the number of nodes. The time required for total computation reaches 4 ms, the limit for stable haptic feedback with this stiffness, when the object has approximately 200 component nodes.

By omitting calculation for regions where the deformation effects are trivial, however, it becomes possible to simulate collisions between two objects with more than 200 nodes within the 4 ms limit. The calculation times for deformation, interaction, and total computation in the rectal palpation simulator without this omission are 1.17, 1.62, and 2.88 ms, respectively.

6.2. Experiments based on simulation

The experiment verifies that the stiffness of a neighbouring object which cannot be touched directly (in this case prostate object) affects the value of the reaction force. Fig. 9 shows a view of the simulation.

In this experiment, the simulator moves the point of manipulation from the initial position towards the prostate object to a depth of 0.5 cm and then calculates the reaction force imposed on the point. The simulation is carried out under three simulated prostate conditions.

Condition 1: No prostate object is set.

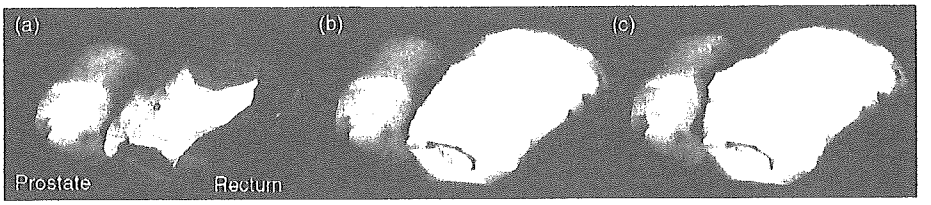

Fig. 9 Simulation view of the rectal palpation simulator. (a) The rectal object is displayed transparently. The sphere in the center of the image is a point of manipulation located in the initial position. (b) The two objects are located in the initial position. (c) The point of manipulation pushes the inner wall of the rectal object towards the neighbouring prostate object, resulting in the deformation of both objects.

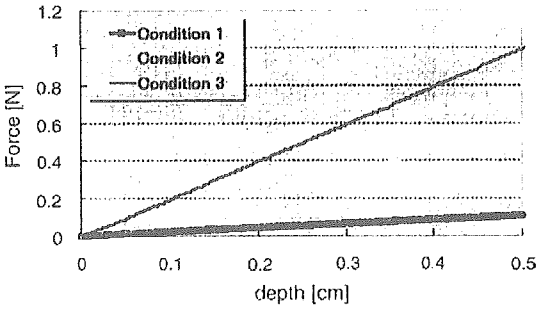

Fig. 10 Reaction forces produced by the proposed model. The forces produced under condition 2 (the softer prostate object) and condition 3 (the harder prostate object) differ in the virtual environment.

Condition 2: Soft prostate object (1.0 MPa Young modulus) is set.
Condition 3: Hard prostate object (5.0 MPa Young modulus) is set.

Soft and hard prostate objects represent a regular prostate gland and a hardened prostate gland due to cancer, respectively.

Fig. 10 shows the values of the haptic forces in each case when applying the proposed model. Fig. 11 shows the values in the model proposed by Sibille et al. [22] (mentioned in Section 2).

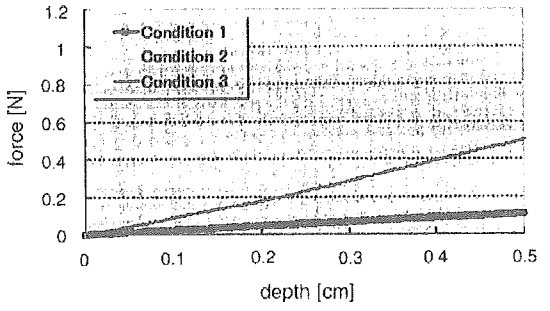

Fig. 11 Reaction force produced by Sibille's model. The forces produced under conditions 2 and 3 are almost identical.

The horizontal axis represents the depth (cm) of pushing of the rectal object and the vertical axis represents the haptic force (N), a parameter which takes a positive value when the force opposes the direction of the pushing. The thick black, white, and grey lines indicate the forces produced under conditions 1, 2, and 3, respectively. In the case of Sibille's model [22], the forces produced under conditions 2 and 3 are almost the same. As a consequence, the plotted lines for conditions 2 and 3 overlap in Fig. 11.

