

Radio induced cancer risk during ERCP. Is it a real clinical problem?

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ABSTRACT

Background: in recent years many factors have been shown to influence dose received by the patient during ERCP. Therefore it is necessary to update radio induced cancer risk.

Objectives: to calculate lifetime attributable risk of cancer during ERCP. To compare the risk with the most common X-ray examinations.

Design: descriptive study with 393 consecutive ERCP performed at one center. Equipment used was Philips BV pulsera. In each exploration demographic and anthropometric variables of the patient were collected. Dosimetric quantities were calculated from exposure parameters. Effective dose was estimated using specific conversion factors. Organ doses and radio induced cancer incidence was estimated.

Results: dose area product was 0.82 mGym² (IQR 0.4-1.5) with an average fluoroscopy time of 2 minutes and 45 seconds. Entrance surface dose was 30.7 mGy (IQR 15-60.8) and effective dose was 0.44 mSv (IQR 0.2-0.9). Multivariate analysis identified that difficult papillary cannulation ($\beta=0.4$; $p = 0.009$), patient age ($\beta=-0.01$; $p = 0.001$) and therapeutic applied ($\beta=0.89$; $p < 0.001$) influenced dose-area product. The ERCP dose would be equivalent to the radiation received by twenty chest radiographs and would be about fourteen times smaller than a barium enema or twenty times less than that received during an abdominal CT. Lifetime attributable risk of cancer incidence was 4.08 and 16.81 per million procedures in diagnostic and therapeutic ERCP respectively.

Conclusions: from the radiological point of view, ERCP is a safe technique that uses low exposure levels compared to other explorations commonly used in medicine. It implies a reasonably low risk of radio induced cancer.

Key words: ERCP. Radio induced cancer. Radiation doses. Effective dose. Dose area product.

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ABBREVIATIONS

- ERCP: endoscopic retrograde cholangiopancreatography
- DAP: dose area product
- NRPB: National Radiological Protection Board
- ICRP: International Commission on Radiological Protection
- IQR: interquartile range
- ESD: entrance surface dose

BACKGROUND

In recent years we have witnessed a significant development of radiological techniques applied to medicine which could mean an increase in radiation exposure for patients. However in ERCP, since the first studies were published more than 30 years ago (1), parallel development of new technologies has allowed us to minimize the radiation dose used and improve the quality of image obtained.

Several factors have been shown to influence the dose received by the patient during this technique. In this sense, the most described is therapeutic indication that could increase the dose area product (DAP) three to four times (2,3). Therapeutic options are becoming more com-

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plex and require increased fluoroscopy time and thus increased patient dose (4). However, other factors like endoscopist experience (5) and time limited fluoroscopy (6) have been reported as able to shorten the fluoroscopy time.

Furthermore, previous studies have suggested that ERCP is safe from the radiological point of view, even in special situations such as pregnancy (7), although a recent study has questioned this assertion by detecting that occasionally exceeding the maximum recommended doses to the fetus (8), especially during the early pregnancy stage. For this reason, in high-risk situations like pregnancy, the priority is to minimize the dose and some authors have reported cases in which fluoroscopy was not needed (9,10).

Considering the factors described above, it is possible that dose received by patient during ERCP has changed in recent years so it is necessary to update it with a large number of patients who can encompass all the current clinical possibilities. This study will reveal the actual risk involved in the radiation used during ERCP. This information may help in the future to minimize risks. The aims of the present study were: a) to estimate patient lifetime attributable risk of cancer incidence during ERCP; and b) to compare the risk with the most common X-ray examinations.

METHODS

This is an observational, descriptive, transversal study with 393 consecutive ERCP performed on 348 patients in one single center between February and September 2009. Explorations were carried out by three different endoscopists assisted by a fellow. All of them were blinded to the study. Experience in ERCP was very homogeneous between participating endoscopists. The number of procedures performed by each endoscopist ranged from 156 to 228 per year with all of them having more than ten years experience. In each exploration, demographic (gender and age) and anthropometric variables (weight, height and thickness) of the patient were registered. We also collected diagnostic or therapeutic intention of the exploration, number of cannulation attempts and treatment applied. Radiological parameters were provided by the equipment (fluoroscopy time, kilovoltage, milliamperage and DAP).

From technique parameters, organ dose and effective dose have been calculated using normalized organ dose data published by the National Radiological Protection Board (NRPB) (11) and weighting factors given by International Commission on Radiological Protection (ICRP) (12). These parameters are crucial to estimate risks and compare with other radiological explorations.

The adult risk coefficients for cancer incidence from BEIR VII (13) were applied to calculate sex- and age-specific whole risk.