As seen in Fig. 10, the forces produced under conditions 2 and 3 differ when applying our newly proposed model. Simply put, the hard prostrate object produces a stronger force than the soft one. On the other hand, the Fig. 11 shows that with the Sibille's model the forces of both cases do not differ. The greater hepatic force produced by this model under condition 3 can be attributed to the consideration of the stiffness of the neighbouring object within this model.

6.3. Subjective experiments

Our subjective experiments confirmed that human examiners can perceive a difference in force based on consideration of the stiffness of a neighbouring object.

The examinations were performed by 15 medical students with no experience in using haptic devices. The examiners were asked to distinguish the stiffness of prostate objects through haptic sensation with their dominant hands. Each examiner touched the prostate object indirectly under conditions 2 and 3 (simulated by the system in random order), then indicated which felt harder. An indication that the hard prostate model (condition 3) felt harder was considered the correct answer. Each examiner performed four tests in each interaction model; the proposed model and the existing model by Sibille et al. [22].

To prevent the movement and position of the hand from influencing the result, the bottom of the

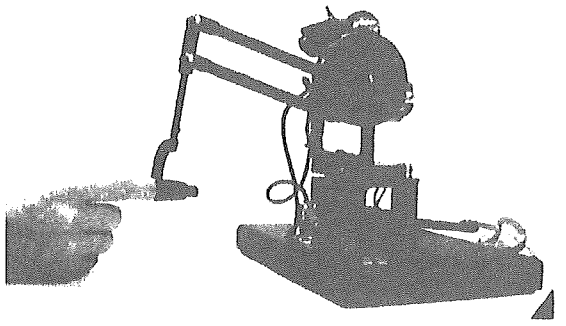

Fig. 12 Hand position and manipulation protocol during the experiments.

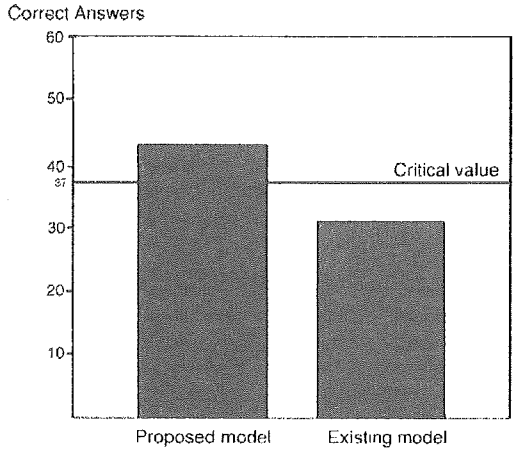

Fig. 13 Results of experiments.

dominant hand was fixed on the desk in a position that enabled leftward and rightward movement of the forefinger, as shown in Fig. 12.

The recorded differences in hand sensations between the hard and soft prostate conditions were tested for each model by a pair test at $p < 0.05$. Fig. 13 shows the experimental results. The critical value, defined as the value that a test statistic must exceed to reject the null hypothesis, was 37 out of 60 samples. In the tests using the proposed model, 43 out of 60 answers were correct (exceeding the critical value). In the tests using Sibille's model, only 31 out of 60 answers were correct (falling below the critical value). We thus confirmed that the proposed model can represent the forces on the basis of the stiffness of a neighbouring object in a manner that people can perceive.

7. Lessons learned and future plans

Nakao et al. [31] have reported that skilled cardiovascular surgeons can accurately recall and identify the relative levels of stiffness of a normal aorta and hardened aorta through the sense of touch. In the present experiments using a simulator of rectal palpation, we had the tests performed by skilled urologists on the assumption that they could accurately recall the tactile sensations of the fingertip when pushing the prostate through the rectal wall. Their answers indicated that the sensation of pushing the simulated prostate object was similar to the real sensation. One examiner commented, however, that the sensation of the simulated prostate examination was more realistic when the rectal object could be smoothly stroked. This seemed to be due to the low resolution of the rectal model, a limitation which resulted in large changes in the direction of the force vector. In the future it will be desirable to develop an efficient algorithm of the proposed model and apply a multiresolution method to reduce computations. In any case, the results of our evaluation suggest that the proposed model produces realistic haptic force when the examiner pushes organs. Needless to say, however, further improvement of the system is desirable.