Technical aspects

The fluoroscopy X-ray unit used during the ERCP examinations was Philips BV Pulsara (Philips Medical Systems, Best, The Netherlands) with high frequency generator. The X-ray tube has a standard filtration of 3 mm aluminum and additional filtration of 0.1 mm copper. The system offers various continuous and pulsed fluoroscopy modes with different dose levels. In all explorations, the mode used was low dose at 12.5 pulses/second. Verification tests were conducted to assess the accuracy of displayed values of peak tube potential (kVp), millamps and time. The kVp and time measurements were made using a PMX III multimeter (RTI Electronics AB, Sweden). The tube output was measured using a 2026C electrometer connected to a model 20X5-3 ionization chamber, both manufactured by Radcal Corporation (Radcal, Monrovia, CA). The system has calibration which is traceable to a national standard. The tube output linearity at 80 kVp for a wide range of tube charge settings (3-100 mAs) was about 2%. The radiation spectra were characterized by the total filtration and kVp. With the PMX III multimeter the half value layer was determined. From this measurement, the total filtration is determined using the conversion tables in the application note of RTI electronics. The X-ray unit had a DAP calculation system which was calibrated *versus* a Vacutec DAP meter (type 70 1159 C).

Statistical analysis

The sample size required should be sufficient to cover all current therapeutic options offered by the ERCP. To do this we take as reference a recent article performed by Kim et al. (4) that evaluated the clinical determinants on fluoroscopy time. In this study the minimum sample size estimated was 117 patients but finally included 388 scans. Our sample size was 393 explorations and we checked using EPIDAT 3.1 that it was sufficient to provide a statistical power of 0.9 and α error of 0.05.

Statistical analysis was performed using SPSS 15.0 for Windows. First we achieved a descriptive study of variables. Quantitative variables are expressed like mean and standard deviation except radiological dose variables that are presented as median and interquartile range (IQR) because of its positive asymmetry. In the posterior analytical phase we applied appropriate hypothesis contrast tests. Finally, multivariate analysis was performed using multiple linear regression to establish those factors independently related with the radiological dose received by the patient and also to monitor possible confounding factors. The model had an associative character and the dependent variable used was DAP. All hypothesis tests were bilateral and considered statistically significant at $p < 0.05$.

Table I. Descriptive study of variables

Variables	Descriptive values	
	Quantitative (mean+/-SD)	Qualitative (n) (%)
Age	75 ± 12.34 years	
Sex		Men 211 (53.7%)
		Women 182 (46.3%)
Weight	69.52 ± 12.73 kg	
Height	1.60 ± 0.09 m	
Thickness	29.62 ± 4.1 cm	
Technique		Diagnostic 52 (13.2%)
		Therapeutic 340 (86.8%)
		• Only sphincterotomy 102 (26%)
		• Sphincterotomy + stone removal 159 (40.6%)
		• Stent placement or removal 79 (20.2%)
Cannulation attempts	Less than five 307 (78.4%)	
		Six to fifteen 51 (12.6%)
		More than sixteen 35 (9%)
Complications		Pancreatitis 10 (2.5%)
		Gastrointestinal bleeding 9 (2.3%)
		Duodenal perforation 2 (0.5%)
Mortality	3 (0.8%)	

RESULTS

We analyzed 393 ERCP performed at our hospital during the above period. Descriptive study is summarizing in table I. Kilovoltage and miliamperage means were 80.25 Kv and 4.15 mA respectively. The average fluoroscopy time was two minutes and forty-five second being the DAP median 0.82 mGym² (IQR 0.4-1.5). ESD median was 30.7 mGy (IQR 15-60.8) and effective dose was 0.44 mSv (IQR 0.2-0.9).

As in previous studies, we observed a positive linear correlation between fluoroscopy time and DAP. Although this relationship was strong and statistically significant ($r = 0.728$; $p < 0.001$), it was not perfect so we made a multiple linear regression analysis to establish what other factors may modify the DAP. In this analysis, therapeutic intention, papillary cannulation difficulty (need of six or more attempts) and younger patients demonstrated an independent association with higher DAP (Table II).

Examining the first point, diagnostic technique involved a DAP median of 0.3 mGym² (IQR 0.05-0.7) while the therapeutic technique median was 0.94 mGym² (IQR 0.5-1.7) ($p < 0.001$). Within the latter group, sphincterotomy alone involved a DAP of 0.54 mGym² (IQR 0.37-1.04) while combining sphincterotomy with stone extraction implied a median of 0.89 mGym² (IQR 0.84-1.56). In the group of stent placement or removal the median was 1.66 mGym² (IQR 1.1-2.74) with significant differences with previous two groups ($p < 0.001$ in both cases) (Fig. 1). With the fluoroscopy time, something similar to the above

Table II. Multiple linear regression

Variable	β coefficient	Confidence interval 95%	p
Therapeutic intention	0.89	0.52-1.27	< 0.001
Cannulation difficulty (< 5 or ≥ 6 attempts)	0.40	0.10-0.70	0.009
Patient age	-0.17	-0.26 - (-0.07)	0.001

Coefficient of determination $R^2 = 0.15$; $F = 1.15$; GL = 5; $p = 0.483$.

happens. The sphincterotomy group introduced an average time of 1 minute and 48 seconds while in the sphincterotomy with stone extraction group was 2 minutes 50 seconds ($p = 0.004$). The stent placement or removal group implied an average fluoroscopy time of 5 minutes and 5 seconds ($p < 0.001$ with both previous). All this suggests that the higher the technique complexity, especially when it involves the placement of biliary stents, a higher fluoroscopy time is needed entailing an increase of DAP to the patient.