Physicians have also suggested that the palpation simulator would be useful to discuss with many physicians, now that recent trends to promote patient rights have reduced the opportunities for more than three physicians to palpate the same patients. Moreover, the detection of internal lesions of the prostate facilitates advanced diagnosis. The proposed system also allows the setting of different physical parameters inside organs. Thus, a future focus of study will be the application of this palpation system with an internal lesion model.

This paper proposed an interaction model for colliding elastic objects designed to produce haptic feedback in consideration of the physical properties of the colliding objects. The interaction model determines boundary deformations by calculating temporary displacements and enables the calculation of the reaction force on the basis of the physical properties of the colliding organ objects. The simulation results confirmed that the proposed method could simulate collisions of two 200-noded FEM objects in real-time. Subjective evaluation using a rectal palpation simulator implementing the proposed method confirmed that the proposed method could express the difference of stiffness of a rear object hidden behind another elastic object in a manner perceivable to a human being. The method will be useful for advanced simulators requiring accurate visual and haptic feedback.

Acknowledgements

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British Journal of Cancer (2005) 92, 1782–1784

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Short Communication

No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan

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In a pooled analysis of two prospective studies with 88 658 Japanese men and women, fruit and vegetable consumptions, were not associated with a lower risk of colorectal cancer (705 cases); multivariate relative risk (95% confidence interval) for the highest *vs* the lowest quartile of intake being 0.92 (0.70–1.19) and 1.00 (0.79–1.27), respectively.
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Keywords: fruit; vegetable; colorectal cancer; prospective study; epidemiology

Although fruit and vegetables have been suggested to confer protection against colorectal cancer, recent prospective studies in Western populations found no or limited associations (Michels *et al*, 2000; Voorrips *et al*, 2000). In Japan, mortality from colorectal cancer increased during 1950–2000, especially in men (age-adjusted rate per 100 000 of 2.9–14.4 for colon and 5.6–9.3 for rectum in men; 3.3–9.5 for colon and 4.2–4.1 for rectum in women) (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor, and Welfare of Japan, 2003). Dietary factors may play a part in this increase, but the role of fruit and vegetables remains unclear. We therefore examined the association between fruit and vegetable consumption and the risk of colorectal cancer in the Japan Public Health Center (JPHC) prospective study on cancer and cardiovascular disease.

MATERIALS AND METHODS

The JPHC study has two population-based cohorts, and study designs are described in detail elsewhere (Otani *et al*, 2003). Briefly, Cohort I started in 1990 and included 40 106 subjects (19 345 men and 20 761 women) who were 40–59 years of age, lived in four Public Health Center districts, responded sufficiently to a self-administered questionnaire, and had no history of cancer (73.7% of the eligible subjects). Cohort II started in 1993 and included 48 552 subjects (23 180 men and 25 372 women) who were 40–69 years of age, lived in five Public Health Center districts, responded sufficiently to a self-administered questionnaire, and had no history of cancer (77.9% of the eligible subjects).

Cohort I questionnaire asked about the average consumption during the previous month of 44 food items including two fruit (fruit and fruit juice) and five vegetables (green leafy vegetables, yellow vegetables, white vegetables, pickled vegetables, and vegetable juice). Cohort II questionnaire asked about the average consumption during the previous month of 52 food items including three fruit (apples, oranges, and fruit juice) and six vegetables (green vegetables, carrot, tomatoes, green pickled vegetables, other pickled vegetables, and vegetable juice). The questionnaires had six frequency categories for fruit juice and vegetable juice that ranged from 'rarely' to '5 glasses day^{-1}', and four (Cohort I) or five (Cohort II) categories for other items that ranged from 'never' or 'rarely' to 'almost everyday'. The amount of consumption of total fruit and total vegetables (g day^{-1}) were calculated from these responses. We documented the questionnaire assessment of fruit and vegetable consumption to be reasonably valid (Kobayashi *et al*, 2002).

We followed up vital and residential status of subjects and incidence of cancer until the end of 1999. During 694 074 person-years of follow-up from the two cohorts, 705 cases of histologically confirmed colorectal cancer (456 colon and 249 rectum) were identified. Five percent of the subjects moved out of the study regions and 0.04% were lost to follow-up.

We used Cox's regression to compute from each cohort relative risk (RR) and 95% confidence interval (CI) of colorectal cancer according to quartiles of total fruit or vegetable consumption with adjustment for potential confounders. We pooled these estimates to obtain summary measures using inverse-variance weighting. As we observed no differential findings between the two cohorts, we present the pooled results only. This study has approximately 80% statistical power, with the two-sided α-error level of 5%, in detecting a true RR of 0.75 among the highest *vs* lowest quartiles of total vegetable consumption.

RESULTS

Compared with men in Cohort I in the lowest quartile of total vegetable consumption, men in the highest quartile were more likely to engage in sports and use vitamin supplements, less likely to be current smokers, and consumed higher amount of meats and fish, but lower amount of cereals. The men in the two groups did not differ with respect to age, body mass index, or the prevalence

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Table 1 Pooled multivariate RR and 95% CI of colorectal cancer for total fruit and total vegetable consumption[a]

	Quartiles of total fruit consumption					Quartiles of total vegetable consumption				
	Lowest	**Second**	**Third**	**Highest**	**Trend *P***	**Lowest**	**Second**	**Third**	**Highest**	**Trend *P***
Person-years in Cohort I	94 449	95 035	94 925	95 901		94 394	94 936	95 360	95 620	
Person-years in Cohort II	78 632	78 285	78 545	78 303		78 581	78 766	78 467	77 950	
Men and women										
Colorectum										
No. of cases	114/94	102/81	97/73	64/80		100/85	91/84	95/78	91/81	
RR (95% CI)	1.00	0.89	0.88	0.92 (0.70–1.19)	0.40	1.00	0.98	0.92	1.00 (0.79–1.27)	0.80
Colon										
No. of cases	77/56	70/51	66/48	43/45		67/50	60/53	68/44	61/53	
RR (95% CI)	1.00	0.89	0.93	0.92 (0.66–1.28)	0.61	1.00	0.99	0.96	1.08 (0.80–1.45)	0.73
Rectum										
No. of cases	37/38	32/30	31/25	21/35		33/35	31/31	27/34	30/28	
RR (95% CI)	1.00	0.88	0.78	0.91 (0.59–1.40)	0.47	1.00	0.95	0.84	0.87 (0.58–1.31)	0.37
Men										
Colorectum										
No. of cases	90/80	81/61	61/43	10/28		83/66	62/55	60/45	37/46	
RR (95% CI)	1.00	0.86	0.79	1.06 (0.70–1.61)	0.34	1.00	0.95	0.82	1.18 (0.88–1.59)	0.86
Colon										
No. of cases	59/51	57/36	42/31	8/16		57/40	42/36	41/27	26/31	
RR (95% CI)	1.00	0.83	0.86	1.02 (0.61–1.70)	0.57	1.00	0.96	0.84	1.24 (0.86–1.79)	0.69
Rectum										
No. of cases	31/29	24/25	19/12	2/12		26/26	20/19	19/18	11/15	
RR (95% CI)	1.00	0.91	0.68	1.19 (0.59–2.36)	0.42	1.00	0.91	0.81	1.06 (0.63–1.78)	0.81
Women										
Colorectum										
No. of cases	24/14	21/20	36/30	54/52		17/19	29/29	35/33	54/35	
RR (95% CI)	1.00	1.02	1.15	0.93 (0.61–1.42)	0.77	1.00	1.03	1.08	0.88 (0.57–1.35)	0.48
Colon										
No. of cases	18/5	13/15	24/17	35/29		10/10	18/17	27/17	35/22	
RR (95% CI)	1.00	1.07	1.19	0.87 (0.49–1.52)	0.86	1.00	1.09	1.25	1.01 (0.58–1.76)	0.96
Rectum										
No. of cases	6/9	8/5	12/13	19/23		7/9	11/12	8/16	19/13	
RR (95% CI)	1.00	0.77	0.95	0.84 (0.43–1.65)	0.77	1.00	0.96	0.84	0.71 (0.36–1.38)	0.27

RR = relative risk; CI = confidence interval. [a]RRs have been adjusted for sex, age (5-year groups), Public Health Centre area, body mass index in kg m^{-2} (less than 19, 19–22.9, 23–26.9, and 27 or more), frequency of sports (never or 1 day/month or more), smoking (never, past, and current), alcohol consumption (non, occasional, 1–149, 150–299, and 300 g week or more), vitamin supplement use, quartiles of energy, cereals, meats, and fish by each cohort. The lowest quartile serves as reference category. The numbers of colon and rectal cancers are from Cohort I/Cohort II.

of regular drinkers. We observed similar tendencies for women in Cohort I, and for men and women in Cohort II.