Papillary cannulation difficulty, measured by the number of attempts necessary to inject contrast in the biliary conduct, influenced DAP in multivariate analysis ($p = 0.009$). In this sense, the group of less than five attempts produced a DAP median of 0.81 mGym² (IQR 0.45-1.43) while the group with six or more attempts produced 1.07 mGym² (IQR 0.34-1.96).

Younger patients had higher DAP so that a 10-year increase in the patient's age meant a decline of 0.17 mGym² in DAP. In order to find the reason for this curious relationship, we separated patients into two groups according to their age. We found that patients younger than 65 years had a higher proportion of stent placement than patients older than 65 years (37.5 and 15.1% respectively; $p < 0.001$). No other variables significantly influenced the DAP.

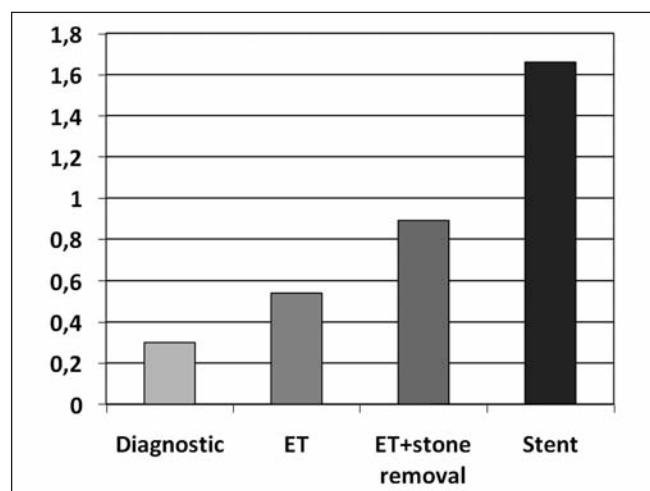


Fig. 1. Therapeutic and DAP. Higher technique complexity implies higher DAP ($p < 0.001$ in all comparisons).

Table III. Organ dose median (mGy) and lifetime attributable cancer incidence (per 1 million explorations). Calculated for 75 years old

Organ	Diagnostic ERCP		Therapeutic ERCP	
	Dose (mGy)	Cancer (per million ERCP)	Dose (mGy)	Cancer (per million ERCP)
Adrenal gland	0.048	0.0160	0.225	0.0745
Breast	0.008	0.0096*	0.037	0.0296*
Gallbladder	0.509	0.1686	2.339	0.7749
Stomach	0.042	0.0535	0.209	0.2664
Small bowel	0.010	0.0132	0.097	0.0321
Colon	0.174	0.6205	0.801	0.3264
Heart	0.019	0.0062	0.093	0.0308
Kidney	0.069	0.0228	0.321	0.1063
Liver	1.018	0.4581	4.628	2.0826
Lung	0.023	0.1857	0.108	0.8721
Ovary	0.012	0.0096*	0.063	0.0504*
Pancreas	0.102	0.0337	0.472	0.1563
Skin	17.10	2,3176	32.82	10.87
Spleen	0.011	0.0036	0.066	0.0218
Thymus	0.003	0.0001	0.019	0.0062
Bladder	0.002	0.007	0.014	0.0493
Esophagus	0.011	0.0036	0.059	0.0195
Uterus	0.009	0.0126*	0.050	0.0175*
Bone marrow	0.025	0.1306	0.115	0.6008
Brain, eye lens and testicles	0	0	0	0
Residual tissues	0.047	0.0155	0.214	0.1418
<i>Total</i>		4.08		16.81

*Applicable for female only.

Effective dose was calculated to estimate risk for patients. In diagnostic explorations, the effective dose median was 0.11 mSv (IQR 0.02-0.5) while in the therapeutic ones it was 0.49 mSv (IQR 0.25-0.94).

Organ doses and lifetime radio induced fatal cancer for each organ are shown in table III. Therapeutic explorations registered higher organ dose. Notice that the highest doses were registered by organs situated closer to the bile duct like the liver (1.61 and 4.62 mGy for diagnostic and therapeutic ERCP respectively) and the gallbladder (0.115 and 0.530 mGy for diagnostic and therapeutic ERCP respectively). Using an average patient age of 75 years old (based on the present study results), we obtained a lifetime risk of radio induced cancer of 4.08 per million diagnostic explorations. In therapeutic ERCP 16.81 radio induced cancer per million explorations was estimated. Finally, with the aim of extending the results of this study to other younger populations, we estimated the risk for patients with a mean of 60 years yielding a value of 7.68 and 31.64 per million explorations for diagnostic and therapeutic ERCP respectively.

DISCUSSION

Over the last few years, dose received by patients during ERCP have declined dramatically. The first high quality

study published on this topic was conducted by Larkin et al. (2). They included 20 procedures and found an average DAP of 1.35 and 6.68 mGym² for diagnostic and therapeutic ERCP respectively. Three years later Bambrilla et al. (14) reported reference dose levels for various radiologic techniques including ERCP with a DAP mean of 3.3 mGym². In the present work, DAP was 0.54 mGym² for diagnostic ERCP and 1.31 mGym² for therapeutic ERCP, values much lower than those referred to above.

Thus, the technological development of more modern equipment that includes modes with low radiation and high imaging quality has played a key role. However, this was not the only factor involved. Fluoroscopy time has halved in diagnostic tests and even more for therapeutic explorations. This may be because endoscopists have more experience in this technique nowadays. In our study, endoscopists experience was assessed. According to the rules published in a recent study (5), the experience of the endoscopists participating in this study was medium-high. We found no differences in fluoroscopy time or DAP between endoscopists.

The results obtained allowed us to compare the risk of radiation-induced cancer in ERCP with other radiological techniques commonly used in medicine. Using data obtained from the European Commission of radiological protection (15), the effective dose found in this study,

would place ERCP in band I (Table IV). The ERCP dose would be equivalent to the radiation received by twenty chest radiographs and would be about fourteen times smaller than a barium enema or twenty times less than that received during an abdominal CT.

In our multiple linear regression model we found that the conduct of therapy, especially the placement of biliary stent, implied a higher DAP. This has already been reported in many previous studies (2-4,8) showing that therapeutic ERCP could be six times higher. In fact, in most studies regarding radiation dose, authors differentiate between diagnosis and therapeutic ERCP, treating them as two different techniques. Difficult papillary cannulation has emerged as another factor that can increase the DAP independently. A previous study (6) showed that this fact implies a prolonged fluoroscopy time but did not confirm an influence in DAP.

Younger patients registered a higher DAP in the present study. This fact has not been previously described and has a very difficult explanation itself. Probably it could be justified by the high proportion of biliary stent placement registered in less than sixty five years old patients in our series as we revealed above. This fact can justify that, younger patients also had longer fluoroscopy time (146.3 and 213.6 seconds respectively; $p = 0.012$).

Finally we would like to emphasize that the fit goodness of the model (R^2) was 0.15 implying that only 15% of the variability of DAP is explained by the variables commented previously. This suggests that there are many other factors involved in the radiation dose received by the patient during ERCP. One of these factors (probably the most important) is fluoroscopy time that was not included in the model because the strong correlation with DAP showed that it could interfere with the other variables. We cannot discard the existence of other variables, especially those related to the equipment's automatic adjustments, that may affect DAP.

Lifetime radio induced cancer incidence was obtained using effective dose and specific organ doses. We calculated 1 fatal cancer per three hundred thousand explorations in diagnostic ERCP and 1 fatal cancer per fifty thousand explorations in therapeutic ERCP approximately. These values are much lower than previously described (2). The most important factor implied in that reduction is lower dose registered. Nevertheless, the aging of the population under this procedure has played a key role. In fact, we showed that, considering a 60 years old population (fifteen years younger than ours), lifetime radio induced cancer risk during ERCP became twice, however it remains low.

We can summarize that the dose received during ERCP has decreased considerably in recent years and may nowadays be regarded as a safe imaging technique compared to other radiological explorations commonly used in medicine. Clinical aspects such as difficult papillary cannulation or more complex therapeutic (especially when biliary stent is placed) can prolong the fluoroscopy time and increase the dose received by the patient. Radio induced can-

Table IV. Band classification of the typical effective doses of ionizing radiation from common imaging procedures (adapted from reference 15)

Band	Typical effective dose (mSv)	Examples
0	0	Ultrasonography, magnetic resonance imaging
I	< 1	Conventional X-ray thorax, limb, pelvis
II	1-5	Conventional X-ray pelvis, CT head and neck, intravenous urogram
III	5-10	CT chest and abdomen, cardiac nuclear medicine
IV	> 10	Some PET

CT: computed tomography; PET: positron emission tomography.

cer risk is reasonably low but is expected to fall further in the coming years with the advent of new technologies and the participation of more experienced endoscopists.

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