We found no significant association between fruit or vegetable intakes and the risk of colorectal cancer (Table 1). Multivariate RRs (95% CI) for the highest *vs* the lowest quartile of intake were 0.92(0.70–1.19) and 1.00(0.79–1.27), respectively, based on 705 cases. We observed no association whether or not colon and rectal cancers were separated, or men and women were separated. Exclusion of colorectal cancer cases diagnosed in the first 3 years of follow-up did not change the findings materially. Stratified analyses by covariates included in multivariate models did not reveal remarkable effect modifications. Analyses based on the octiles of total fruit or vegetable consumption did not show significant associations. No individual fruit or vegetables showed significant relations with risk.

DISCUSSION

This is the first prospective cohort study of fruit and vegetable consumption and incident risk of colorectal cancer in Japan. Our results are consistent with the recent prospective studies in Western populations showing no substantial protective associations (Michels *et al*, 2000; Voorrips *et al*, 2000).

Our food frequency questionnaires had relatively small number of fruit and vegetable items and limited range of frequency categories. Nevertheless, we had observed in Cohort I an inverse association between fruit and vegetable intakes and the risk of gastric cancer (Kobayashi *et al*, 2002). It is therefore unlikely that failure to observe protective association was due to the crude designs of our questionnaires.

While mortality from colorectal cancer in Japan increased during 1950–2000, the average consumption of fruit and vegetables also increased during this period (42–117 and 242–311 g day^{-1}, respectively) (Kenko Eiyo Joho Kenkyukai, 2002). Our results, along with these time trends, suggest that low consumption of fruit and vegetables is not primarily responsible for the increased rate of colorectal cancer in Japan.

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Appendix A

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Phase II Study of Sequential Methotrexate and 5-Fluorouracil Chemotherapy Against Peritoneally Disseminated Gastric Cancer with Malignant Ascites: a Report from the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group, JCOG 9603 Trial

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Background: The efficacy of systemic chemotherapy against peritoneal dissemination from advanced gastric cancer (AGC) remains unclear, because the peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies. In this study, we evaluated the efficacy and toxicity of sequential MTX and 5FU therapy (MF) in chemotherapy-naive patients with AGC accompanied by malignant ascites in a phase II setting.
Methods: The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 every 6 h, for a total of six times) was commenced 24 h after MTX administration.
Results: Thirty-seven chemotherapy-naive patients with AGC presenting with malignant ascites were enrolled in this trial. The median age was 60 years (range, 25–74 years) and most patients (86%) had a performance status of 0–1. In total, 355 administrations of the sequential MTX/5FU therapy were performed. Major toxicity consisted of myelosuppression and gastrointestinal toxicity. Grade 4 neutropenia occurred in 10.8% of the patients. The overall objective response rate was 5.7% (two partial responses in 35 patients; 95% confidence interval: 0.7–19.2%). However, the response rate of ascites was 35.1% (complete disappearance in three patients and apparent decrease in 10 patients; 95% confidence interval: 20.2–52.5%).
Conclusions: Sequential MTX/5FU therapy is effective against AGC with malignant ascites with acceptable toxicity and warrants further investigations in a phase III setting.

Key words: sequential MTX/5FU chemotherapy – gastric cancer, peritoneal dissemination – ascites – clinical trial

INTRODUCTION

Despite a declining incidence in many industrial countries, gastric cancer remains one of the most common malignancies globally. Although this tumor is potentially curable with surgery when diagnosed at an early stage, the prognosis for patients with unresectable or metastatic disease is very poor, with a median survival of 3–4 months when they receive the best supportive care without palliative surgery or chemotherapy (1–3). Gastric cancer can progress to systemic disease through various routes such as direct invasion or lymphatic or vascular spread. Peritoneal dissemination, i.e. peritoneal carcinomatosis, which occurs mainly as a result of direct invasion and/or lymphatic spread, is very common in advanced gastric cancer and is considered an incurable disease state (4). Peritoneal dissemination may cause serious complications, such as

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intestinal obstruction, massive ascites and hydronephrosis associated with the clinical presentation of abdominal pain and fullness, vomiting, constipation, malnutrition and renal dysfunction. From the clinical point of view, palliative management of those complications warrants special considerations and represents a therapeutic challenge in oncology (5,6). Although the major treatment option for unresectable or metastatic gastric cancer is systemic chemotherapy, this strategy has been generally believed to have little effect on peritoneal dissemination, because the drugs could not be delivered sufficiently through the peritoneum–plasma barrier to the disseminated tumor cells (7). However, the efficacy of systemic chemotherapy against peritoneal dissemination from gastric cancer remains unclear, because peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies and therefore few reports are available about the efficacy of systemic chemotherapy against peritoneal dissemination. 5-Fluorouracil (5FU) remains the mainstay for chemotherapy against gastric cancer and a variety of drugs have been tested as modulators to increase its chemotherapeutic efficacy. The modulators that have been most widely used in clinical practice against gastrointestinal tract cancers are folinic acid (leucovorin) and methotrexate (MTX) (8,9). MTX enhances 5FU cytotoxicity via DNA and/or RNA synthesis inhibition when the two drugs are administered in sequence, with 5FU administered a few hours after MTX (10,11). A meta-analysis of randomized trials of sequential MTX/5FU therapy revealed a higher response rate than for single agent bolus 5FU in colorectal cancer (12). The toxicity of these sequential MTX/5FU regimens was comparable to that of 5FU alone (i.e. vomiting, stomatitis, diarrhea and leukopenia). The sequential MTX/5FU therapy was found in phase II trials for advanced gastric cancer to have antitumor activity against advanced gastric cancer (13,14). A Japanese phase II trial of sequential MTX/5FU therapy against advanced gastric cancer demonstrated that low- and intermediate-dose MTX regimens achieved response rates of 23% (13 PRs/56 patients) and 41% (15 PRs/37 patients), respectively (15). Sequential MTX/5FU therapy is widely used as one of the standard treatment regimens for patients with unresectable or metastatic gastric cancer at present in Japan. Konishi et al. reported that sequential MTX/5FU therapy was effective in patients with peritoneal dissemination with a response rate of 23% (6/26) and that ascites disappeared in eight of 16 patients (50%) treated with this therapy (16). Those findings suggest that sequential MTX/5FU might be effective in advanced gastric cancer with peritoneal dissemination.

The objective of this study was to evaluate the efficacy and toxicity of sequential MTX/5FU chemotherapy in advanced gastric cancer with malignant ascites in order to determine whether this regimen is worthy of further investigation in a phase III trial for the treatment of patients with peritoneal dissemination from advanced gastric cancer. The primary endpoints planned for this study were tumor response rate and response rate in ascites. Secondary endpoints were overall survival and toxicity. To our knowledge, there has been no prior study that evaluated the efficacy and toxicity of systemic chemotherapy in a phase II setting in patients with advanced gastric cancer who have peritoneal dissemination with malignant ascites.

SUBJECTS AND METHODS

Eligibility

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) histologically confirmed gastric cancer; (2) unresectable or recurrent disease; (3) peritoneal dissemination with cytologically confirmed malignant ascites evaluable by CT scan or ultrasonography; (4) measurable or evaluable disease; (5) age 20–75 years; (6) performance status (PS) ≤2 on Eastern Cooperative Oncology Group (ECOG) scale; (7) no prior chemotherapy with the exception of one adjuvant chemotherapy; (8) adequate bone marrow function (WBC ≥4000/mm^3 and platelets ≥100 000/mm^3) (9) adequate liver function (serum bilirubin level ≤2.0 mg/dl and serum transaminase level ≤2.5-fold the upper limit of normal; (10) adequate renal function (serum creatinine and blood urea nitrogen within the upper limit of normal; (11) serum albumin ≥2.6 g/dl; (12) normal ECG; (13) currently hospitalized; (14) life expectancy at least 8 weeks; (15) written informed consent. Patients with active bleeding from the gastrointestinal tract, other active synchronous carcinoma, central nerve metastasis or concurrent uncontrolled medical illness and pregnant or lactating women were excluded. Patients with massive ascites that required drainage for the relief of symptoms were also excluded. The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center.

Treatment Plan

The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 orally or i.v. every 6 h, six times) was commenced 24 h after MTX administration. To prevent toxicity from MTX, acetazolamide (250 mg) was given intravenously immediately after the infusion of MTX and sodium bicarbonate (33.3 mequiv.) added to 500 ml of electrolyte solution was administered by drip infusion for urine alkalinization during the 3 h interval between the administration of MTX and 5FU. The plasma level of MTX was monitored 24 h after MTX administration and leucovorin rescue at 10 mg/m^2 was administered every 6 h until the plasma level of MTX was $<1 \times 10^{-6}$ mol/l. At the time of each administration, patients were required to fulfill the following criteria: leukocyte count ≥3000/ mm^3; platelet count ≥75 000/ mm^3; adequate liver and renal function as eligibility criteria; PS 0–2; and absence of toxicity grade 2 or greater. The treatment was repeated unless disease progression or severe toxicity was observed. The treatment was terminated when the ascites did

Table 1. Patients' characteristics

Characteristic	Total (n = 37)
Gender	
Male	21
Female	16
Age (years)	
Median	60
Range	25–74
ECOG performance status score	
0	8
1	24
2	5
Histological type	
Intestinal type	
Well-differentiated tubular adenocarcinoma	4
Moderately differentiated tubular adenocarcinoma	7
Papillary adenocarcinoma	1
Diffuse type	
Poorly differentiated adenocarcinoma	6
Mucinous adenocarcinoma	2
Signet-ring cell carcinoma	17
Macroscopic type of primary tumor	
Scirrhous type	21
Non-scirrhous type	16
Metastatic sites	
Lymph nodes	25
Liver	7
Krukenberg's tumor	2
Douglas's metastasis	1
Lung	2
Bone	1
Pleural effusion	4

not improve within 8 weeks or when toxicity did not disappear within 6 weeks.

Response and Toxicity Evaluation

Tumor response was assessed by CT scan or ultrasonography of the target lesions every 4 weeks after the first administration of MTX. Complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were defined according to the response assessment criteria proposed by the Japanese Research Society for Gastric Cancer (17). The response in ascites was evaluated by abdominal CT scan or ultrasonography based on the following specific criteria used in this study: (1) disappearance of ascites – disappearance of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (2) decrease of ascites – apparent decrease of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (3) no response of ascites – no change of ascites volume visualized by CT scan or ultrasonography. The data for tumor response in all responders was confirmed by an extramural review. The toxicity was evaluated according to the JCOG common toxicity criteria (18).

Statistical Analysis

The sample size was determined based on the precision of the estimates. The efficacy for malignant ascites was expected to be 30%. Fifty subjects and an observed efficacy of 30% would provide a 95% confidence interval of 17.9–44.6% or width of 26.7%. The expected accrual period was 1.5 years. Interim analysis was planned to test for inefficacy of the treatment by examining whether a 90% upper confidence bound of efficacy would exceed 25% for first 20–25 patients. The overall survival was calculated for the period from the date of registration to the date of death. Overall survival was calculated by the Kaplan–Meier method and confidence intervals were calculated based on Greenwood's formula.

RESULTS

Patient Population and Study Treatment

Between February 1997 and October 1999, 37 patients were enrolled in this trial from nine out of 13 participating institutions. Although this study was originally planned as a phase II study in which 50 patients would be enrolled within 1.5 years of the start of the study, the patient enrollment was delayed and was finally terminated before the projected number of patients had been achieved based on the decision of the JCOG monitoring committee that the evaluation of efficacy and toxicity was possible even with only 37 enrolled patients. Table 1 lists the demographic data, baseline disease and pretreatment characteristics of all patients. Twenty-one males and 16 females were registered as receiving first-line chemotherapy. The median age of the patients was 60 years (range, 25–74 years) and the majority of the patients (86%) had a good performance status of 0–1. Twenty-one patients (57%) had macroscopically scirrhous-type advanced gastric cancer. Twenty-five patients had histologically diffuse types (six poorly differentiated adenocarcinoma, two mucinous carcinoma and 17 signet-ring cell carcinoma). Two patients had undergone surgery prior to enrollment in this trial (one palliative total gastrectomy and the other exploratory laparotomy resulting in no resection). One patient suffered from hemilateral hydronephrosis due to peritoneal dissemination with normal range of renal function tests.

In total, 355 administrations of the sequential MTX/5FU therapy were performed in 37 patients. The median number of administrations was eight (range, 1–42). Twenty-nine of 37 enrolled patients (78%) received at least four administrations of the sequential MTX/5FU therapy. All patients were assessable for toxicity and response of ascites to chemotherapy. Thirty-five patients were assessable for objective tumor